# CONTENTS

I

# BLMP-1 Contributes to Collagen-related Morphogenesis in *C. elegans*

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**Abstract:** *C. elegans blmp-1* is the homologue of mammalian *Blimp1* (*B Lymphocyte-Induced Maturation Protein-1*) and encodes a zinc finger and SET domain-containing protein.   Genetic and molecular analysis of *blmp-1* revealed that downregulation of this gene leads to morphological defects that include a dumpy, uncoordinated phenotype, short rays on male tails, and a weak cuticle. Downregulation of typical collagen genes, such as *dpy-2,-3,-7,-8,* and *-13*, enhance the dumpy phenotype caused by *blmp-1* deletion. Worm cuticle images captured by in cryo scanning electronen microscope demonstrated the annuli defect of *blmp-1(tm548)* mutants. In conclusion, *blmp-1* plays a role in morphogenesis through the effect on cuticle.

## 1. Introduction

*Blimp1/PRDM1* was originally identified as a zinc finger transcriptional repressor, due to its ability to silence beta-interferon gene expression and act as a key regulator of plasma cell differentiation in mammalian cells(Turner, 1994). In addition, this protein also controls paradigms of gene expression in different cell types, such as T lymphocytes (Kallies, 2006, Martins, 2006), macrophages (Chang, 2000), and the sebaceous gland (Horsley, 2006). Blimp1 orchestrates plasma cell differentiation by inhibiting the mature B cell gene expression program (Shaffer, 2002). Studies in mouse demonstrated that Blimp1 represses the initiation of the somatic program and instead promotes progression toward the germ-cell fate (Ohinata, 2005, Vincent, 2005). Another study in which *blimp-1* was conditionally deleted in mice revealed that Blimp-1 is an important regulator of the transition of keratinocytes from the granular to the cornified layer of the epidermis (Magnusdottir, 2007). Blimp1 may also have a role in the maintenance of early germ cell fate by promoting the transition from a somatic fate and preventing reversion to a pluripotent stem cell state (Hayashi, 2007). Additionally, Blimp1 has a critical role in the foundation of the mouse germ cell lineage, because disruption of *blimp1* causes a block early in the process of primordial germ cell formation (Ohinata, *et al.*, 2005).

*C. elegans blmp-1* is the homologue of mammalian *Blimp1* (*B Lymphocyte-Induced Maturation Protein-1*), which encodes a zinc finger and SET domain-containing protein (Andersen, 2007). In mammals, *Blimp-1/PRDM1* is expressed in skin epithelial cell lineages (Horsley, *et al.*, 2006, Magnusdottir, *et al.*, 2007, Chang, 2002), which may be analogous to the hypodermis and seam cells in worms. Indeed, in *C. elegans*, a *blmp-1::gfp* transcriptional fusion protein is expressed from late embryogenesis through adulthood and found in a variety of tissues, including hypodermis, seam cells, gonad distal tip cells and vulva, ventral nerve cord, amphids and phasmids, and rectal muscles (Reece-Hoyes, 2007).

Though much has been published regarding lymphocyte maturation and germ-cell fate decision, little is known about *blmp-1* functions in the morphogenesis and skeleton biosynthesis. *C. elegans* is an excellent model for studying morphogenesis and skeleton biosyntheses because the surface of the worms is covered with a flexible and resilient exoskeleton called a cuticle(Cox, 1981, Cox, 1981). The cuticle facilitate locomotion by muscle attachment, protects the organism from the environment. The cuticle is synthesized once in the embryo and again at the end of each larval stage before molting, which serves to regulate the growth rate and restrict the size of the worms (Kramer, 1988, von Mende, 1988). The cuticle is a highly structured extracellular matrix (ECM) that is primarily composed of cross-linked collagens and insoluble proteins like cuticlins, glycoproteins and lipids. The cuticle collagens are encoded by a large gene family with over 150 members (Johnstone, 2000), which are subject to strict patterns of temporal regulation such that RNAi knockdown of less than 30 of these genes results in an obvious phenotype. Cuticle collagen

synthesis involves translation of the preprocollagen peptide followed by the processing, secretion and crosslinking of the collagen. Procollagen processing occurs after secretion, and crosslinking occurs after collagen processing and assembly. This complex process requires a series of specific enzymes and chaperones (Prockop, 1995, Myllyharju, 2004), several of which are potential therapeutic targets for the treatment of collagen-associated diseases (Myllyharju, 2001). Mutations in individual collagen genes and their biosynthetic pathway components can result in a number of defects, ranging from abnormal morphology (dumpy and blister) to embryonic and larval death, confirming an essential role for this structure and highlighting its potential as an ECM experimental model system.

In this study, we use *C. elegans* as a model to investigate the function of *blmp-1* in collagen-restricted morphogenesis. We found that reduced expression of *blmp-1* leads to morphological defects, such as *Dpy, Unc,* short rays on male tails, and formation of a weak cuticle. Epistasis analysis indicated that *blmp-1* function is independent of the classic collagen genes. Collagen biogenesis and ECM function play a critical role in organogenesis and body morphogenesis in all metazoans. Defects in these processes result in a variety of human osteogenesis imperfecta, including Epidermolysis bullosa, Ehlers-Danlos syndrome, several chondrodysplasias and excessive fibrosis associated with wound healing and liver disease. Additionally, the ability to control and engineer ECM synthesis will be critically important in any future attempts at organ culture. This study contributes to our understanding of the fundamental mechanisms of these diseases and provides insight into additional possible targets for osteogenesis disease therapy.

## 2. Materials and Methods

### 2.1 Worm strains

*C. elegans* strains N2 and *blmp-1(tm548)* were generously provided by Dr. Chonglin Yang. *CB4088 him-5(e1490)V* and *EM733, pkd-2::gfp,him-5(bxIs34)* were generously provided by Prof. Hong Zhang.

### 2.2 RNA interference

The *blmp-1* RNAi clone was obtained from the Ahringer library and induced with 1 mM IPTG one day before feeding on Nematode Growth Medium (NGM) plates.
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### 2.3 Lifespan assay

Synchronized eggs grown to the young adult stage were distributed onto RNAi or non-RNAi plates containing 20 μg/ml FUdR to prevent the growth of progeny. RNAi bacterial clones were selected from

Ahringer's RNAi feeding bacteria library (Kamath, 2003), and RNAi was induced with 1 mM IPTG. Bacteria carrying empty vector were used as controls in all experiments. The worms were cultured at 20℃. Worms that crawled off were excluded from all experiments. The number of dead worms was counted every other day. All experiments were performed at least twice. The P-value was calculated with a log-rank test on the Kaplan–Meier curves.

### 2.4 Male tail observation

Worms were cultured with or without *blmp-1* RNAi on plates; male worms were subsequently picked up to check the tail fan and rays. Strains N2; *EM733, pkd-2::gfp, him-5(bxIs34);* and *CB4088 him-5(e1490)V* were used in this assay.

### 2.5 NaClO lysis assay

Synchronized N2 or *blmp-1* mutant worms were grown on NGM plates until one day after entering adulthood. Next, the worms were transferred into M9 buffer (22 mM $KH_2PO_4$, 34 mM $K_2HPO_4$, 86 mM NaCl, 1 mM $MgSO_4$) in a 96-well plate, with each well containing 20-30 worms. An equal volume of bleach buffer (1/10 5 N NaOH, 1/20 NaClO solution) was added to each well to lyse the worms. Images were taken once every minute using a dissecting microscope (Motic) to monitor the lysis.

### 2.6 cryo scanning electronen microscope (Cryo-SEM)

Cryo-SEM is used for observing cuticle surface of *C. elegans*. SEM involves freezing worms with liquid nitrigon, conductive Pt coating , and imaging on an SEM at -130℃.

## 3. Results

### 3.1 Downregulation of blmp-1 causes defects in wild-type N2 worms

The *blmp-1* gene was first identified in our lifespan screen of histone modification-related genes. We used a feeding RNAi approach to knock down endogenenous *blmp-1* expression in *C. elegans*. RNAi targeting of *blmp-1* at the Larval 1 (L1) stage resulted in a significantly decreased lifespan (Figure 1A), which is consistent with previous data (Greer, 2010). To confirm the association between *blmp-1* and aging, we examined the lifespan of worms with *blmp-1* knocked down at adulthood. To our surprise, *blmp-1* knockdown worms from adulthood did not display the short lifespan phenotype (Figure 1B), suggesting that the short lifespan of L1 stage *blmp-1* mutants is caused by a developmental defect. Indeed, we observed a number of defects at developmental stages when RNAi was applied from the L1 stage; the most obvious phenotypes were dumpy (*Dpy*) and

uncoordinated (*Unc*), which were also reflected by an abnormally locomotion trace (Figure 1C). We subsequently investigated whether the function of blmp-1 in germ cell fate decision is conserved from mammals (Hayashi, de Sousa Lopes and Surani, 2007) to *C. elegans*. We found that *blmp-1* RNAi worms had a decreased brood size (Figure 1D), indicating that there is a defect in a germ cell formation-associated process. Additionally, the *blmp-1* RNAi male worms' tails were small with short rays and insufficiently expanded fans, though there was no fusion or loss of the rays (Figure 1E), suggesting that the abnormal tail phenotype is caused by a cuticle defect. Furthermore, *blmp-1* mutants grow more slowly than wild-type worms, reaching adulthood about 12 h later than N2 worms, and some mutants had a protruding vulva. In conclusion, *blmp-1* knockdown contributes to a series of morphological phenotypes that suggest cuticle defects, and these defects consequently contribute to a short lifespan in worms.

### 3.2 blmp-1 morphological defects are independent of HOX genes

HOX genes have roles in morphogenesis in many species; therefore, we wanted to know if the morphological defects in the *blmp-1* mutant are caused by misregulation of HOX genes or are only a result of the cuticle defect. To test this hypothesis, we examined male tail development. In *C. elegans*, male tail development can be used to examine the HOX gene network, including such genes as *egl-5* (Nicholas, 2009, Toker, 2003, Chisholm, 1991) and *mab-5* (Jungblut, 1998, Gutierrez, 2003). We used a GFP labeled *pkd-2* transgene, which functions as an indicator of HOX gene function and ciliary trafficking and targeting, to trace neuron development and migration in the tail (Bae, 2008, Bae, 2006, Knobel, 2008). RNAi knockdown of *blmp-1* was induced at the L1 stage, and GFP fluorescence was assessed on day 1 of adulthood; we were unable to discern any difference between *blmp-1* RNAi and control worms. This finding suggests that *blmp-1* activity during morphogenesis is not mediated via HOX gene activity (Figure 2A). Therefore, the cuticle defect caused by disrupted expression of collagens or collagen biogenesis genes is probably responsible for the morphological defect in the male tail(Roushdy,2011).

To confirm that an abnormal cuticle causes the morphological defects that we observed in the mutant, we designed an assay to assess the strength of the cuticle by examining the worm's resistance to a strong oxidative solution. To determine the rate at which the worms were lysed, adult wild-type and *blmp-1* mutant worms were immersed in a 50% bleach solution in which NaClO was the main active component. All

worms were alive at the time the bleach solution was applied; after 4 minutes, the majority of the *blmp-1* mutants but not the N2 worms had lysed, indicating that the *blmp-1* mutant worms did not have as strong a cuticle wild-type worms (Figure 2B). This indicates that the *blmp-1* mutant cuticle does indeed have defects that could be responsible for the dumpy phenotype.

To further investigate the structure of culticle surface in blmp-1 mutant, we observed both WT and mutant sample in cryo scaning microscopy. Cryo-SEM shows that the surface of *blmp-1* mutant worms in the adult stage is abnormal, the alae and annulus are not as clearly as wild type (Figure 2C). It is the direct evidence that abnormal cuticle cause the morphological defects.

### 3.3 Knockdown of the typical collagen genes dpy-2,-3,-7,-8, and -13 in blmp-1(tm548) mutant worms enhances the dumpy phenotype.

The cuticle is synthesized several times before molting occurs in the embryo and at the larval stage. The main component of the cuticle is collagen. To date, mutations of more than 30 collagen genes have been found to result in dumpy or other abnormal phenotypes. As the most obvious phenotype resulting from *blmp-1* RNAi or mutation is dumpy, which probably arises from a defect in collagen, we tested whether collagen disruption is responsible for the dumpy phenotype in the *blmp-1* mutant.

From Wormbook.org, we already know that *dpy-2,-3,-7,-8,* and *-10* mutants are dumpy and have no cuticular annuli, while *dpy-5,* and *-13* mutants have narrow annuli. Worms that are mutant for both a "no annuli" gene and a "narrow annuli" gene will have a more severe dumpy phenotype, while a worm mutant for two genes within the same group will not. To determine which group of dumpy genes is regulated by *blmp-1*, we used RNAi to knock down each of these genes in N2 worms to confirm the knockdown phenotype for each gene, as well as the effect of the RNAi technique. Next, we performed RNAi for each of the dumpy genes in a *blmp-1(tm548)* genetic background to determine if it resulted in a compound phenotype. We observed that downregulation of each of these genes leads to a dumpy phenotype in N2 worms (Figure 3A) and a compound dumpy phenotype in a *blmp-1(tm548)* background (Figure 3B). This finding suggests two possibilities; *blmp-1* does not regulate these collagen genes, or *blmp-1* regulates these genes redundantly with some other factor(s). If either of these possibilities is true, then these collagen genes are at least partially expressed in the *blmp-1(tm548)* mutant.

Figure 1
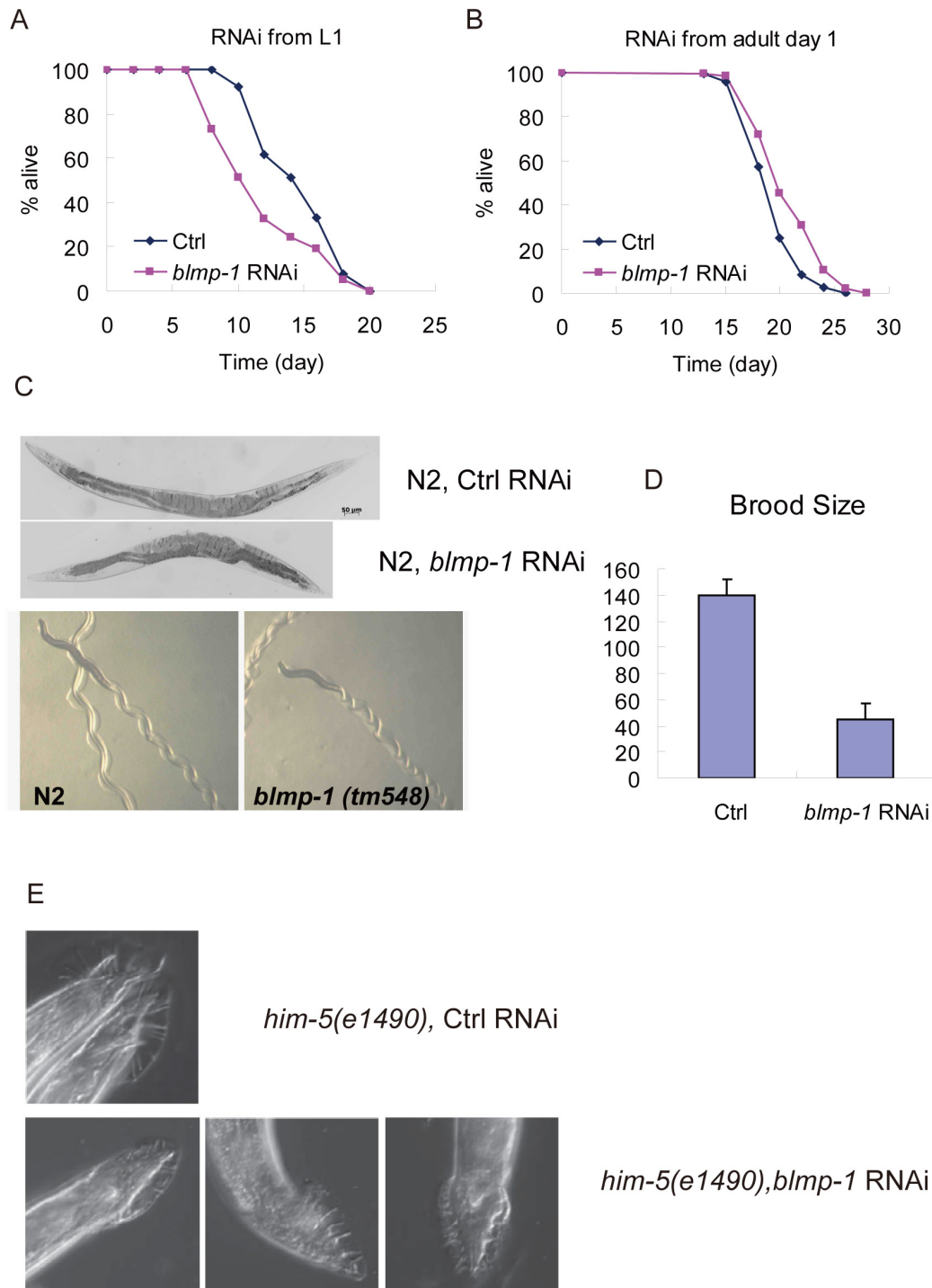


**Figure 1. Typical phenotype of *blmp-1* knockdown in *C. elegans*.**
(A) *blmp-1* RNAi at the L1 stage decreases lifespan in wild-type N2 worms (vector RNAi, n=39; *blmp-1* RNAi, n=37; long-rank test, p<0.01). (B) *blmp-1* RNAi at adulthood results in a slightly increased lifespan of N2 worms (vector RNAi, n=148; *blmp-1* RNAi, n=134; long-rank test, p<0.01). (C) *blmp-1* RNAi and *blmp-1(tm548)* worms have several morphological defects, such as short body length, dumpy (*Dpy*), uncoordinated (*Unc*), and abnormal movement. (D) *blmp-1* knockdown affects germ cells and results in a decreased brood size. (E) *blmp-1* RNAi worms have abnormal male tail morphology. The rays are all short with insufficiently expanded fans.

Figure 2

A

*pkd-2::gfp (bxIs34)*

DIC                GFP



Ctrl

*blmp-1* RNAi

B

Time(min)  0          1          2          4          6



N2

*blmp-1(tm548)*

C



N2

*blmp-1(tm548)*
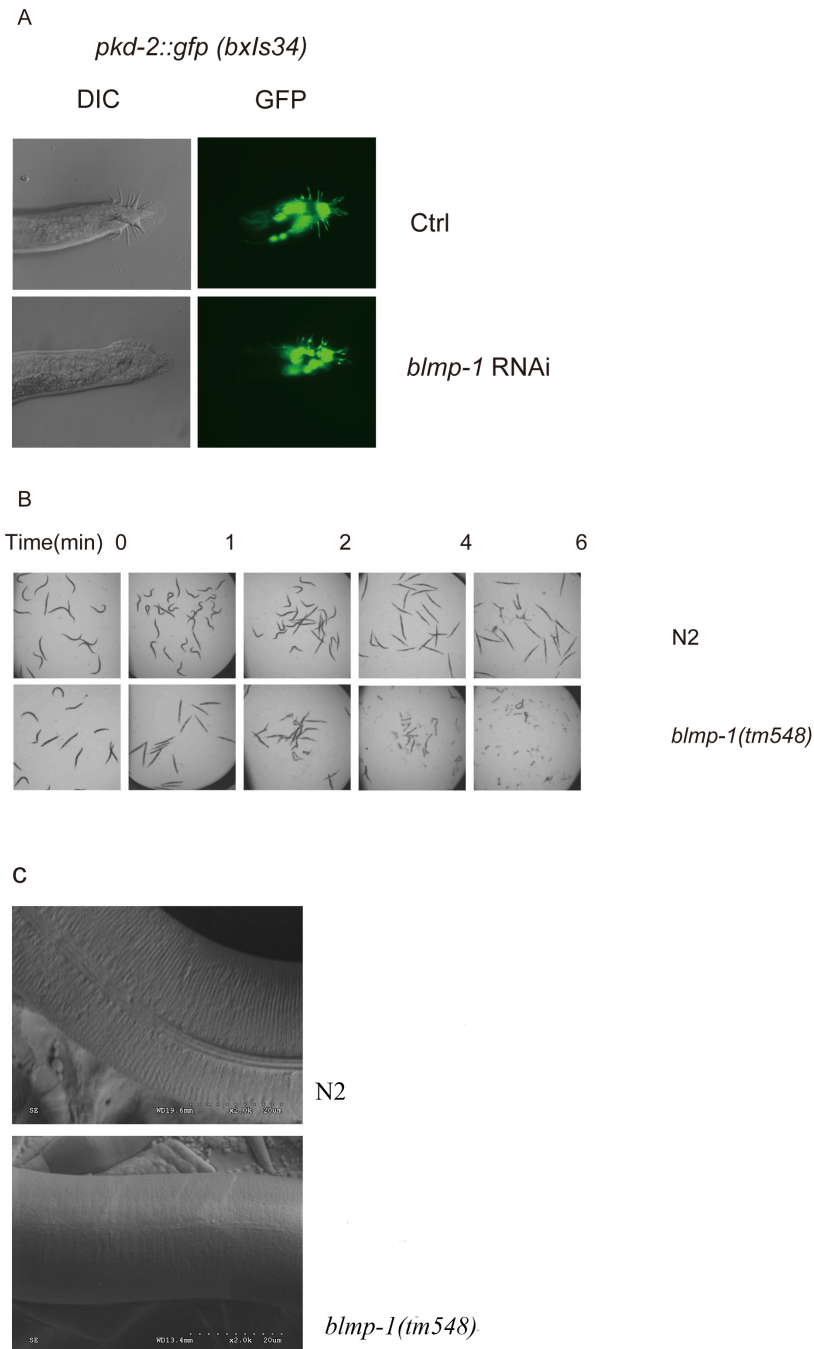
**Figure 2. Morphological defects are associated with the cuticle but not Hox genes.** (A) Representative observation of the *pkd-2::gfp* labeled male tail. There are no neuron development defects that can be visualized by *pkd-2::gfp*; however, the male tail defect can clearly be seen in the *blmp-1* mutant male worm's tail, indicating that the defect is likely caused by collagen disruption but is independent of HOX gene function in development. More than 30 worms were observed for each group, and typical images are shown here. (B) *blmp-1* mutant worms are more sensitive to the oxidative reagent. In the oxidative reagent NaClO, *blmp-1* mutants are lysed faster than wild-type N2 worms. (C) The surface of all *blmp-1* mutant worms(n=38) don't have clearly alae in the adult stage while N2 (n=36) have clearly alae at 2000x.

Figure 3

A

N2

B
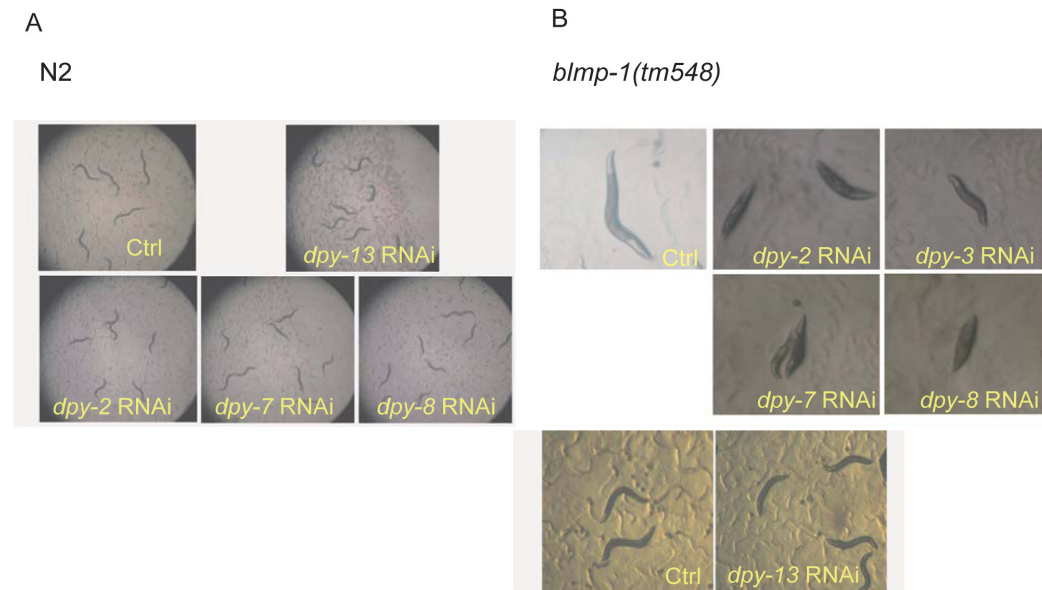
blmp-1(tm548)



**Figure 3. Typical collagen genes that cause *Dpy* phenotype in N2 worms also induce a more severe dumpy phenotype in *blmp-1(tm548)* mutants.**
(A) *Dpy-2 -7*, and *-8* ("no annuli" genes) and *dpy-13* ("narrow annuli" gene) RNAi in N2 worms all lead to *Dpy* phenotype. (B) *dpy-2,-3,-7,* and *-8* RNAi and *dpy-13* RNAi in *blmp-1(tm548)* worms all lead to a compound dumpy phenotype.

Because the mature cuticle is formed by several processing steps after the collagen peptides are translated, any defect in the collagen biosynthesis pathway should be considered in further investigation.Collagen biosynthesis is a complex multi-step process in vertebrates. The main process involves prolyl 4-hydroxylation, procollagen registration and trimerization, transit from the ER, procollagen processing and crosslinking, N-terminal processing, C-terminal processing, and structural crosslinking。

A genome-wide study examining targets of BLMP-1 by ChIP-seq in *C. elegans* has recently become available. The peak significant values for several of the identified gene targets are 1.48E-269 for *bli-4* (NM_001026370), 8.36E-52 for *dpy-10* (NM_062965), and 1.20E-51 for *dpy-2* (NM_062966). This study demonstrates that the *bli-4* locus has a very high signal of BLMP-1 occupation (Niu, 2011), which suggested multiple factors, including collagen and collagen biosynthesis genes are targets of BLMP-1.

**4．Discussion**

In this study, we investigated the function of *blmp-1* in morphogenesis using *C. elegans* as a model system. Knockdown of *blmp-1* by RNAi or deletion by the

mutation *blmp-1(tm548)* results in a number of phenotypes, including dumpy, uncoordinated, a reduced brood size, small tail rays and short lifespan; however, the most remarkable phenotype is the abnormal morphology of the mutants. Using a *pkd-2::gfp* transgene, which allows you to visualize Hox gene function, and an oxidative resistance assay, we ruled out Hox gene dysfunction as a cause of the morphogenesis phenotype and instead identified an abnormal cuticle as being primarily responsible for the morphological defects seen in the *blmp-1* mutants., and further supported by SEM result. The dumpy phenotype could be caused by a collagen biosynthesis defect or a disruption in a collagen gene; however, it was not clear which of these events was downstream of *blmp-1* and causing the mutant phenotype. Because collagen gene expression fluctuates during development, it is not suitable for quantitative PCR analysis, so we were unable to precisely assess changes in the transcription of these genes upon *blmp-1* knockdown. Our data show that knockdown of typical collagen genes in the *blmp(tm548)* mutant lead to a more severe dumpy phenotype, which indicates that collagen biosynthesis may be disrupted in the *blmp-1* mutant.

The abnormal male tail phenotype has also been

found in a genome-wide RNAi screen (Nelson, 2011), which suggests that male tail morphogenesis is governed by a gene regulatory network with a bow-tie architecture that functions to orchestrate regulation of Hox genes, the TGF-beta pathway, nuclear hormone receptors, GATA transcription factors and *blmp-1*, supporting our findings in this study. Our studies suggest that the *blmp-1* mutant male tail defect is caused by abnormal cuticle morphogenesis.

The SET domain is present in numerous histone lysine methyltransferases that are involved in chromatin remodeling (Dillon, 2005). Though there is no data suggesting *Blimp-1* acts on its own to modify histones, this protein may have multiple binding partners such as the H3K9 methytransferase G9a (Gyory, 2004), which directly binds to LSD1 and plays a key role in gene silencing and the mediation of plasma cell differentiation (Su, 2009). This possibility suggests that BLMP-1 may function in epigenetic regulation. In the context of aging, *blmp-1* was identified in a screen for lifespan regulators and, consistent with this finding, RNAi targeting *blmp-1* at the developmental stage shortened the lifespan significantly (Greer*, et al.*, 2010). In our study, we further examined this shortened lifespan phenotype by inducing RNAi at different developmental stages. *Blmp-1* RNAi at adulthood does not affect lifespan and may even increase lifespan slightly, which highlights the multiple functions of BLMP-1 in developmental and post-developmental stages.

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# Food knowledge and preferences of pulmonary tuberculosis patients at Saudi Arabia "A case study"

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**Abstract:** The aim of the current study is to identify the food awareness and preferences of Saudi and non Saudi's patients suffering from pulmonary tuberculosis (TB) at Chest Hospital, Taif, Kingdom Saudi Arabia. The current study showed that the Saudi's patient ages were statistically significantly varied and ranged between 14 and 81 years old with an average of 37.12 years ( SD ± 10.03), whereas the non-Saudi patient ages were lowered (between 14 and 50 years with an average of  27.88 (SD ± 10.03) years). It could be also found that the education level as well as the nutrition and healthy knowledge were higher among Saudi's patients than that compared with the non- Saudi's patients. Poor eating habits,  such as the intake was consisted of only one or two meals, the low intake of high antioxidant foods and vitamins (i.e., fruit and vegetables) and the high intake of  high energy foods and soft drinks, were detected among  patients, especially in case of non Saudi's patients. It could also observed that there were highly statistically significant differences among the Saudi and non Saudi's patients in the preferences of some specific foods and their consumption amounts. In general detailed studies, related to nutrition and health education, especially in case of chronic disease ' patinas and how to deal with such status, as well as the nutrients and antioxidants resources and their utilization in nutrition and therapeutic roles, are necessary.
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## 1. Introduction

The Healthy report of the Ministry of Health, KSA in 1430 H confirmed that the prevalence of tuberculosis among the population of Saudi Arabia recently increased and the total number of pulmonary tuberculosis and pneumonia cases in Saudi Arabia reached 3949. It was also reported that the infection rate in 2009 became 15.59 case/100,000 inhabitants of population. Of such cases, the proportion of Saudi's patients amounted 51.5% versus 48.5% of non- Saudi's patients. This increment may be due to the continuous improvement of recording and reporting the patient cases, and also due to the ongoing education of the community at different occasions (Health Statistical Year book, 2009). Despite the welfare living and abundance of toll-free medical insurance in Saudi Arabia, the recent studies showed a high incidence level in urban areas (10%) and a low one in the rural areas (2%). It was due to that these areas receive annually more than million pilgrims, in addition to the escape of some population from carry out the TB test which has to apply to people from some countries suffering from the disease such as Yemen and Somalia, in addition to the foreign workers, labor from abroad, particularly domestic workers, drivers and pilgrims coming from infected areas (Bener, 1990; Al-Kassimi *et al.*, 1993; Milaat *et al*., 1994; Al-Hajoj

*et al*., 2007). The previous studies and reports also pointed out that the risk of TB is affected by the nutritional status (NICUS, 2008; Cegielski, and Mc Murray, 2004; Paton *et al*., 2004; Hanekom *et al*., 1999) and dietary behavior of each individual at the population society (Van Dillen *et al*., 2008) and also the nutritional and healthy awareness. The studies of Khan *et al*., (2006) and Singh *et al*., (2002) revealed that the lack of knowledge about tuberculosis could be considered as an alarming tool and there is a critical need for more health education programs and overcome their misconceptions. It was also found by the studies of both Baldwin *et al*., (2004) and lönnroth *et al*., 2010) showed that TB patients possessed a lower level awareness toward their diets and its impacts on health. The study of Legesse *et al*., (2010), also, added that there are some misconceptions health behaviors among patients and 87.6% of such patients are sharing in utilization the common cups.

The incidence of tuberculosis affected in changing a lot of food habits, especially the wrong of them; The study of Vumiria (2008) showed that there were wrong dietary habits between patient whom were curing in the hospitals such as: irregularly meals eating; specially the dinner where the patient delete such meal and wait for the next day to get the breakfast meal and the other deals with only two meals a day. According to the Tungdim and Kapoor (2008) study, there is a reduction in energy consumption among people with TB. It was because of eating lower food amount and poor eating habits or loss

of appetite. Gupta *et al*., (2009) reported that providing the dietary advices to increase the amount of energy with the provision of food supplements, resulted in a significant increase in body weight gain, weight mass, fat and also improve the immunity after 6 weeks of treatment, and such improvement could facilitate in returning to productive activities.

There is a scarcity of conducted studies involved in identification of the awareness and custom and dietary behavior and also the impacts of the residence on the improvement of weight and body mass for pulmonary tuberculosis' patients in relative to the non-Saudian patients at the hospital of the Kingdom of Saudi Arabia. Therefore the backbone of the research objective is to identify the awareness and preference of food items for patients with pulmonary tuberculosis Saudi and non Saudi at Chest Diseases Hospital inpatients at Taif, Saudi Arabia.

## 2. Materials and Methods
### Research sample

The internal Saudi and non Saudi patients at all departments of the Chest Diseases Hospital during the period of 1429-1430 AH, reached 373 patients. Of them, the number of Saudi admissions was 244 patients (65.41%), while non-Saudi patients reached to 129 patients (34.59%). 128 patients of them only were shared as a representative sample of patients (34%). It was due to the forbidden of allowance to the author to enter the men's section, according to the regulations the hospital, and the rest of the sample refused to participate in the study. The study sample was divided into two groups: the first group was Saudi patients and it was represented a 66.4% ratio of the total sample, while the second group was the non-Saudi patients and it was represented a 33.6% % ratio of the total sample. The descriptive and analytical approach was used due to its suitability to the nature of the study (comparative approach).

### Research Tools
#### The Socioeconomically data:

Such as age, place of birth, sex, nationality, educational status of the research sample (divided into three levels (high, medium, and low) and the monthly income of the family, were gathered by a previously prepared questionnaire.

#### The awareness and eating habits:

It was divided into the following items:

#### a- Health knowledge:

It included 41 questions, in order to measure the health knowledge. The question must be answered by one of the given three options. The three answers were yes, no and I do not know. The correct answer was given two degrees, the wrong answer was given zero and in case of no answer, reflecting no knowledge case, the recorded degree was one. The lowest degree recorded zero and the highest one recorded 82 degrees. The total score of the questions was summed and it was represented the health awareness degree. According to the total score the health awareness degree could be classified into the following four groups.

-The health awareness is very low when the health awareness degree was less than 55%,

- The health awareness is low when the health awareness degree was in the range of 55-70%,

- The health awareness is medium when the health awareness degree was in the range of 70-85 %, and

- The health awareness is high when the health awareness degree was higher than 85%.

#### b- Nutrition Knowledge:

It included 42 questions related to the nutrition information. The answers and the score system were as the same in case of health knowledge. The total score, represented the nutritional and the healthy awareness degree, could be classified, into the four groups as previously mentioned in case of health knowledge.

#### c- Custom and nutrition habits:

It included a number of questions relating to information concerning the custom and nutrition habits. Its response was always, sometimes and not.

#### d- Food preference:

It is very useful to identify the dietary behavior of individuals and used to collect the information about the individual consumed food items. Food preference groups and nutrition history were classified according the major food groups, i.e., meat and their analogue group; milk and milk product groups; bread and cereal groups; fruits and vegetable groups and numerous food group.

#### Scale and ruler metric:

It was used to measure the height and weight and then calculate body mass index to identify the improvement level in weight and conseqyently the nutritional status of patients. The individual height was measured without shoes, where a person stands in an upright position with the paste heels against the wall and take the sign of the scale over the top of the head; then recorded the reading to the nearest 0.5 cm. The weight was measured while the person was wearing light clothing and without shoes by the nursing staff interior departments and recorded in the medical records.

BMI is an indicator to measure the prevalence of malnutrition of the research sample according to the classification of Zachariah *et al*., (2002) and Garrow (1989). It was calculated according the following equation:

Body mass index (BMI)=(weight in kg)/(height$^2$ in m$^2$)

Reliability and validity of questionnaire

#### (1) Accuracy of judgment:

The initial questionnaire was firstly presented to some of the faculty staff whom were specialized in nutrition and food sciences, a staff of chest diseases hospital in Taif and a staff of Research Center, King Faisal Specialist Hospital, Riyadh. It was to give their opinions about the questionnaire questions and themes of resolution and the clarity and coherence and suitability for use and achieve the objectives of the study. Most of the arbitrators showed their approval on the majority of the phrases, with some modifications on some statements which were restructured to make the questionnaire more subjected to the reliable and valid of the content.

**(2) The stability of the questionnaire:**

Cronbach Alpha test was used to measure the stability of the questionnaire. It recorded 0.78 for the stability degree of custom and nutrition habits. Such value seemed to be a slightly fairly constant average and the custom and nutrition habits questionnaire recorded a highly stability values (0.95 and 0.93, respectively).

**Statistical analysis**:

The obtaining data from the field study was statistically analysed using the statistical data descriptive statistical SPSS program package in order to calculate the mean, standard deviation, frequencies, percentages and chi square test and $t$ - test, correlation coefficient and Pearson and Cronbach alpha. The differences could be statistically significant considered at the 0.05 and 0.001 level.

**3. Results**

**The socioeconomically data:**

**a. Age:**

Data presented in Table (1) showed that the age of Saudi patients was ranged between 14-81 years with an average of $37.12 \pm 10.03$ years. Tthe age of non-Saudi patients was, on contrary, lower and ranged between 14-50 years, with an average of $27.88 \pm 10.03$ years and the differences was statistically significant (the values of $t = 3.32$ at moral level of = 0.001). The same Table showed, also, that the majority of Saudi patients (64.7%) and non-Saudi (76.8%) patients were not exceeded the 50 years old, meaning most of the patients were within the working and production age did of age.

**b- Sex:**

Table (1) showed that the proportion of non-Saudi female patients was high (62.8%) compared to that of Saudi patients (58.8%). It was also noted that the of Saudi male patients proportion was higher (41.2%) than the non-Saudi patients (37.2%).

Upon inquiry on the nationalities, of the pulmonary (TB) patients, the results (non tabulated) showed that 62.8% of the patients were from Africa, 32.5% were from India and the rest of the of the individual study (4.7%) was from South-East of Asia.

**Table (1): Age and sex distribution of the Saudi and non Saudi patients**

| Age distribution in | | | | |
|---|---|---|---|---|
| **Age** | Saudi | | Non Saudi | |
| | *f | % | *f | % |
| >20 year | 10.0 | 11.8 | 10.0 | 23.2 |
| 20-<50 | 54.0 | 64.7 | 33.0 | 76.8 |
| > 50 | 20.0 | 23.5 | 0.0 | 0.0 |
| total | 85.0 | 100 | 43.0 | 100 |
| MEAN±SD** | 37.12±16.25 | | 28.02±10.03 | |
| **Sex distribution (**%) in | | | | |
| **Sex** | Saudi% | | Non Saudi | |
| Male | 41.20 | | 37.20 | |
| Female | 58.80 | | 62.80 | |

* Frequency        ** statistically significant at 0.01

**c – Education status:**

The education status of pulmonary TB patients in the current study is showed in Table (2). It could be noticed that there were a detect Table decrement in the incidence of such disease among those with a higher education level. The incidence of the disease in the highest education level was 9.41 and 7% among Saudi patients and patients of non-Saudi, respectively. On the other hand, the pulmonary TB incidence was statistically significantly higher, in case of individual with medium and low education levels.

**d - Family's monthly income**:

Table (2) shows the relation between pulmonary TB incidence and monthly income of the family It was showed that a high proportion tuberculosis incidence in Saudi and non Saudi (54.1 and 86.1%, respectively) was detected in case of low income (**<2500** LB). An opposite trend was detected in case of the highest family income (**>10000** LB), wherein, pulmonary TB incidence in Saudi and non Saudi was 2.4 and 0.0%, respectively).

**Table  (2): The educational status and f**amily's  monthly income **of the Saudi  and non-Saudi patients patients**

| Education | Saudi | | Non Saudi | |
|---|---|---|---|---|
| | *f | % | *f | % |
| Low | 38 | 44.71 | 17 | 39.50 |
| **Medium** | 39 | 45.88 | 23 | 53.50 |
| High | 8 | 9.41 | 3 | 7.00 |
| Total | 85 | 100 | 43 | 100 |
| Family's Monthly income (in LB) | | | | |
| Very low (< 2500) | 46 | 54.10 | 37 | 86.10 |
| Low (2500>5000) | 25 | 29.40 | 5 | 11.60 |
| Medium (5000-10000) | 12 | 14.10 | 1 | 2.30 |
| High (> 10000) | 2 | 2.40 | 0 | 0.00 |
| Total | 85 | 100 | 43 | 100 |

     * Frequency

**The awareness and eating habits**:
**a. Health knowledge:**

The healthy awareness concept is intended to supply the popular some of the healthy information, facts and their sense responsibilities towards their own and other health. The health awareness possessed, also, an important role in the prevention of disease and reduce the setback and the frequency of hospital residences and maintain the health of individuals and their families. Data presented in Table (3) show that there was a high significant difference among patients of non-Saudi compared to patients Saudi, in case of the health knowledge. It was also noted that the average level of knowledge as the average degrees of health literacy recorded 63.60 (SD ± 10.07) degrees for Saudi patients while it was increased to 66.90 (SD ± 10.41) degrees among patients of non-Saudi. It was found that more than half of the sample of non-Saudi patients (51.2%) possessed a high health awareness. Such value was lower (34.1%) in case of the Saudi patients. While health knowledge of the Saudi patients was increased among middle, low and very low levels compared to non-Saudi patients.

**b. Nutritional knowledge of knowledge of food:**

Table (3) There was a non significant difference in the nutritional knowledge of food among the patients of non-Saudi compared to patients Saudi, since the average degree of nutritional knowledge at the Saudi patients recorded 51.97 (SD± 9.71) degrees, and increased in non-Saudi  patients to 53.05 (SD± 7.85) degrees. It declined to be 44.7% in case the Saudi patients and to be 32.6% in case the non-Saudi patients.

**c. Health and food habit**
**1-  Health practices of hygiene practices:**

The effect of awareness and health knowledge on health habit in Saudi and non-Saudi patients are shown in Table (3). The majority of

Saudi and non-Saudi patients possessed a health practices ranged from the level of medium and good without significant differences. Wherein, it was found that more than half of Saudi patients (51.8%) and non-Saudi (52.4%) gained the acceptable level of health practices, including medium.

On contrary, as noted from the study, not tabulated, about half of the sample of patients does not care about sterilize their personal instruments, and about 90% do not play sports, while 42% of patients did not exposed their bodies to sunlight a day.

**Table (3): Health and nutritional knowledge status and level of health practice of the Saudi and non-Saudi patients**

| Health knowledge | Saudi | | Non Saudi | |
|---|---|---|---|---|
| | *f | % | *f | % |
| High | 29 | 34.1 | 22 | 51.2 |
| Medium | 36 | 42.4 | 14 | 32.6 |
| Low | 12 | 14.1 | 3 | 7.0 |
| Very low | 8 | 9.4 | 4 | 9.3 |
| MEAN±SD | 63.60±10.07 | | 66.90± 10.41 | |
| Nutritional knowledge | | | | |
| High | 3 | 3.5 | 9 | 20.9 |
| Medium | 18 | 21.2 | 20 | 46.5 |
| Low | 26 | 30.6 | 14 | 32.6 |
| Very low | 38 | 44.7 | 0.00 | 0.00 |
| MEAN±SD | 51.97±9.71 | | 53.05±7.85 | |
| The level of health practices | | | | |
| Good | 32 | 37.6 | 15 | 35.7 |
| Medium | 44 | 51.8 | 22 | 52.4 |
| Low | 9 | 10.6 | 5.0 | 11.9 |
| Very low | --- | --- | --- | --- |

* Frequency

**2- Feeding habit:**

The results showed that there are many bad dietary habits between the study patients, especially among Saudi than non-Saudi individuals, such as

intake only one or two meals a day, a low intake of rich antioxidants and vitamins (vegetables and fruits) foods and a high intake of soft drinks and rich energy foods. Detailed discussion on such practices is followed:

**a -Number of meal intakes:**

The number of meal intakes, in a day, which reflect the state of health and appetite of the Saudi and non-Saudi individual patients are mentioned in Table (4). Number of meals is affected by the healthy status and the lower appetite. As the appetite is lower, the meal intake is decreased. Wherein, the tuberculosis patients are usually suffering from the low appetite. It is clear from the Table (4) that 54.1% of the Saudi and 46.5% of non-Saudi patients eat three meals a day, while there was a significant variation in whose take only one meal or two meals a day. As noted, also, there was a non significant increase in the intake of non Saudi for four meals a day compared to Saudi patients. It was inquired that the reasons for not eating meals could be attributed to a loss of appetite and lack of desire to eat. While the other reasons were varied between snacks intake or plenty drinking fluids before meals.

**b - Feeding habit in case of meal rejection:**

Table (4) showed some of the food practices for patients in the absence of desire to eat. It was found that 67.1% of Saudi patients, sometimes, force themselves to eat a meal. While such phenomena was raised among non-Saudi patients,

where it reached to 72.1%. It was, also, noted that a higher number with statistically significant differences (P <0.05) of non-Saudi patients (76.7%) sometimes interest to intake delivery meals than that of Saudi patients (63.5%).

**c- Favorite cooking methods:**

The cooking method affect on the sensory attributes of processed meal in terms of taste, flavor and odor. The cooking method affect, also, on the nutritional value of meal and increase the amount of food intake. Table (9) showed that the majority of patients reject to identify any specific cooking method. It was found that they ate food cooked by several methods and the cooking by the steam method was the least favorable method without any statistically significant differences.

**d – Beverages and stimulants**

Drinking natural beverages and stimulants such as tea provide patient by antioxidant compounds that improve the nutritional status and help speed healing. It was shown from Table (4) that beverages and stimulants were more consumed by Saudi patients than non-Saudi. Exactly 55.3% of the Saudi patients prefer to drink tea, while the percentage dropped to 32.6% in case of non-Saudi patients and the differences statistically significant values were P = 0.05. It was also noted that 35.3% of the Saudi patients prefer to get the soft drinks and the percentage dropped to 11.6% in case of the non-Saudi patients with a statistically significant difference values of P = 0.05.

**Table (4): The feeding habit of the Saudi and non-Saudi patients**

| Number of meals | Saudi | | | Non Saudi | | |
|---|---|---|---|---|---|---|
| | **Yes** | **Sometimes** | **Not** | **Yes** | **Sometimes** | **Not** |
| **One Meal** | 8.2 | 3.5 | 88.3 | 9.3 | 2.3 | 88.4 |
| **Two meals** | 17.6 | 5.9 | 76.5 | 7.0 | 4.7 | 88.3 |
| **Three meals** | 54.2 | 12.9 | 32.9 | 46.5 | 9.3 | 44.2 |
| **Four meals** | 12.9 | 7.1 | 80 | 20.9 | 7.0 | 72.1 |
| **Feeding habit in case of meal rejection** | | | | | | |
| Do not care | 18.8 | 67.1 | 14.1 | 25.6 | 69.8 | 4.6 |
| Force my self to eat | 17.6 | 65.9 | 16.5 | 18.6 | 72.1 | 9.3 |
| Identify the meal is necessary | 9.4 | 76.5 | 14.1 | 14.0 | 76.7 | 9.3 |
| Intake delivery meals | 17.6 | 63.5 | 18.9 | 2.4 | 76.7 | 20.9 |
| **The preferable cooking methods** | | | | | | |
| Blanching | 17.9 | 31.9 | 50.2 | 16.6 | 16.3 | 67.1 |
| Frying in fats | 20.0 | 27.1 | 52.9 | 13.3 | 23.9 | 62.8 |
| Grilling | 23.5 | 20.0 | 56.5 | 11.6 | 20.9 | 67.5 |
| Oven | 10.6 | 17.6 | 71.8 | 9.3 | 20.9 | 69.8 |
| Steam | 3.5 | 10.6 | 85.9 | 4.7 | 4.7 | 90.6 |
| **The preferable beverage consumption** | | | | | | |
| Tea* | 55.3 | 28.2 | 16.5 | 32.6 | 32.6 | 34.9 |
| Natural juices | 22.4 | 23.5 | 54.1 | 14 | 30.2 | 55.8 |
| Canned juices | 27.1 | 23.5 | 49.4 | 23.3 | 30.2 | 46.5 |
| Soft drinks* | 35.3 | 18.8 | 45.9 | 11.6 | 23.3 | 65.1 |

*Statistically significant

**3- Food preference:**

The preference of food could be considered as one of the affecting factors on the nutrition custom and habits. The results show a higher variation with statistically significant differences in eating preferences of some foodstuffs and the rate of their consumption among Saudi and non-Saudi. It was found that, except of rice, there was no significant difference in the preference of food, and the following a detailed recorded of these results could be found: -

**a- Milk and milk products:**

Milk and milk products are one the main source of proteins which provides the individuals by their daily requirements of high biological value proteins, calcium and vitamins $B_2$ and $B_{12}$. The fortified milk, also, provides by a large amount of vitamins A and D. The presented data in Table (5) shows that there is a statistically difference between Saudi and non-Saudi patients in milk and milk products preference. Wherein, an increment in preference was detected in case of the Saudi acidified milk (80%) and yoghurt (71.8%) consumption compared to non-Saudi with statistically significant differences. The preference percentage of milk (88.4%) and cheese (88.4%) was higher for non-Saudi in relative to the Saudi patients with a statistically significant difference. It was also became clear from the Table that there were differences in the rate of consumption, including either daily or weekly consumption.

**Table (5): Food preference among Saudi and non-Saudi patients ***

| Item | Saudi | | | Non Saudi | | |
|---|---|---|---|---|---|---|
| | **Yes** | **Not** | Consumption rate | **Yes** | **Not** | Consumption rate |
| **Milk and milk products group preference** | | | | | | |
| Milk** | 85.9 | 12.1 | Daily | 88.4 | 11.6 | Daily |
| Laban*** | 80.0 | 20.0 | Daily | 74.4 | 25.6 | Weekly |
| **Yogurt*** | 71.8 | 28.2 | Weekly | 65.1 | 34.9 | Daily |
| **Cheese*** | 75.3 | 24.7 | Daily | 88.4 | 11.6 | Daily |
| **Meat and their alternatives group preference** | | | | | | |
| **Red meat**** | 82.4 | 17.6 | Weekly | 72.1 | 27.9 | Weekly |
| **Chicken** | 85.9 | 14.1 | Daily | 86.0 | 14.0 | Daily |
| **Fish**** | 78.8 | 21.2 | Weekly | 74.5 | 25.5 | Weekly |
| **Eggs** | 71.8 | 28.2 | Daily | 79.1 | 20.9 | Daily |
| **Legumes**** | 65.9 | 34.1 | Weekly | 46.5 | 53.5 | Weekly |
| **Bread and cereal group preference** | | | | | | |
| **White read**** | 68.2 | 31.8 | Daily | 74.4 | 25.6 | Daily |
| **Whole read**** | 52.9 | 42.4 | Daily | 37.2 | 62.8 | Daily |
| **Rice** | 94.1 | 5.9 | Daily | 90.7 | 9.3 | Daily |
| **Pasta**** | 71.8 | 28.2 | Weekly | 76.7 | 23.3 | Weekly |
| **Cornflakes**** | 30.6 | 69.4 | Weekly | 53.5 | 46.5 | Daily |
| **Indomie**** | 50.6 | 49.4 | Daily | 62.8 | 37.2 | Daily |
| **Fruit** and vegetables **group preference** | | | | | | |
| **Fresh vegetables**** | 71.8 | 28.2 | Daily | 83.7 | 16.3 | Daily |
| **Cooked vegetables**** | 61.2 | 38.8 | Weekly | 67.4 | 32.6 | Daily |
| **Fresh Fruit**** | 76.5 | 23.5 | Daily | 79.1 | 20.9 | Daily |
| **Preserved fruit**** | 22.4 | 77.6 | Weekly | 30.2 | 69.8 | Weekly |
| **Dates**** | 60.0 | 40.0 | Daily | 48.1 | 41.9 | Weekly |
| **Miscellaneous food group preference** | | | | | | |
| **Honey** | 60.0 | 40.0 | Daily | 58.1 | 41.9 | Daily |
| **Jam**** | 41.2 | 58.8 | Daily | 48.8 | 51.2 | Weekly |
| **Nuts**** | 47.1 | 52.9 | Weekly | 41.9 | 58.1 | Monthly |
| **halva** | 49.4 | 50.6 | Weekly | 51.2 | 48.8 | Weekly |
| **Olive oil**** | 55.3 | 44.7 | Daily | 44.2 | 55.8 | Weekly |

**\*, \*\* and \*\*\* = significantly at 0.05, 0.01 and 0.001.**

**b- Meat and their alternatives:**

Meat and meat products are one the main source of biological value proteins. Beans could be used as successful meat substitutes, due to their protein high content and fat low content, and the complementary meals usually recommended to have a combination of animal and vegetable proteins. It is because such combination supplies the individuals with plenty of iron, zinc, magnesium and vitamin H. Such nutrients are of important elements in the acceleration of patients curing suffering from pulmonary tuberculosis. It was found from Table (5) that there is a significant difference at the meat and their alternatives preference of eating. It was found a high preference of the Saudi to red meat, fish, legumes compared to non-Saudi patients. While there is a difference in the rate of consumption, including either daily or weekly consumption for non-Saudi in case of chickens and eggs, as observed from the same Table.

**c- Bread and cereal group**

The whole grain or fortified flour could be considered a good source of vitamins B complex, iron and magnesium. It is also considered a mineable source of protein, which is characterized by low biological value. One of the recent recommended is the intake of whole grain products like high fiber bread. It is because they contain a high percentage of fiber, vitamins and minerals. Data presented in Table (13) confirmed that there is a variation in the proportion of bread and cereals group preference. Such preference, for bread and white pasta and cornflakes vermicelli, instant (Indomie), was higher in case of non-Saudi compared to the Saudi with a high significant differences. On the other hand, the preference of the Saudi to whole bread intake did not show any statistical significant differences for rice and their consumption rate.

**d- Fruits and vegetables group:**

Fruits and vegetables group are characterized by their low fat and protein content and as good sources of vitamins, minerals, antioxidants compounds and dietary fiber. Table (5) indicated that the research sample of Saudi and non Saudi showed a high preference for fruit and vegetables group. Since, the preference of non-Saudi for fresh vegetables used in salad, cooked vegetables and fresh fruit was higher than that of Saudi patients. While the preference of the Saudi to dates was higher but the majority of research sample did not preferred the preserved fruits, especially the Saudi patients.

**E- Miscellaneous food group:**

This group includes oils, fats and sugar, which is usually added during the process of preparing food to complete the nutrient requirements of the person's daily calories. Table (5) showed a high preference of the Saudi for honey, nuts and olive oil compared to non-Saudi. While the non-Saudi preferred jam and halva with statistically detectable significant differences.

**4- Effect of hospital residence on body weight:**

A marked improvement in the weight average of Saudi and non Saudi patients, after entering the hospital under the direct supervision, were detected as shown in Table (6). The initial average weight (when entering the hospital) was recorded 53.85 (SD ± 13.80) and 50.72 kg (SD± 11.72) for Saudi and non-Saudi patients, respectively. The final average weight (after the hospital stay) of Saudi patients was changed to 56.49 kg (SD± 13.97). The final average weight (after the hospital stay) of non-Saudi reached to 54.16 kg (SD ± 13.15) compared to the initial one (before entering the hospital) with statistically significant differences (T = 4.64; p = 0.001), suggesting that the patients recovered some of their weight loss.

**Table (6): The average body weight\* of Saudi and non-Saudi patients after admission to hospital**

| Nationality | Weight when entering the hospital | Weight at the end of the study | T test | Significance |
|---|---|---|---|---|
| Saudi | 53.85±13.80 | 56.49±13.97 | 4.64 | 0.000 |
| Non Saudi | 50.72±11.74 | 54.14±13.15 | 5.46 | 0.000 |
| MEAN±SD | 52.86±13.22 | 55.78±13.72 | 6.69 | 0.000 |

\* MEAN±SD

**5- Effect of hospital residence on body mass:**

As seen from Table (7), there was a significant increase in the average body mass index before entering the hospital among Saudi patients 20.13 kg/m$^2$ (SD± 5.74) compared to non-Saudi 18.43 kg/m$^2$ (SD± 3.95). The same Table, also, showed a non statistically significant improvement in the body mass index average among Saudi patients (21.32 kg/m$^2$ ± SD 5.31) compared to non-Saudi (19.89 kg/m$^2$ ± SD 4.06) at the study end (after the hospital stay), which confirms that the patients recovered some of their weight after a hospital stay.

**Table (7): The body mass index average\* of Saudi and non-Saudi patients after admission to hospital**

| Nationality | BMI when entering the hospital | BMI at the end of the study | T teast | Sig |
|---|---|---|---|---|
| Saudi | 20.13±5.74 | 21.32±5.31 | 4.48 | 0.000 |
| Non Saudi | 18.43±3.95 | 19.89±4.06 | 5.87 | 0.000 |
| MEAN±SD | 19.58±5.08 | 20.87±4.96 | 6.55 | 0.000 |

**\* MEAN±SD**

## 4. Discussion

The region of Mecca, including Taif province, occupied the first ranked as the most regions of the Kingdom of Saudi Arabia suffering from tuberculosis disease. It was due its geographical location and the presence of a large proportion of foreign employers, mostly from countries with endemic disease. As a result of the keenness of the wise leadership on the community health and safety, a royal decree (No., 7 / 58 505, dated 12.03.1424 e) ensures free treatment for those infected with the disease of the resident "non-Saudi" until curing. The Ministry of Health Kingdom data of Saudi Arabia for the year 2008 refers to that the rate of injury in Mecca was 49.3% (Health Statistical Year book, 2008) and the results of the current study confirmed that this ratio showed to slightly higher than that recently detected. Since, the Mecca region includes Taif, Jeddah and the Holy City, the results indicate that 34.59% of the individual hospital residence were non-Saudi. Such results were to be different than that found in the study of Qari (2002) which was carried out at King Abdulaziz Hospital in Jeddah. It showed that the proportion of non-Saudi amounted 64%, suggested the need to find successful mechanisms to prevent the entrees of foreign employers suspected to be pulmonary TB into Saudi territory.

The Ministry of Health adopted a national program to combat tuberculosis through stages objectives aimed to enhance the level of healing to more than 85%. It could be done by following the modified treatment short-term strategy under the direct control, and early detection of more than 70% of infected cases (Abba *et al*., 2010). Despite all the efforts made by the Kingdom of Saudi Arabia, according to Health Ministry reports in its report for the year of 2008, the disease still possess a danger factor to the society, especially in slums and poor neighborhoods in major cities. Most infected cases was detected among individuals aged 15-44 years. It was, also, noted that tuberculosis is associated with poverty and working and hard living conditions. The incidence forced the patients to the lowest levels of poverty because it means many years of disease and long months of treatment. Such finding is consistent with the results of the current study, which found that the most age groups infected by the disease, especially among non-Saudi individuals, were in who ranged in the age of 20-50 years. It simply meaning at the suitable working and production age and the monthly income of more than 86% was around 2,500 LB (riyals). Such case represents an economic burden on the Kingdom of Saudi Arabia, especially as the cost of the free treatment of the disease may doubled if the patient is infected with a highly resistance strain. The presence of imported strains from the disease entered the Kingdom (Al-Hajoj and Rastogi, 2010; Al-Hajoj, 2010), more attention are required to that slides and oriented the charitable institutions and civil society to exchange relief material to raise the economic level of the patients. It was especially since the results of the current study agreed with many of studies. The study of Leung *et al*., (2004) concluded that the social and economic factors (education, occupation, unemployment and income) affected on the rates of infection. The study of Peabody *et al*., (2005) found that the economic costs have affected the high incidence of the disease. The study of Chakraborty *et al*., (2006) that the lower monthly family income are more closely related to a rate of infection and the study of Jackson *et al*., (2006) recommended to condense the economic programs to reduce the incidence of the disease. The study of Santos *et al*., (2007) suggests that socio-economic is a responsible factor for 87% of the cases and the study of Hoa *et al*., (2011) concluded that tuberculosis disease is widely spread among people living below the poverty line.

Numerous studies and reports explained that the risk of TB is affected by the nutritional status and the lack of nutrition, weight and body mass index, awareness of health and nutrition and dietary behavior. Eating habits and preference of food is one of the risk factors that contribute to its development. The results show that the health awareness and nutrition among patients were ranged between medium and low. It may be due to the level of education, which requires further programs of nutrition education and health about infectious diseases and methods of prevention of them, and the sources of nutrients, antioxidants and importance of food and treatment. This findings differed with that found by Ailinger *et al*., (2003) who detect a higher level of health awareness among patients. While the study of West *et al*., (2008) confirmed that in spite of the high level of health awareness as a result of disease infection, there are some wrong information

related to modes of transmission, infection and treatment the disease among patients. The studies of both Mesfin *et al*., (2009) and Long *et al*., (2008) referred to that TB patients have low levels of knowledge and awareness. The study of Qureshi *et al*., (2008) concluded that the low level of health awareness about the disease among patients can affect the patient health through following some of the behaviors that can assisst in infection the other healthy people. The study recommended, also, to focus on increasing the awareness on TB disease in the community to reduce the delay in seeking the disease and treatment it.

The behavior and food consumption pattern affects on the improvement of the nutritional and health status of the Saudi and non-Saudi patients. The results showed the existence of some good food habits among Saudi and non-Saudi patients. It was also noted that there was a discrepancy and the statistically significant differences in food preference for the four food groups. Consequently, it affecting on the nutritional status of the patients during their hospitalization and improved both of weight and body mass, suggesting the influence of dietary behavior in the hospital in improved the nutritional status. Such results are consistent with the study of Edimo *et al*., (1996) who conducted on 20 patients and conclude that there were a high consumption of fruits and vegetables by the research sample (70%). The fruits and vegetables consumption frequency was once a week at least and 55% of the study sample intake there protein requirements through many sources. The rate of consumption of starchy foods was lowered to be 30% of the study sample and the study confirmed the existence of a change in some dietary habits, once the individual study sample aware that they being exposed to disease infection. The http://www.diethealthclub.com, 2010 nutrition site offers some advices related to pulmonary tuberculosis patient feeding. Some of such advices are eating meals with small portion and easy to digest, avoiding fatty foods, spices and the eating high amounts of fruits and vegetables such as starchy vegetables, citrus, and leafy green vegetables, legumes, whole grains, milk and dairy products with adequate rest and stay at home. Pat (2009) confirms on the importance of weight gain, and consults a dietician or nutritionist to take an adequate diet to meet the requirements of the patient's nutritional and health.

The weight factor is one of the most important physical measures, which must be recorded in case the incidence of chronic diseases, especially tuberculosis patients. It was because patients with active TB are very thin and possess a low body mass index compared to healthy people (Eick *et al*., 2009 and Ng and Paton 2006). The results showed that the body mass index was within normal limits before entering the hospital, with a significant improvement in body mass index after the hospitalization of the patients. On contrary of such result, the study of Niyongabo *et al*., (1999) conducted on 33 patients with pulmonary TB showed a physical measurement ($18.6$ kg/m$^2$) than the standard values. The study of Metcalfe (2005) conducted on 50 patients with TB showed a lower average body mass index ($16.2$ kg/m$^2$) in patients compared to that found in the healthy people ($24$ kg/m$^2$) and the study recommended the patients to receive nutritional supports through the nutrients medicine supplementation to improve the health status of patients. The study of Yüksel *et al*., (2003) referred that TB patients are suffering from low standards physical measurement prior to treatment and after six months of treatments an increase in weight was detected. The study of both of Leung *et al*., (2008) and Khan *et al*., (2006) noted that the weight loss and food depletion of is common phenomena in patients with tuberculosis at the stage of diagnosing the disease. It was also reported that obesity is associated with a lower risk of active tuberculosis Pulmonary among the elderly and the possibility of patients relapse is high among persons of low weight or body mass index. It was concluded that it is easy to identify these patients in the low resources environments as mentioned by Chi-Chiu and Kwok-Chiu (2008) that obesity could be considered a good tool to prevent of the disease infection.

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# Light and Electron Microscopic Study on the Effect of Different Forms of Allopurinol on the Kidney and Liver of Adult Male Albino Rat

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**Abstract:** Allopurinol is used in the treatment of gout, leishmaniasis, renal stone formation and in prophylaxis of hyperuricemia and its compilations associated with radiation therapy. Allopurinol is associated with multiple side effects in certain cases which include glomerulonephritis, nephritis, elevated hepatic enzymes, hepatic necrosis, leucopoenia, purpura and allergic diseases. Little researches showed that a steep dose-response relationship exists between allopurinol and its side effects. Some of these researches on the microcapsulation of allopurinol, which can reduce its side effects to a great extend. The aim of the present study was to investigate and compare the effects of sustained release microcapsule, no uric allopurinol and pure allopurinol on the kidney and liver of adult male albino rats. The present study was conducted on 40 adult male albino rats of Sprague-Dawley strain (from Assiut University animal house). The rats were randomly classified into four groups (ten rats each). The control group, rats of which were left in animal house without any treatment and received vehicle only. The three treated groups received three different forms of allopurinol at dose 25 mg/kg of body weight daily for 14 consecutive days. Group II (the sustained release allopurinol microcapsule group) rats of which were given the allopurinol microcapsule suspension which proved sustained release. Group III (the No-Uric group) rats of which were given no-uric suspension. Group VI (the pure allopurinol group) rats of which were given pure allopurinol suspension. Both kidneys and liver of the four groups were removed from the animals and processed for routine histological and electron microscopic examination. Kidney and liver of group II (the sustained release allopurinol microcapsule group)is more or less similar to the control group. In group III (the No-Uric group) and group IV (the pure allopurinol group) the glomerular space is significantly dilated, the proximal convoluted tubules are significantly reduced in their epithelial height and areas of hemorrhage observed between the tubules and deposits inside the loop of Henle. The electron microscopic picture of the glomeruli shows partial thickening of the glomerular basement membrane, disturbed capillary endothelium, irregularity of the minor processes of the podocytes and areas of glomerular sclerosis. The proximal and distal convoluted tubules shows cytoplasmic vaculation, cytoplasmic dense bodies, degenerated mitochondria and decrease basal enfolding. The proximal convoluted tubules shows destruction of the microvilli. The liver of group III (the No-Uric group) and group IV (the pure allopurinol group) shows areas of hemorrhage both in the central part of the hepatic lobule and on the peripheral part. The electron microscopic picture of the hepatocytes show vaculated cytoplasm, necrotic changes and the cord pattern is disturbed. The electron microscopic picture of the hepatocytes show marked reduction of the cytoplasmic organelles, degenerative changes in the mitochondria and little amount of rough endoplasmic reticulum. The nucleus is shrunken, little chromatin material and the nuclear membrane is irregular. Conclusion: the sustained release microcapsule allopurinol may lead to prolonged activity with avoidance of renal and hepatic side effects of frequent administration of allopurinol. These results may have clinical significance in the prevention of some side effects of allopurinol on kidney and liver.

## 1. Introduction

Allopurinol is a xanthine oxidase inhibitor used widely in treatment of gout, leishmaniasis, renal stones and compilations associated with radiation therapy (Martindale, 1999; Tausche *et al*., 2008 and Aldaba-Muruato *et al*., 2012). Allopurinol is widely used and generally well-tolerated (Dawson *et al*., 2009 and Woo *et al*., 2012). However, in certain cases it may have toxic effects, such as vasculitis, toxic epidermal necrolysis, eosinophilia, hepatitis, reduced renal function and bone marrow suppression,

known as allopurinol hypersensitivity syndrome (Liu *et al*., 2008; Teo *et al*., 2011 and Biagioni *et al*., 2012). But this syndrome is rare (Arabi *et al*., 1996; El-Gibaly, 1998 and Horiuchi *et al*., 2000). Several studies in the past two decades have suggested that elevated serum uric acid levels are associated with cardiovascular diseases (Viazzi *et al*., 2006; Lippi *et al*., 2008; Neogi *et al*., 2011 and Krishnan *et al*., 2011). Simultaneous reduction in uric acid levels by allopurinol might contribute to the reduction in its

side effects (Stocker & Keaney, 2004; Glantzounis *et al*., 2005 and Puddu *et al*., 2012].

George *et al*. 2006 showed that a steep dose-response relationship exists between allopurinol and its effects on endothelial dysfunction in patients with chronic heart failure.

Limited work has been reported on the different forms of allopurinol, which can reduce the side effects of the drug to a great extend (Spiegl & Abd-El-Fatah, 1977 and El-Gibaly *et al*., 2003).

Various techniques of sustained release microcapsulation can be employed for the production of multiparticulated sustained-released polymeric drug delivery system (Deasy, 1984 and Arshady, 1989). The oil-in-water meltable disperse-phase encapsulation method has been reported to be simple and useful in the preparation of beeswax matrix microspheres loaded with appropriate drugs without using harmful organic solvents (Bodmeier *et al*., 1992; Adeyeye and Price, 1994; Giannola *et al*., 1995 and Uddin *et al*., 2001).

**Aim of the Work:**

The aim of the present work is to investigate and compare the effects of different forms of allopurinol in adult male albino rat's kidney and liver.

**2. Material and Methods**

The present study was conducted on 40 adult male albino rats of Sprague-Dawley strain (from Assiut University animal house). Rats were selected for age (2-3 months) and weight (150-200 grams). They were put at constant normal temperature with the natural light dark cycle. Manipulations throughout test were carried out by the same person. The rats were fed a standard diet of commercial rat chow and tap water and left to acclimatize to environment for two weeks prior to inclusion in the experiment. All experiments were performed during the same time of day, between 10 am and 1pm to avoid variations due to diurnal rhythms.

The rats were randomly classified into four groups (ten rats each) and received the tested compound by gastric intubation (in 0.1 M NaHCO$_3$ containing 0.02% of Tween 80, PH7.4). All treatments were administered into rats following 12 hours of fasting. All the materials used in this study were of analytical reagent grade and were used as received.

Group I: control group, rats of which was left in animal house without any treatment and received vehicle only.

Group II: the sustained release allopurinol microcapsular group, rats of which was given the allopurinol microcapsule suspension (mean size 120 µm) (1 gm / 20 ml) at dose 25 mg/kg of body weight daily for 14 consecutive days**.**

Group III: the no-uric group, rats of which was given No Uric 100 mg tablet in the form of suspension by mouth (100 mg/12 ml) at dose 25 mg/kg of body weight daily for 14 consecutive days.

Group IV: the pure allopurinol group, rats of which was given pure allopurinol suspension (8 mg/ ml) at dose 25 mg/kg of body weight daily for 14 consecutive days**.**

**Preparation of allopurinol loaded microparticle formulations:**

Microparticle formulations are produced using the modified emulsion encapsulation procedure adopted (Vilivalam and Adeyeye, 1994). The microparticles formulations were prepared by melting the wax components (4g), unless otherwise specified, consisting of beeswax and wax modifiers. This constitutes the organic or oil phase. The drug was dispersed in the respective molten wax (in a 1:4 drug to wax ratio) under continuous stirring using a magnetic stirrer (J.P. Selecta, s.a., Spain) until a homogeneous blend was attained. This mixture was then poured into 100 ml of the encapsulation dispersant (PF-68: 0.25g) solution (aqueous phase) with constant stirring using a mechanical stirrer (Wheaton Instrument, Millville, NJ, USA) at a predetermined speed of 400 rpm to form an oil-in-water emulsion. During the emulsification step (1 min), the temperature of the aqueous phase was kept slightly higher (~5$^o$C) than the highest melting point of any of the oil phase. The molten mass upon dispersion in the aqueous medium formed a spherical oily particle, which solidified enveloping the drug upon rapid cooling of the emulsion using chilled water (4 $^o$C). The resultant microparticles were then filtered extensively washed with deionized water and air dried at room temperature for 48hrs.

**Histological Methods:**

Liver and kidney were removed from animals and fixed in 10% formaldehyde, dehydrated in ascending grades of alcohol, and then after embedded in paraffin wax. Serial sections (10 µm) thickness were prepared and stained with Haematoxylin and Eosin stain and others by Van Gisson stain, then examined by light microscopy (Drury & Willington, 1980 and Bancroft & Stevens, 1982).

Other specimens of the kidney and liver were prepared for electron microscopic study according to (Griffith *et al*., 1973). The specimens were fixed in 2.5% gluteraldehyde for 2 hours. Then washed 3 times (5 minutes each) in phosphate buffer and were postfixed in 1% osmium tetroxide for 2 hours, then washed 3 times (5 minutes each) in phosphate buffer.

The specimens were dehydrated in ascending grades of ethyl alcohol: 50%, 60%, 70%, 80 %,90 % and in absolute alcohol (two changes, 30 minutes

each), then in propylene oxide (two changes, 30 minutes each). They were ultimately immersed in a propylene-epon mixture (1:1) for 24 hours.

The specimens were embedded in plastic capsules containing epon and left to polymerize in an incubator at 60 ºC for 3 days. The ultrathin sections were stained with 1% uranyl acetate and 1% lead citrate and examined by transmission electron microscope.

**Morphometric Methods:**

The glumerular diameter, glumerular space and the tubular epithelial thickness (of the proximal convoluted tubules) were measured by using a scale slide and Lucida lens. Five slides from each animal were used for these measurements. The slides were chosen from mid area of the kidney and the hilum was taken as a guide for this site. The equation used was: *Magnification = Image length / Natural length*.

Statistical analysis of the data was done using student t-test and the data expressed in mean and stander deviation.

**3. Results**

Kidney Results

The structure of the kidney of the rats received the microcapsular allopurinol preparation is more or less similar to the control group both by Haematoxylin and Eosin stain (fig. 1,2, 9&10) and also by Van Gisson stain (fig. 5,6, 13&14). The glomeruli are surrounded by proximal and distal convoluted tubules. The glomerular capillaries have darkly-stained nuclei. The glomerular capsule is surrounded by the glomerular space that lined externally by flat darkly stained nuclei. The afferent arteriole is adherent to one pool of the glomerulus. The proximal convoluted tubules stained more deeply relative to the distal tubules and have an obvious brush border. The proximal convoluted tubules tend to be larger in diameter and more irregular than those of distal convoluted tubules. The distal convoluted tubules are paler and the nuclei of their cells appear more regularly arranged (fig. 1 & 2). The glomerular capillaries are composed of condensed capillary tuft with deeply stained nuclei and deeply stained cytoplasm. The parietal part of glomerular capsule show flat darkly stained nuclei (fig. 1 & 2).

The glomeruli of the rats received no-uric and pure allopurinol show significant dilatation of their glomerular space (fig. 3& 4 and tab. 1) on comparing with the control rats. They also show significant reduction in their size (figs 3& 4 and tab. 1) on comparing with the control rats.

The proximal convoluted tubules of the rats received no-uric and pure allopurinol show significant reduction. epithelial thickness on comparing with the control rats (fig. 3&4 and tab. 1), and areas of hemorrhage (fig. 7, 8, 11 & 12) in between them. Casts inside the loop of Henle (fig. 15&16) also observed.

The electron microscopic picture of the renal glomeruli of the rats received no-uric and pure allopurinol show partial thickening of the glomerular basement membrane, disturbed capillary endothelium, irregularity of the minor processes of the podocytes and areas of glomerular sclerosis (figs. 27 and 28) comparing with the control animals (fig. 25). The electron microscopic picture of the renal glomeruli of the rats received the sustained release microcapsular preparation (fig. 26) is more or less similar to the control group (fig. 25).

The electron microscopic picture of the proximal convoluted tubules of the rats received no-uric (fig. 31) and pure allopurinol (fig. 32) show vaculated cytoplasm, cytoplasmic dense bodies, bizarre shape mitochondria, secondary lysosomes, partial loss of the apical microvilli and decrease basal infolding. The nucleus is shrunken and the nuclear membrane is irregular comparing with the control animals (fig. 29). The electron microscopic picture of the proximal convoluted tubules of the rats received the sustained release microcapsular preparation (fig. 30) is more or less similar to the control group.

The electron microscopic picture of the distal convoluted tubules of the rats received no-uric (fig. 35) and pure allopurinol (fig. 36) show vaculated cytoplasm, less cytoplasmic organelles, cytoplasmic dense bodies, degenerated mitochondria and decrease basal infolding. The nucleus is shrunken and the nuclear membrane is irregular comparing to the control animals (fig. 33). The electron microscopic picture of the distal convoluted tubules of the rats received the sustained release microcapsular preparation (fig. 34) is more or less similar to the control group.

**Table (1):-** The mean values of the glumerular diameter, glumerular space and tubular epithelial height (of the proximal convoluted tubules) of the control group compared with that of the sustained release microcapsule group, no-uric group and pure allopurinol group.

| | Control (C) | Micro-capsule (M) | No-uric (N) | Pure-drug (P) | CvM | CvN | CvP |
|---|---|---|---|---|---|---|---|
| **Glomerular Diameter** | 50.7µ +1.9 | 49.5µ +1.8 | 46.0µ +2.1 | 45.6µ +2.8 | 0.1[ns] | 0.001[**] | 0.004[**] |
| **Glomerular space** | 11.1µ +1.6 | 11.7µ +1.2 | 12.5µ +1.3 | 12.5µ +1.3 | 0.09 [ns] | 0.03[*] | 0.04[*] |
| **Epithelial height** | 11.7µ +1.2 | 11.49µ +1.0 | 10.1µ +0.9 | 10.1µ +1.4 | 0.6[ns] | 0.01[*] | 0.03[*] |

Liver Results

In the control group the liver cords arranged in rays around the central vein. The central vein is lined by healthy flattened endothelial cell and is surrounded by healthy liver cell cords (figs. 17&21).

The histological picture of the rats received sustained release microcapsules preparation is more or less similar to the control group both by Haematoxylin and Eosin stain (fig. 18) and by Van Gisson stain (fig. 22).

The histological picture of the rats received no-uric and pure allopurinol show areas of hemorrhage between the cords near to the central vein. The central veins are dilated, liver cords are of disturbed pattern. The hepatocytes are vaculated with necrotic changes (figs. 19, 20, 23&24).

The electron microscopic picture of the hepatocytes of the rats received no-uric (fig. 39) and pure allopurinol (fig.40) show marked reduction of the cytoplasmic organelles, destructive mitochondria and little amount of the endoplasmic reticulum. The nucleus is shrunken, little chromatin material and the nuclear membrane is irregular comparing to the control animals (fig. 37). The electron microscopic picture of the hepatocytes of the rats received the microcapsular preparation (fig. 38) is more or less similar to the control group.
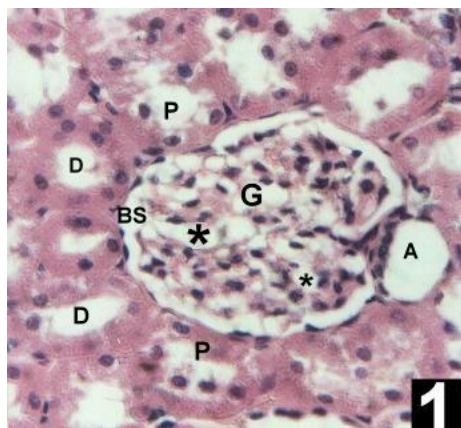


**Fig. (1)** shows: glomerulus (G), proximal convoluted tubules (P), distal convoluted tubules (D), glomerular capillaries (*), glomerular space (BS) and afferent arteriole (A) of control albino rat kidney. (Hx&E X 400)

**Fig. (2)** shows: glomerulus (G), proximal convoluted tubules (P), distal convoluted tubules (D), glomerular capillaries (*), afferent arteriole (A) and glomerular space (BS) of albino rat kidney receiving sustained release microcapsules preparation of allopurinol. (Hx&E X 400)
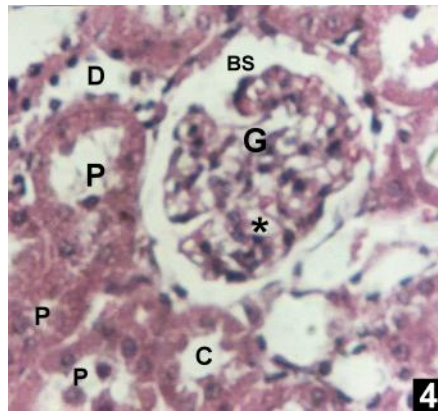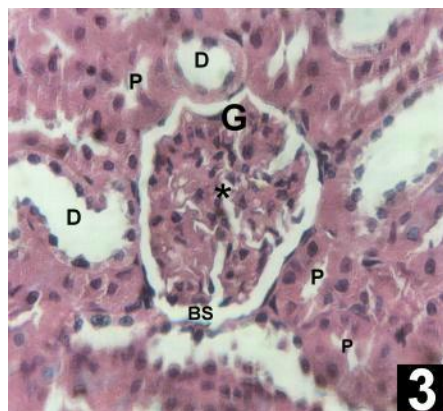


**Fig. (3)** shows: glomerulus (G), proximal convoluted tubules (P), distal convoluted tubules (D), glomerular capillaries (*), glomerular space (BS) of albino rat kidney receiving no-uric preparation. (Hx&E X 400)

**Fig. (4)** shows: glomerulus (G), proximal convoluted tubules (P), distal convoluted tubules (D) and glomerular space (BS) of albino rat kidney receiving pure allopurinol preparation. The glomerular capillaries (*) are lined by more compact cells relative to the control with deeply-stained nuclei and cytoplasm. (Hx&E X 400)
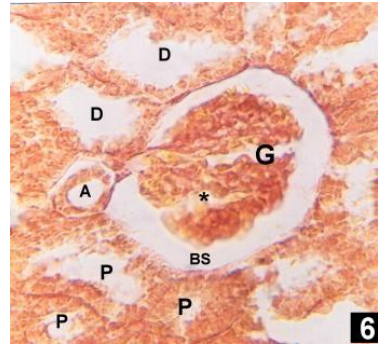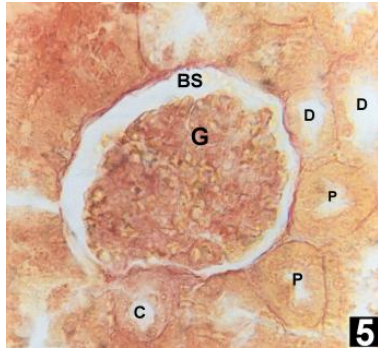
**Fig. (5)** shows: glomerulus (G), the proximal convoluted tubules (P), distal convoluted tubules (D), collecting tubules (C) and glomerular space (BS) of control albino rat. (Van Gisson X 400)
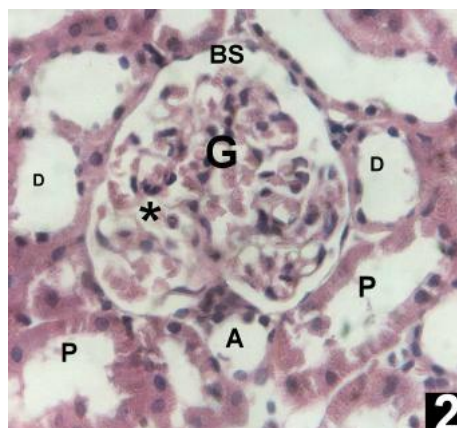
**Fig. (6)** shows: glomerulus (G), proximal convoluted tubules (P), distal convoluted tubules (D), glomerular capillaries (*), glomerular space (BS), afferent arteriole (A) of albino rat kidney receiving sustained release microcapsule preparation.(Van Gisson X 400)
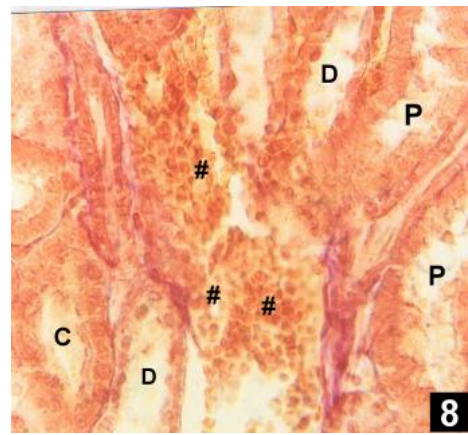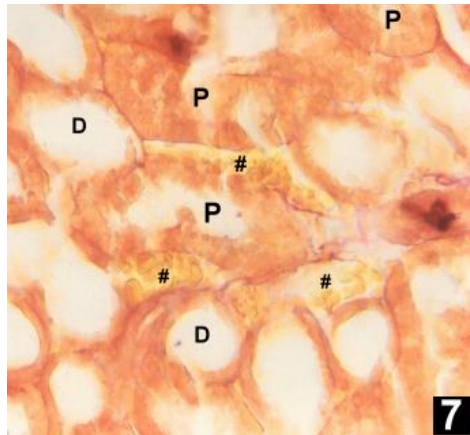




**Fig. (7)** shows: areas of hemorrhage (#) in between the proximal (P) and distal (D) convoluted tubules of albino rat kidney receiving no-uric preparation.                    (Van Gisson X 400)

**Fig. (8)** shows: the areas of hemorrhage (#) in between the proximal (P) and distal (D) convoluted tubules of the kidney of albino rat receiving pure allopurinol preparation.          (Van Gisson X 400)
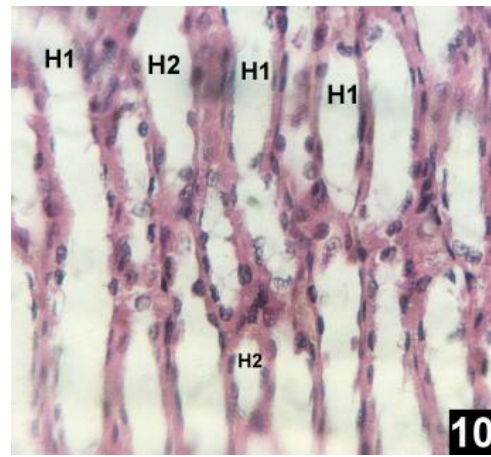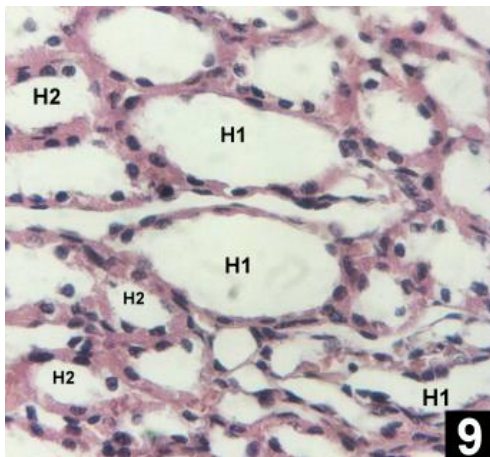




**Fig. (9)** shows: ascending loop of Henle (H1) lined by squamous epithelium and descending loop (H2) lined by columnar epithelium of control albino rat kidney.                    (Hx&E X 400)

**Fig. (10)** shows: the ascending loop of Henle (H1) and the descending loop (H2) of albino rat kidney receiving sustained release microcapsule preparation.               (Hx&E X 400)
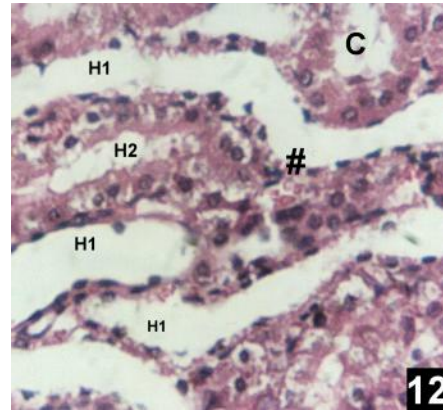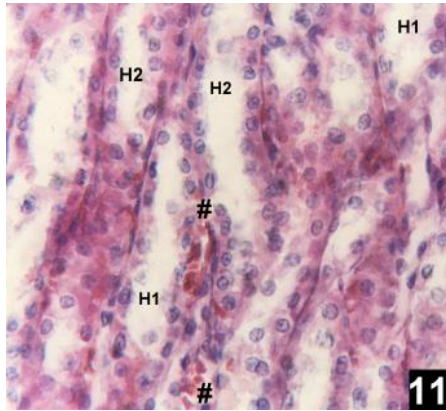
**Fig. (11)** shows: ascending loop of Henle (H1), descending loop (H2) and areas of hemorrhage (#) in between of albino rat kidney receiving no-uric preparation.                     (Hx&E X 400)

**Fig. (12)** shows: the ascending loop of Henle (H1), the descending loop (H2) and areas of hemorrhage (#) in albino rat kidney receiving pure allopurinol preparation.                     (Hx&E X 400)
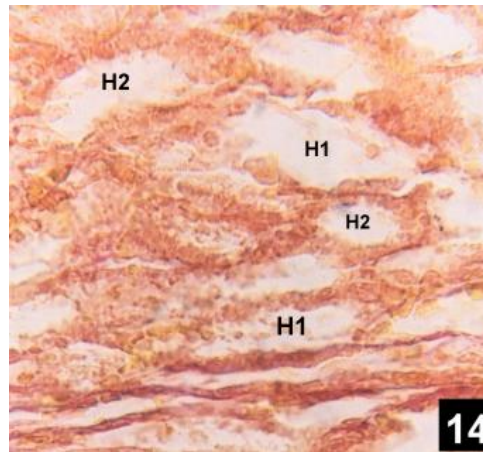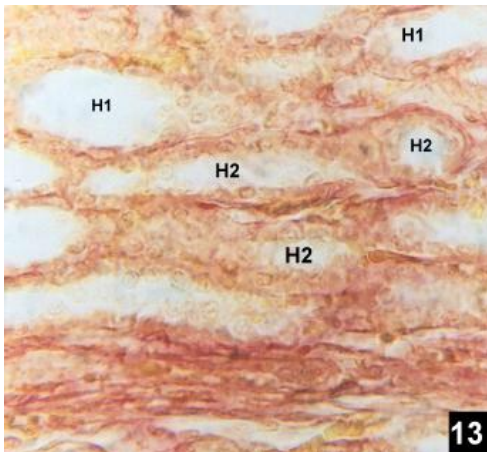




**Fig. (13)** shows the ascending loop of Henle (H1) and the descending loop (H2) of control albino rat kidney.(Van Gisson X 400)

**Fig. (14)** shows: the ascending loop of Henle (H1) and the descending loop (H2) of albino rat kidney receiving sustained release microcapsule preparation.                     (Van Gisson X 400)
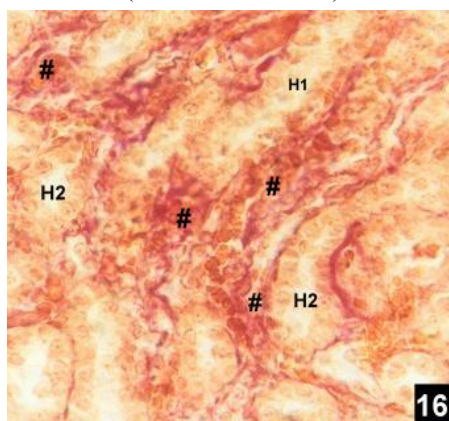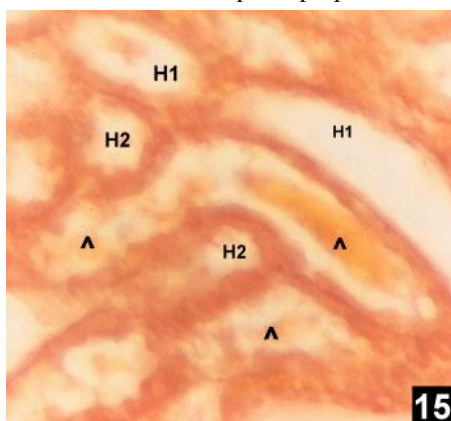




**Fig. (15)** shows: collections (^) inside the ascending (H1) and the descending loop (H2) of albino rat kidney receiving no-uric preparation.                     (Van Gisson X 400)

**Fig. (16)** shows: areas of hemorrhage (#) in between the ascending loop of Henle (H1) and the descending loop (H2) of albino rat kidney receiving pure allopurinol preparation.                     (Van Gisson X 400)
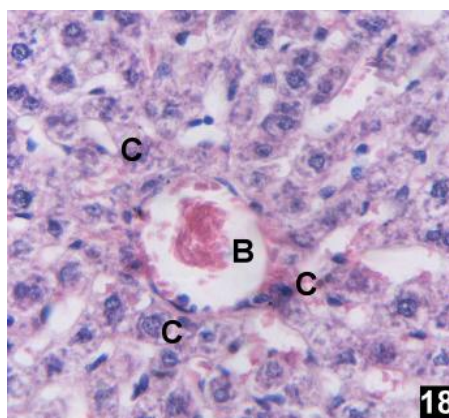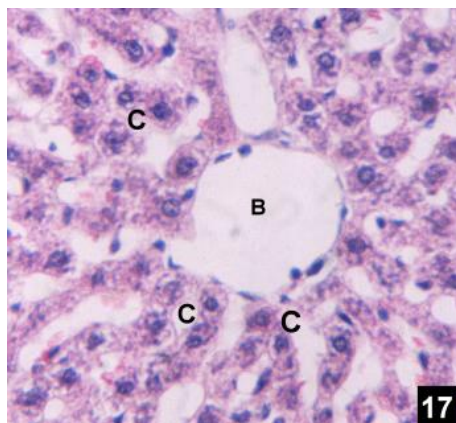
**Fig. (17)** shows: central vein (B) surrounded by liver cell cords (C) in part of hepatic lobule of control albino rat liver.     (Hx&E X 400)

**Fig. (18)** shows: central vein (B) surrounded by healthy liver cell cords (C) in part of hepatic lobule of albino rat liver receiving sustained release microcapsule preparation.          (Hx&E X 400)
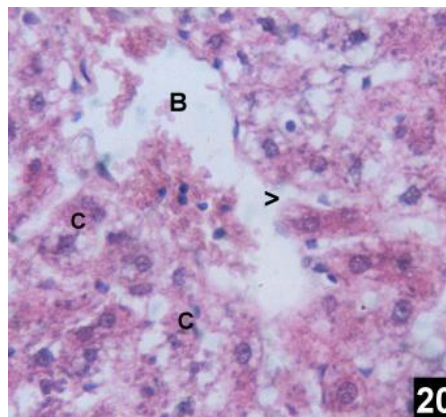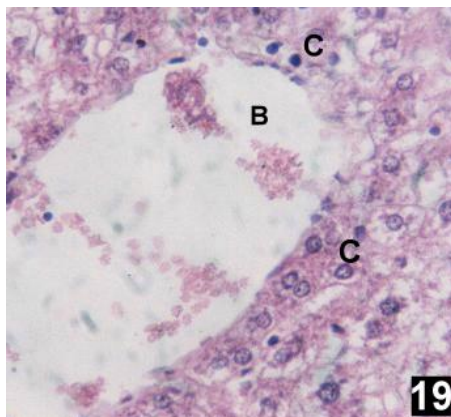


**Fig. (19)** shows: dilated central vein (B) lined by interrupted endothelium, areas of hemorrhage between the disrupted liver cell cords (C) in part of hepatic lobule of albino rat liver receiving no-uric preparation. (Hx&E X 400)

**Fig. (20)** shows: areas of hemorrhage between the disrupted liver cell cords (C) and dilated central vein (B) lined by interrupted endothelium (>) in part of hepatic lobule of albino rat liver receiving pure allopurinol preparation.     (Hx&E X 400)
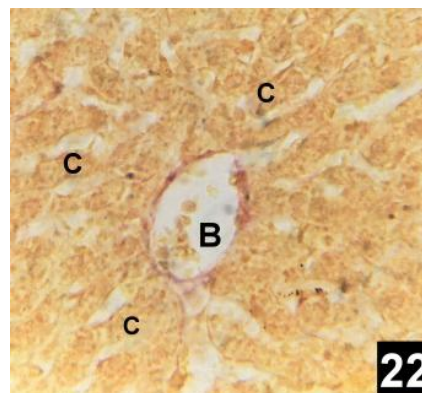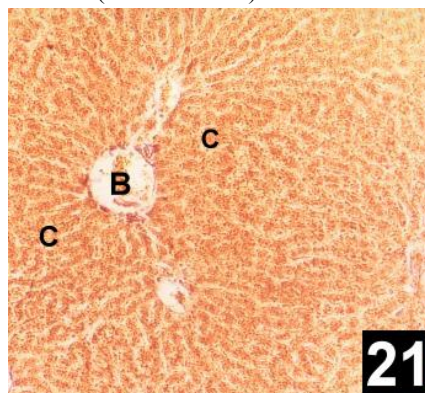


**Fig. (21)** shows: central vein (B) surrounded by healthy liver cell cords (C) in part of hepatic lobule of control albino rat liver.  (Van Gisson X 100)

**Fig. (22)** shows: central vein (B) surrounded by healthy liver cell cords (C) in part of hepatic lobule of albino rat liver receiving sustained release microcapsule preparation.          (Van Gisson X 400)
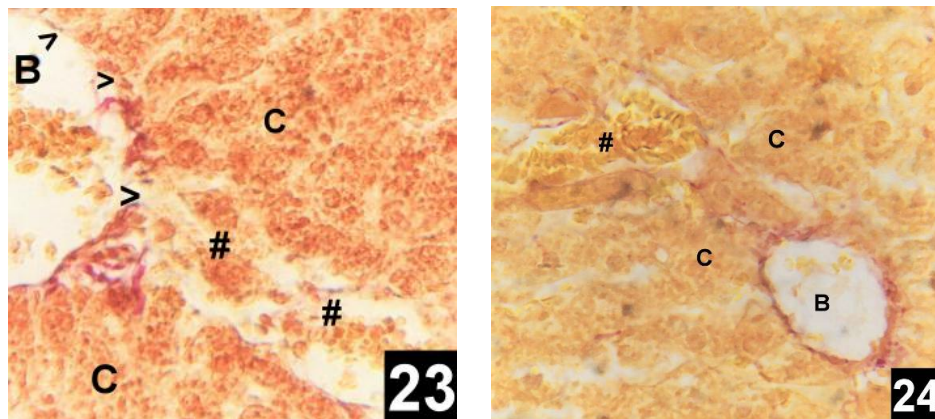
**Fig. (23)** shows: central vein (B), areas of hemorrhage (#) between the disrupted liver cell cords (C) in part of hepatic lobule of albino rat liver receiving no-uric preparation.          (Van Gisson X 400)

**Fig. (24)** shows: central vein (B) with interrupted endothelium and disrupted cords (C) in part of hepatic lobule of albino rat liver receiving pure allopurinol preparation.          (Van Gisson X 400).
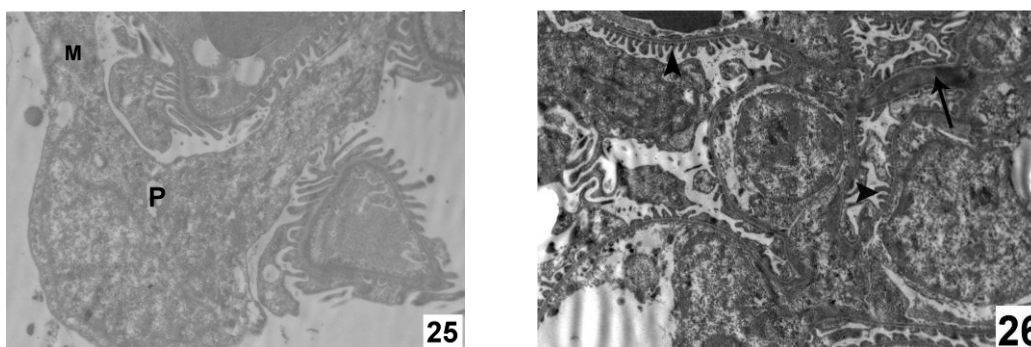




**Fig. (25)**: an electron micrograph of the cell body of the podocyte (P) of the renal glomerular capillary and its major process (M) of control albino rat kidney.      (Uranyl acetate and lead citrate X 5800)

**Fig. (26)**:- An electron micrograph of the renal glomerular capillary of rat received microcapsular preparation showing an area of partial thickening of the basement membrane (arrow) and regular minor processes of podocytes (arrow heads). (Uranyl acetate and lead citrate X 4800)
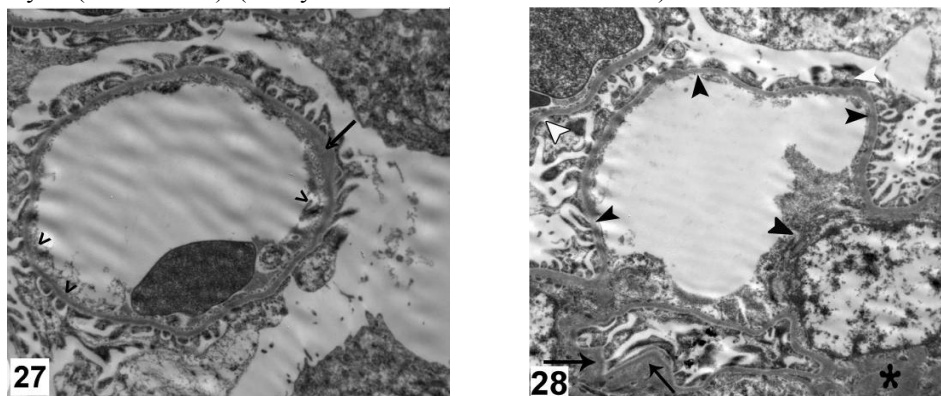




**Fig. (27)**:- An electron micrograph of the renal glomerular capillary of rat received no-uric preparation showing partial thickening of the basement membrane (arrow) and disrupted capillary endothelium (>). (Uranyl acetate and lead citrate X 7200)

**Fig. (28)**:- An electron micrograph of the renal glomerular capillary of rat received pure allopurinol preparation showing partial thickening of the basement membrane (arrow), disrupted capillary endothelium (black arrow heads) and irrigular minor processes of podocytes (white arrow heads). The asterisk (*) points to an area of sclerosis. (Uranyl acetate and lead citrate X 7200)
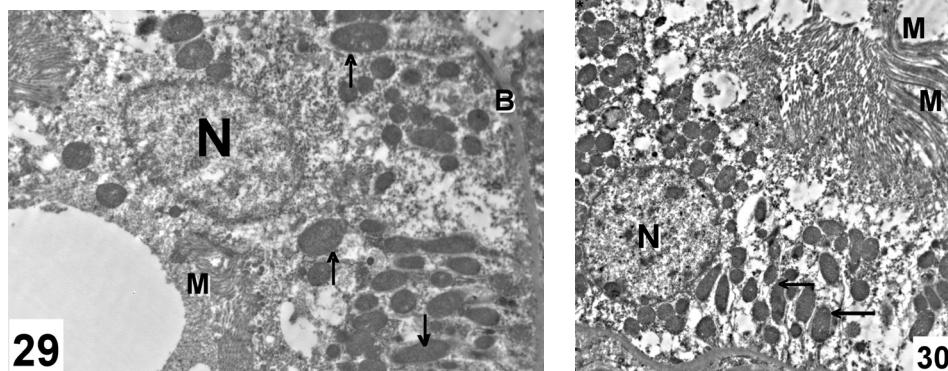
**Fig. (29)**:- An electron micrograph of the proximal convoluted tubule cell of control albino rat kidney shows the open-face nucleus (N) with well defined nuclear membrane and basement membrane (B). The cytoplasm contains large number of normal mitochondria (arrow) and regular microvilli (M). (Uranyl acetate and lead citrate X 4800)

**Fig. (30)**:- An electron micrograph of the proximal convoluted tubule cell of rat received microcapsular preparation showing rounded nucleus (N) with abundant nuclear sap and well defined nuclear membrane. The cytoplasm contains large number of elongated mitochondria (arrow) and regular apical microvilli (M). (Uranyl acetate and lead citrate X 4800)
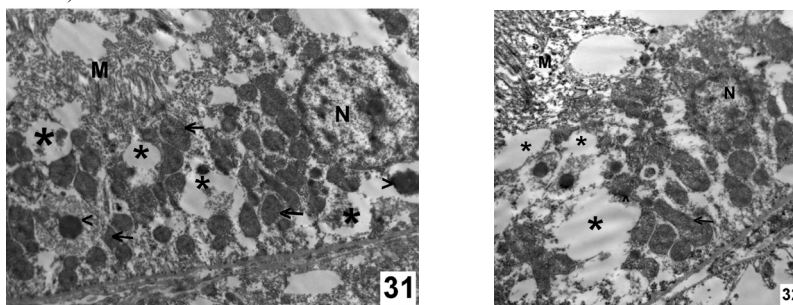


**Fig. (31)**:- An electron micrograph of the proximal convoluted tubule cell of rat received no-uric preparation showing rounded nucleus (N) with abundant nuclear sap and well defined nuclear membrane. The cytoplasm contains large number of bizarre shaped  mitochondria (arrow), wide cytoplasmic spaces (*), electron dense bodies (<) and partial loss of  apical microvilli (M). (Uranyl acetate and lead citrate X 4800)

**Fig. (32)**:- An electron micrograph of the proximal convoluted tubule cell of rat received pure allopurinol preparation showing rounded small nucleus (N) with abundant nuclear sap and well defined nuclear membrane. The cytoplasm contains large number of bizarre shaped  mitochondria (arrow), wide cytoplasmic spaces (*), secondary lysosomes (^) and partial loss of  apical microvilli (M). (Uranyl acetate and lead citrate X 7200)
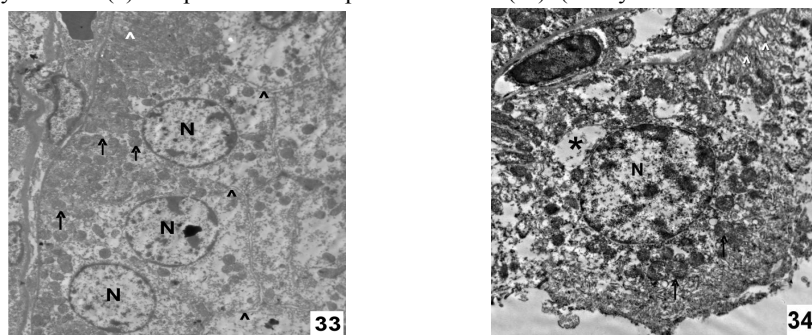


**Fig. (33)**:- An electron micrograph of the cell lining of the distal convoluted tubule of control albino rat kidney shows rounded nucleus (N) with well defined nuclear membrane and abundant nuclear sap. The cell border is well defined (black arrow heads). The cytoplasm contains regular mitochondria (arrow) inside regular basal enfolding (white arrow heads). (Uranyl acetate and lead citrate X 2900)

**Fig. (34)**:- An electron micrograph of the cell lining of the distal convoluted tubule of rat received microcapsular preparation showing rounded nucleus (N) with well defined nuclear membrane and abundant nuclear sap. The cytoplasm contains normal mitochondria (arrow) inside regular basal enfolding (white arrow heads) and cytoplasmic spaces (*) . (Uranyl acetate and lead citrate X 7200)
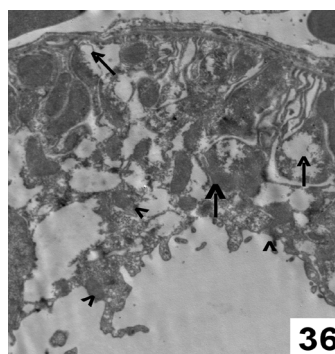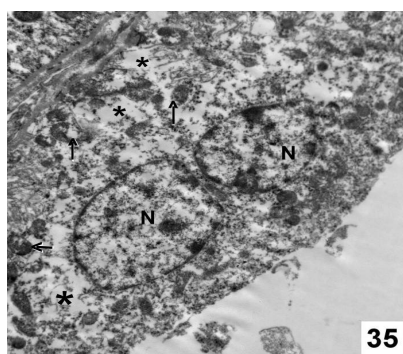
**Fig. (35):-** An electron micrograph of the distal convoluted tubule cell of rat received no-uric preparation showing nucleus (N) with abundant nuclear sap. The cytoplasm contains damaged mitochondria (arrow) and cytoplasmic spaces (*). (Uranyl acetate and lead citrate X 7200)

**Fig. (36):-** An electron micrograph of the distal convoluted tubule cell of rat received pure allopurinol preparation showing swollen degenerated mitochondria (arrow) and luminal cytoplasmic debris (arrow heads). (Uranyl acetate and lead citrate X 4800)
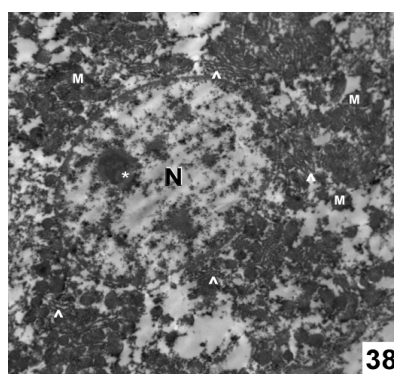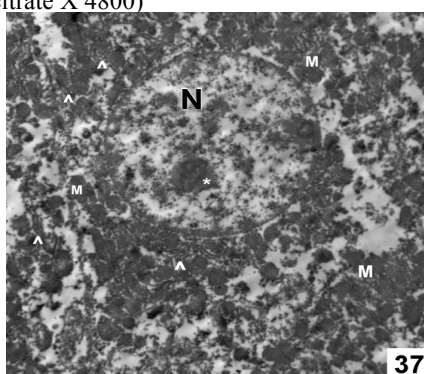




**Fig. (37):-** An electron micrograph of hepatocyte of control albino rat liver. the nucleus (N) with prominent eccentric nucleolus (*) and well defined nuclear membrane. The cytoplasm contains large number of normal mitochondria (M), free ribosomes and rough endoplasmic reticulum (^). (Uranyl acetate and lead citrate X 4800)

**Fig. (38):-** An electron micrograph of hepatocyte of albino rat liver receiving sustained release microcapsules preparation of allopurinol. The nucleus (N) with prominent eccentric nucleolus (*) and well defined nuclear membrane. The cytoplasm contains large number of normal mitochondria (M), free ribosomes and rough endoplasmic reticulum (^). (Uranyl acetate and lead citrate X 4800)
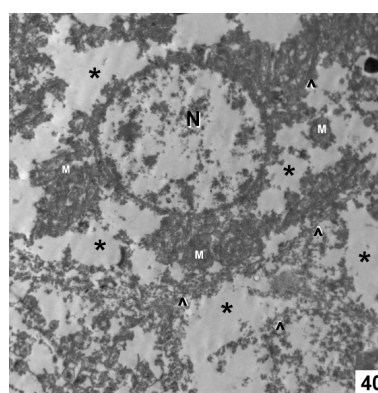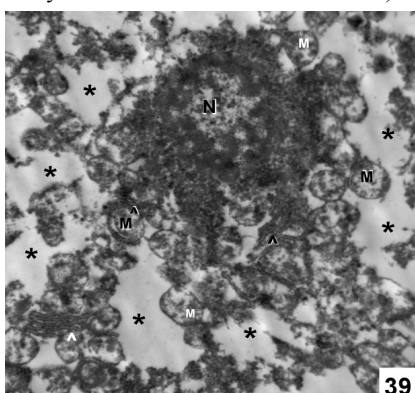




**Fig. (39):-** An electron micrograph of hepatocyte of albino rat liver receiving no-uric preparation of allopurinol. the nucleus (N) is shrunken with clomping of the chromatin on the inner nuclear membrane. The cytoplasm contains little amount of degenerated mitochondria (M), wide cytoplasmic spaces (*) and little rough endoplasmic reticulum (^). (Uranyl acetate and lead citrate X 10000)

**Fig. (40):-** An electron micrograph of hepatocyte of albino rat liver receiving pure allopurinol. the nucleus (N) is shrunken devoid of nucleolus. The cytoplasm contains little amount of degenerated mitochondria (M), little rough endoplasmic reticulum (^) and wide cytoplasmic spaces (*). (Uranyl acetate and lead citrate X 4800)

## 4. Discussion

The present study was conducted on adult male albino rats. Males have been chosen in this study to avoid the hormonal changes, which may be faced in females and may affect the results (Hamada, 1979; Messow *et al*., 1980 and Yabuki *et al.,* 1999).

Liver and kidney have been chosen in this study because they are target organs for drug toxicity (Nakatani *et al*., 2000 and Saraste & Pulkki, 2000).

The liver is a specialized organ in terms of its metabolic, synthetic and detoxifying function (Nakatani *et al*., 2000 and Saraste & Pulkki, 2000). Liver and kidney are the primary target for a variety of noxious agents inducing inflammation, necrosis and fibrosis (Meki *et al*., 2001; Yabuki *et al*., 2003 and Ishibashi *et al.,* 2009).

Side effects of allopurinol in the present study are more pronounced in the kidney and liver of pure allopurinol treated rats and to a less extent in the kidney and liver of no-uric treated rats. The glumeruli of the rats received no-uric and pure allopurinol show significant reduction in their size on comparing to the control rats and also show significant dilatation of their glomerular space. More over significant reduction in epithelial thickness of proximal convoluted tubules with areas of hemorrhage in between them also recorded. George *et al*. 2006 showed that a steep dose-response relationship exists between allopurinol and its effects on endothelial dysfunction in patients with chronic heart failure. High-dose allopurinol will result in high plasma concentration of the drug and so more side effects. The slowly released microcapsular preparation maintain a suitable level of the drug for a long period of time so minimize the side effects (El-Gibaly and Abdel-Gaphar, 2005).

The liver in the present study showed areas of hemorrhage between the hepatic cords. These findings are in accordance with that reported by Tam and Carroll (1989), El-Gibaly and Abdel-Gaphar (2005) and Fagugli *et al*. (2008) and Lindh (2009). Tam and Carroll (1989) through autopsy reported fatal allopurinol hepatic toxicity in human in the form of central necrosis. Pereira *et al*. (1998) and El-Gibaly and Abdel-Gaphar (2005) reported that free allopurinol-treated rats showed marked hydropic degeneration of the hepatocytes at the periphery of the hepatic lobules. Besides, the hepatocytes in the center of the lobules underwent necrotic changes.

In this study allopurinol sustained release capsular formula shows the least significant side effects compared with the control group both on the kidney and liver. These findings are similar to that reported on the liver by El-Gibaly and Abdel-Gaphar (2005). They found that the liver of sustained release formula group was more or less normal.

As mentioned before the liver of microcapsule group is more or less normal. These findings considered by El-Gibaly and Abdel-Gaphar (2005) due to the modification in the dissolution rate of allopurinol and also control of the *in vivo* release by microcapsule preparation, so that prolonged absorption properties with a lower allopurinol concentration are maintained in blood over a long time. This may result in increasing the antigout efficiency of allopurinol and minimizing its dangerous effects on liver and other organs.

It is known that the pattern of release of active agent from microparticles depends on the particle size of the core material (Gence *et al*., 1998). Higher burst release and release rate constants from this preparation were thus expected due to larger surface area and the decreased diffusion path length and wall thickness of the preparation (El-Gibaly and Abdel-Gaphar, 2005). The spherical matrix model for a heterogenous matrix can best be used to describe the overall release pattern of a dissolved drug from a spherical microcapsule form (Lewis *et al.,* 1998).

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# Synthesis of new Ester Entities of NSAIDs with Nitric Oxide Releasing Properties

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**Abstract:** All NSAIDs are suffering from deadlier GIT toxicity. The free carboxylic group is thought to be responsible for this toxicity. In this work, the main motto was to develop new chemical entities as potential anti-inflammatory agents with no gastric toxicity. In this work we esterified some commonly used NSAIDs as ibuprofen, mefenamic acid and indomethacin to p-aminophenol. These esters were then converted to their nitrate derivative to combine the benefits of both esterification and nitrate releasing properties on the GIT. The newly synthesized compounds were biologically evaluated as anti-inflammatory and analgesic. The ulcerogenicity of these compounds was also determined. The new compounds showed similar or enhanced anti-inflammatory and analgesic activities with reduced ulcerogenic potential.

**Key Words:** NSAIDs; Esters; Nitric oxide; Gastric toxicity.

## 1. Introduction

Non steroidal anti-inflammatory drugs (NSAIDs) are among the most widely prescribed drugs worldwide [1-3]. Despite the intensive research that has been aimed at the development of NSAIDs, their clinical usefulness is still restricted by their gastrointestinal side effects like gastric irritation, ulceration, bleeding and in some cases may develop into life threatening condition [4]. The damaging effect of some NSAIDs upon the stomach and intestine is generally believed to be caused by two different mechanisms. The first mechanism involves a local action composed of a direct effect, while the other mechanism has indirect effect on the GIT mucosa. The direct effect can be attributed to a combination of a local irritation produced by acidic group of NSAIDs and local inhibition of prostaglandin synthesis in the GIT tract [5-7]. The use of prodrug to temporarily mask the acidic group of NSAIDs has been postulated as an approach to decrease the GIT toxicity due to direct contact effect [8, 9]. These prodrugs release the parent moieties after absorption by undergoing enzymatic or chemical hydrolysis. Moreover it has repeated that conversion of the carboxylic group of NSAIDs to ester and amide makes them more selective towards COX 2 enzyme [10]. Recent strategies adopted to minimize the side effects of NSAIDs involve the use of hybrid molecules of NSAIDs and nitric oxide donating moiety. This approach is one of the most promising ones because nitric oxide supports endogenous GIT defense mechanism including increase in mucus, increase in mucosal blood flow and inhibition of the activation of proinflammatory cells [11]. In addition to the beneficial effects of NO on cardiovascular system, these drugs are expected to be devoid of the potential cardiovascular adverse effects associated with the use of selective COX 2 inhibitors [12-14]. Nitric oxide is also known to spare the renal system mainly through stimulating the renal blood flow [15]. Promoted with the above mentioned studies the present study aimed to prepare the NO derivatives of NSAIDs esters to combine the three bioactive entities (NSAIDs, p-aminophenol esters and nitric oxide) into one compact structure in order to retain the anti-inflammatory activity and improve the ulcerogenicity.

## 2. Experimental
### 2.1 Chemistry

All melting points are uncorrected and determined by the open capillary method using Gallenkamp melting point apparatus (MFB-595-010M; Weiss Gallenkamp, London, UK). IR spectra were recorded on a Shimadzu 435 Spectrometer (IR-435; Shimadzu, Japan) using KBr disks. ^{1}HNMR spectra were recorded on a Perkin-Elmer NMR FXQ-200 MHZ Spectrometer (Tokyo, Japan), using TMS as internal standard. Elemental analyses for C, H, and N were within ±0.4% of the theoretical values and were performed at the Microanalytical Center, Cairo University, and they were of the theoretical values. Progress of the reactions was monitored by TLC using precoated aluminum sheets silica gel MERCK 60 F254 (Merck, Germany) and was visualized by UV lamp.

### 2.1.1 General procedure for the preparation of 4-aminophenyl esters 2a-c.

Appropriate NSAIDs was esterified according to the reported method [16].

### 2.1.2 General procedure for the preparation of 4-(2-chloroacetamido) phenyl esters 3a-c.

Compounds **2a-c** (10.00 mmol) was dissolved in dry benzene (50 mL). Pyridine (0.02 mL) was added to the solution, and then chloroacetyl chloride (2.26 g, 20.00 mmol) was added. The mixture was then refluxed for 6-7 hrs. The excess solvent was then removed under vacuum and the products were crystallized from ethanol/ether mixture.

### 2.1.2.1  4-(2-Chloroacetamido)  phenyl-2-(4-isobutylphenyl) propanoate. 3a

Yield 65%; mp: 210 $^0$C. IR (cm$^{-1}$) :3320 (NH), 1720,1639    (2CO),    $^1$H-NMR(DMSO-d6) δppm:1.02(d,6H,2 CH$_3$,J= 7.2Hz), 1.83 (d,3H,CH$_3$, J=7.1),2.30 (m,1H, CH(CH$_3$)$_2$), 2.42(d,2H, CH$_2$-CH-(CH$_3$)$_2$,J=6.5),     2.95    (m,1H,CH-CO), 3.40(s,2H,CH$_2$-Cl),    7.13-7.25(m,8H,Ar),    8.40 (s,1H,NH). Anal. Calcd. for C$_{21}$H$_{24}$ClNO$_3$ (373.87): C 67.46, H 6.47 and N 3.75. Found: C 67.51, H 6.12 and N 3.50.

### 2.1.2.2 4-(2-Chloroacetamido) phenyl 2-(2,4-dimethylphenylamino) benzoate 3b.

Yield 55%; mp: 234 $^0$C. IR (cm$^{-1}$) :3320 (2 NH), 1720,1639    (2CO),    $^1$H-NMR(DMSO-d6) δppm:2.20(s,6H, 2CH$_3$), 3.20(s,2H,CH$_2$), 6.90-7.90 (m,11H,Ar),8.20 (s,1H,NH) , 10.00 (s,1H,NH). Anal. Calcd. for C$_{23}$H$_{21}$ClN$_2$O$_3$ (408.88): C 67.56, H 5.18 and N 6.85. Found: C 67.20, H 5.40 and N 6.70.

### 2.1.2.3 4-(2-Chloroacetamido) phenyl 1-(4-chlorobenzoyl)-2-methyl -5-methoxy indol-3-yl acetate 3c.

Yield 60%; mp: 280 $^0$C. IR (cm$^{-1}$) :3320 (NH), 1720,1639    (3CO),    $^1$H-NMR(DMSO-d6) δppm:2.32(s,3H,CH$_3$),   3.40(s,2H,CH$_2$-CO),3.70(s, 3H, OCH$_3$),  4.20  (s,2H,CH$_2$-Cl),  6.75-7.80 (m,11H,Ar),  10.01(s,1H,NH).  Anal.  Calcd.  for C$_{27}$H$_{22}$Cl$_2$N$_2$O$_5$ (525.38): C 61.72, H 4.22 and N 5.33. Found: C 61.84, H 4.50 and N 5.50.

### 2.1.3 General procedure for the preparation of 4-(2-nitrooxyacetamido) phenyl esters 4a-c.

Chloroacetamidophenyl esters **3a-c** (18 mmol) was dissolved in acetonitrile (100 mL) by stirring for 10 minutes. Silver nitrate (3.40 g, 20 mmol) was dissolved in acetonitrile (50 mL), and then added to the previous solution. The mixture was then stirred over night at room temperature. The precipitate formed was filtered and the solution was evaporated to dryness under vacuum to obtain the products. The products were recrystallized from ethanol.

### 2.1.3.1  4-(2-Nitrooxyacetamido)  phenyl  2-(4-isobutylphenyl) propanoate 4a.

Yield 50%; mp: 250 $^0$C. IR (cm$^{-1}$) :3350 (NH), 1720,1639    (2CO),    $^1$H-NMR(DMSO-d6) δppm:1.21(d,6H,2CH$_3$,J= 7.6Hz), 1.92 (d, 3H, CH$_3$, J= 6.0Hz ), 2.00 (m,1H,CH(CH$_3$)$_2$), 2.30 (d,2H,CH$_2$-CH-(CH$_3$)$_2$,  J=  6.5) ,  3.84  (m,1H,CH-CO),  5.50 (s,2H,CH$_2$ONO$_2$) , 7.01-7.55 (m,8H,Ar) , 8.24 (s,1H,NH ).Anal. Calcd. for C$_{21}$H$_{24}$N$_2$O$_6$ (400.43): C 62.99, H 6.04 and N 7.00. Found: C 62.61, H 6.40 and N 6.70.

### 2.1.3.2  4-(2-Nitrooxyacetamido) phenyl 2-(2,4-dimethylphenylamino) benzoate 4b.

Yield 52%; mp: 230 $^0$C. IR (cm$^{-1}$) :3350 (2NH), 1720,1639 (2 CO), $^1$H-NMR(DMSO-d6) δppm: 2.28 (s, 6H, 2CH$_3$), 5.43 (s, 2H, CH$_2$ONO$_2$) , 6.87-7.56 (m, 11H,Ar),8.10 (s,1H,NH) 10.00 (s ,1H ,NH ). Anal. Calcd. for C$_{23}$H$_{21}$N$_3$O$_6$ (435.43): C 63.44, H 4.86 and N 9.65. Found: C 63.51, H 4.50 and N 9.70.

### 2.1.3.3  4-(2-Nitrooxyacetamido)  phenyl  1-(4-chlorobenzoyl)-2-methyl -5-methoxy indol-3-yl acetate 4c.

Yield 51%; mp: 195 $^0$C. IR (cm$^{-1}$) :3350 (NH), 1720,1639 (3 CO), $^1$H-NMR(DMSO-d6) δppm: 2.35 (s, 3H, CH$_3$), 3.30 (s, 2H, CH$_2$-CO),3.70(s,3H,OCH$_3$),4.47 (s, 2H, CH$_2$ONO$_2$) , 7.60-7.80 (m, 11H,Ar),10.01 (s,1H,NH). Anal. Calcd. for C$_{27}$H$_{22}$ClN$_3$O$_8$ (551.93): C 58.76, H 4.02 and N 7.61. Found: C 58.41, H 4.30 and N 7.52.

### 2.2 Nitric oxide releasing measurements

A solution of the appropriate compound (20 µL) in dimethylsulfoxide (DMSO) was added to 2 mL of 1:1 v/v mixture of 50 mM phosphate buffer (pH 7.4) with MeOH, containing $5\times 10^{-4}$ M L-cysteine. The final concentration of drug was $10^{-4}$ M. After 1 hr at 37 $^0$C, 1 mL of the reaction mixture was treated with 250 µL of Griess reagent [sulfanilamide (4 g), N-naphthylethylenediamine dihydrochloride (0.2 g), 85% phosphoric acid (10 mL) in distilled water (final volume was100 mL)]. After 10 min at room temperature, the absorbance was measured at 540 nm. Sodium nitrite standard solutions (10–80 nmol/mL) were used to construct the calibration curve.The results were expressed as the percentage of NO released (n=2) relative to a theoretical maximum release of 1 mol NO/mol of test compound (Table 4).

**2.3 Biological activity**
**2.3.1Materials and Methods**
**2.3.1.1 Animals**
          Adult rats of both sexes weighing 180-200 gm and adult mice weighing 25-30 gm were used in the present study. The animals were kept under natural conditions for light, temperature, ventilation, water and food. Experiments were carried out on groups of 5 animals each .All experimental procedures used in the present study followed the Institutional Animal Ethics Committee regulations. All experiments were performed in the morning according to the guidelines for the care of laboratory animals.

**2.3.1.2 Drugs and chemicals**
          Formaldehyde, sod. CMC and acetic acid were obtained from Sigma Chemical Co. (St.Louis, MO, USA), while indomethacin (Indocid), was obtained from Kahira Pharmaceutical company(Cairo, Egypt).
**2.3.1.3 Statistical analysis**
          Results of anti-inflammatory and analgesic activity were represented as mean ± S.E "standard error". The significance difference between groups was tested using one way ANOVA followed by Dunnett's test at $p \leq 0.05, 0.01, 0.001$ .
**2.3.2 Anti-inflammatory activity**
          Wister albino rats of either sex were divided into 5 groups of 5 animals each. They were treated via oral rout. The first group was given sod.CMC (1% w/v) watery suspension and kept as control. The second group was administered indomethacin (10 mg/kg b.wt) as standard drug, the tested compounds **4a-c**, in the form of CMC suspensions, were given at a dose of 100 mg/kg b.wt. to the last three groups. The initial paw thickness was measured for each animal using caliber before induction of edema. After one hour 0.1 ml of 2% formaldehyde was injected into the foot pad of the left hind paw of each rat for induction of paw edema. The increase in this thickness was determined after 30 min, 1, 2, 3 and 24 hrs after formaldehyde injection .The anti-inflammatory activity was expressed as inhibition percent in paw thickness in treated groups compared to the control one using the formula
Edema inhibition percent = $T_c - T_t / T_c \times 100$
          Where, $T_c$ and $T_t$ represent the average paw thickness in the control and treated groups, respectively.
**2.3.3 Analgesic activity**
 **2.3.3.1 Acetic acid induced writhing test:**
   Five groups of mice (5/group) were used in this test. The first group of animals was treated orally with sod.CMC watery solution (2% w/v) (5ml/kg),

served as control. The second group of animals was treated with indomethacin (10 mg/kg) as standard. The tested compounds **4a-c** in the form of CMC watery suspensions (100 mg/kg bwt) were given to the animals of the rest groups. Muscle contractions were induced in mice by intraperitoneal injection of 0.6% solution of acetic acid(10ml/kg) after 30 minutes of drug administration. Immediately after administration of acetic acid, each animal was placed separately in a glass cage, and the number of stretching per animal was recorded during the following 15 min. Writhing movement was accepted as contraction of the abdominal muscles accompanied by stretching of hind limbs. The percentage inhibition of writhing was calculated.
**2.3.3.2 Hot plate test:**
          The animals were divided into control, standard and tested groups of 5 mice each. In the first group animals were orally administered sod.CMC watery solution (2% w/v) (5ml/kg) served as control one. Indomethacin (10 mg/kg bwt) was administered as standard to the second group .The tested compounds **4a-c** in the form of CMC watery suspensions (100 mg/kg bwt) were given to the animals of the rest groups. The hot plate (Model 7280, Ugo Basile, Italy) was maintained at $55.0 \pm 0.2\ ^0$ C and each animal was placed into a glass beaker on the heated surface. The time to discomfort reaction (licking paws or jumping) was recorded as a response latency time at, 30 min, 1hr and 2hrs after administration in each group. A cut-off period of 15 sec was considered as maximum latency time to avoid injury to the paws. The pain inhibition percentage (PIP) was calculated according to the following formula:
Pain inhibition percentage (PIP) = $( T_t - T_c ) / T_c$  x 100
Where $T_t$ is drug latency time and $T_c$ is control latency time.
**2.3.4 Ulcerogenic liability**
          Rats of either sex were divided into five groups of five animals each. The animals were fasted 18 hrs before drug administration. One group was treated with 5ml /kg sod. CMC watery suspension (2% w/v) as a control group. Another one was treated with indomethacin (10 mg/kg b.wt) as a standard one. The tested compounds **4a-c** in the form of CMC watery suspensions (100 mg/kg b.wt) were administered each in one of the rest three groups. Treatment was continued once daily for 3 successive days in all groups. One hour after the last dose, the animals were sacrificed and the stomach was removed, opened along the greater curvature and rinsed with saline. The gastric mucosa was examined with a magnifying lens (10 $^x$) for the presence of lesions in the form of hemorrhages or linear breaks and erosions. The ulcer index was calculated and the degree of ulcerogenic effect was expressed in terms of:
1. Percentage incidence of ulcer divided by 10.
2. Average number of ulcers per stomach.
3. Average severity of ulcers.

The ulcer index is the value that resulted from the summation of the above three values.

2.3.5 Acute toxicity and lethality test

In the first stage of the test, three groups (of 9 animals each) were used for each tested compound, each one of these compounds was administered orally in the form of sod. CMC watery suspension (1% w / v) at a dose of 10, 100, and 1000 mg/kg (n = 3). Animals were observed continuously for the first three hours for any toxic symptoms after administrations and number of deaths within 24hrs. No death occurred in any of these groups for each compound. A second stage of the test was conducted in which 1500, 2000 and 3000 mg/kg doses of each compound were administered to a fresh groups of animals (n = 1) and no death was recorded within 24 hrs. Thus, the oral $LD_{50}$ in mice were found to be greater than 3000 mg/kg for each tested compound.

# 3. Results and Discussion
## 3.1 Chemistry

Compounds **2a-c** were synthesized by esterification of NSAIDs with p-aminophenol using N, N` dicyclohexylcarbodiimide. Reaction of these esters with chloroacetyl chloride in benzene using pyridine as catalyst yields compounds **3a-c.** Treatment of **3a-c** with silver nitrate in acetonitrile affords the corresponding nitrate derivatives **4a-c**. The structures of the prepared compounds were confirmed on the basis of their IR,^{1}HNMR Mass spectra and elemental analyses. The reaction sequences are outlined in scheme 1.

## 3.2 Nitric oxide releasing measurements

The nitric oxide releasing properties of such class of compounds were assessed in phosphate buffer of pH 7.4 with Griess reagent. The reaction was carried out in the presence of L-cysteine as a source of SH group. The amount of NO released from the tested compounds was measured relative to nitric oxide released from standard sodium nitrite solution [17].

## 3.3 Biological activity
### 3.3.1 Anti-inflammatory activity

The newly synthesized compounds **4a-c** were evaluated for their anti-inflammatory activity using formalin induced rat paw edema described by Dharmasiri *et al.* [18]. Rats were administered indomethacin orally (10 mg/kg b.wt) as standard. The tested compounds **4a-c** were given at a dose of 100 mg/kg bwt. Paw volume was determined after 30 minutes, 1, 2, 3 and 24 hrs after formaldehyde injection. The results are listed in table 1 and illustrated in figure 1. It was clear that all tested compounds possess anti-inflammatory activity compared to the standard indomethacin.

### 3.3.2 Analgesic activity
### 3.3.2.1 Acetic acid induced writhing test:

This test was done using the method described by Collier *et al.* [19]. Muscle contractions were induced in mice by intraperitoneal injection of acetic acid 10 ml/kg b.wt. The tested compounds were given orally in a dose of 100 mg/kg b.wt while indomethacin was given in a dose of 10 mg/kg b.wt as standard. The number of stretching per animal was recorded. The results are listed in table 2 and illustrated in figure 2. All compounds showed good analgesic activity in this test.

### 3.3.2.2 Hot plate test:

Analgesic activity was determined in mice by hot plate method described by Hosseinzadeh *et al.* [20]. Indomethacin (10 mg/kg b. wt) was used as standard, while the tested compounds **4a-c** were used orally in a dose of 100 mg/kg b. wt. Each animal was placed into a glass beaker on the heated surface and the time for licking paws or jumping was recorded as a response latency time. The results were represented in table 3 and figure 3 as pain inhibition percent. It was found that all the tested compounds possess good analgesic activity under this study.

### 3.3.3 Ulcerogenic liability

Being many of the compounds tested have pronounced anti-inflammatory and analgesic activity compared to the standard (indomethacin), therefore the ulcerogenic liability for all the compounds was evaluated in albino rats following the reported method [21]. As shown in table 4 and figure 4, the ulcerogenic liability was decreased for all compounds compared by indomethacin. The potential medicinal value of these compounds as anti-inflammatory and analgesic agents is that they have higher safety margin on gastric mucosa than NSAIDs.

### 3.3.4 Acute toxicity and lethality test

The acute toxicity and lethality ($LD_{50}$) of the tested compounds was estimated in mice using the method described by Klimmek *et al* [22]. It was found that $LD_{50}$ for these compounds in mice is greater than 3000 mg/kg bwt.
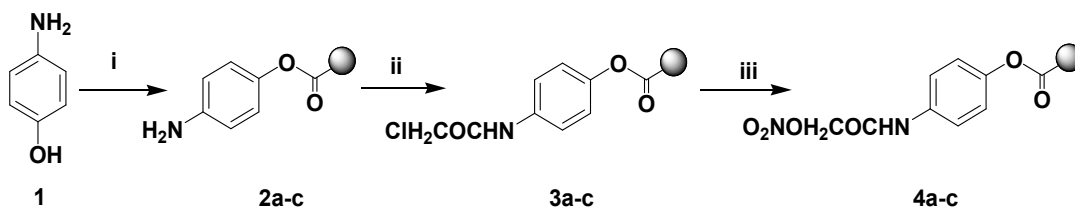
Scheme 1. General method for the preparation of  (**2a-c**) , (**3a-c**), and (**4a-c**). Reagent and conditions: (**i**) esterification; (**ii**) chloroacetylation by chloroacetyl chloride; (**iii**) silver nitrate.



= Non Steroidal Antiinflammatory moiety (NSAID)



**a = Ibuprofen**

**b =Mefenamic acid**

**c =Indomethacin**
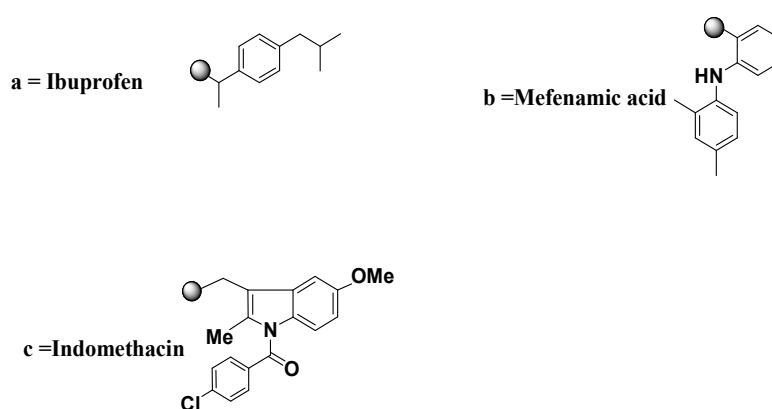
**Table (1): Anti-inflammatory activity of the tested compounds (100 mg/kg bwt, P.O) using formalin induced paw edema method.**

| compound | Paw edema thickness ( m.m) | | | | | Inhibition % | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 30 min | 1hr | 2hrs | 3hrs | 24hrs | 30min | 1hr | 2hrs | 3hrs | 24hrs |
| Control | 0.53 ± 0.013 | 0.57 ± 0.014 | 0.57 ± 0.014 | 0.58 ± 0.012 | 0.44 ± 0.018 | 0 | 0 | 0 | 0 | 0 |
| Indomethacin | 0.23 ± 0.009 [a] | 0.22 ± 0.006 [a] | 0.15 ± 0.005 [a] | 0.03 ± 0.002 [a] | 0 | 56.60 | 70.18 | 74.14 | 88.64 | 100.00 |
| 4a | 0.24 ± 0.011 [a] | 0.22 ± 0.013 [a] | 0.17± 0.009 [a] | 0.15 ± 0.006 [a***] | 0.05± 0.002 [a***] | 54.72 | 56.60 | 70.18 | 74.14 | 88.64 |
| 4b | 0.17 ± 0.008 [a***] | 0.15 ± 0.009[a***] | 0.15 ± 0.007 [a] | 0.15 ± 0.007[a***] | 0.12 ± 0.005[a***] | 67.93 | 73.68 | 73.68 | 74.14 | 72.73 |
| 4c | 0.18 ± 0.009[a***] | 0.17 ± 0.008[a***] | 0.17 ± 0.006[a*] | 0.15 ± 0.008[a***] | 0.08 ± 0.003[a***] | 66.04 | 70.18 | 70.18 | 74.14 | 80.00 |

a Significantly different from the control value at $p \leq 0.001$, * significantly different from the indomethacin value at $p \leq 0.05$, *** significantly different from the indomethacin value at $p \leq 0.001$ ,results are means of five experiments ± S.E.

**Table (2): Analgesic activity of the tested compounds (100 mg /kg bwt ,p.o ) on acetic acid writhing abdominal contractions .**

| Treatment | No of contractions/15 min | Inhibition % |
|---|---|---|
| Control | 45.70± 2.09 | 0 |
| Indomethacin | 12.18  ± 0.27 [a] | 73.35 |
| 4a | 20.23 ±  0.85 [a***] | 55.73 |
| 4b | 14.68± 0.58 [a**] | 67.88 |
| 4c | 17.49 ± 0.64 [a***] | 61.73 |

a Significantly different from the control value at $p \leq 0.001$, ** Significantly different from the indomethacin value at at $p \leq 0.01$, *** Significantly different from the indomethacin value at  $p \leq 0.001$ , results are means of  five experiments ± S.E.

**Figure 1: Anti-inflammatory activity of the tested compounds (100 mg/kg bwt,P.O) in formalin induced paw edema method .**
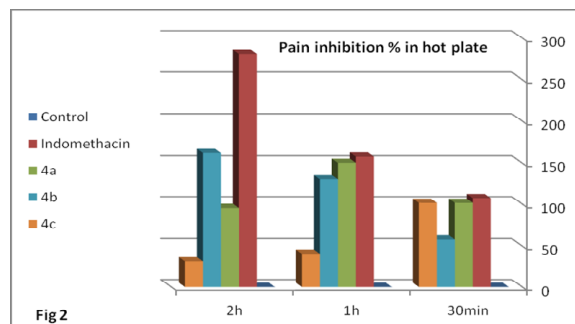


**Figure 3: Analgesic activity of the tested compounds (100 mg/kg bwt, P.O) in hot plate method .**
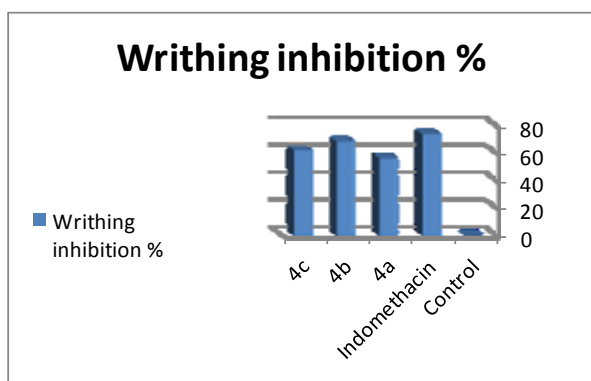


**Figure 2: Analgesic activity of the tested compounds (100 mg /kg bwt ,p.o ) on acetic acid writhing abdominal contractions .**
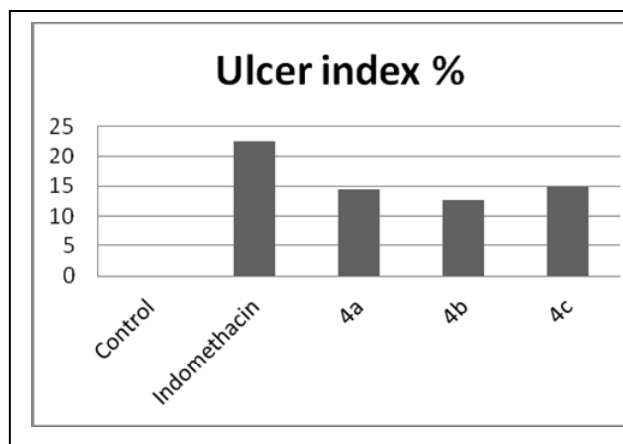


**Figure 4: Ulcer index % of the synthesized compounds**

**Table ( 3 ): Analgesic activity of the tested compounds (100mg/kg bwt, P.O ) using hot plate method .**

| | Latency time (min) | | | Pain inhibition percent (PIP) | | |
|---|---|---|---|---|---|---|
| | 30 min | 1hr | 2hrs | 30 min | 1hr | 2hrs |
| Control | 2.74 ± 0.12 | 2.9 ± 0.13 | 2.73 ± 0.12 | 0 | 0 | 0 |
| Indomethacin | 5.68 ± 0.25 $^a$ | 7.48 ± 0.44 $^a$ | 10.32 ± 0.68 $^a$ | 107.29 | 157.93 | 280.95 |
| 4a | 5.52 ± 0.38 $^a$ | 7.26 ± 0.33 $^a$ | 5.33 ± 0.32 $^a$*** | 101.46 | 150.34 | 95.24 |
| 4b | 4.33 ± 0.32 $^a$* | 6.67 ± 0.43 $^a$ | 7.16 ± 0.36 $^a$*** | 58.03 | 130.00 | 162.27 |
| 4c | 5.52 ± 0.29 $^a$ | 3.84 0.19 $^a$*** | 3.80 ± 0.17 $^a$*** | 101.46 | 40.66 | 31.03 |

a Significantly different from the control value at p ≤ 0.001, * significantly different from the indomethacin value at p ≤ 0.05, *** significantly different from the indomethacin value at p ≤ 0.001 ,results are means of five experiments ± S.E.

**Table (4): Ulcerogenic liability and % NO release of the synthesized compounds**

| Compound | Number of animals with ulcers | % incidence divided by 10 | Number of ulcers | Severity of ulcers | Ulcer index | % NO release |
|---|---|---|---|---|---|---|
| Control | 0 | 0 | 0 | 0 | 0 | 0 |
| Indomethacin | 5/5 | 10 | 10.6 ± 0.71 $^a$ | 2.06 ± 0.224 $^a$ | 22.66 ± 1.89 $^a$ | 0 |
| 4a | 4/5 | 8 | 4.7 ± 0.38*** | 1.7 ± 0.183 | 14.4 ± 0.93** | 0.51 |
| 4b | 4/5 | 8 | 3.5 ± 0.29*** | 1.25 ± 0.158* | 12.75 ± 0.66** | 0.60 |
| 4c | 5/5 | 10 | 3.8 ± 0.26*** | 1.1 ± 0.05$^b$** | 14.9 ± 0.89** | 0.54 |

a Significantly different from the control value at p ≤ 0.001, * significantly different from the indomethacin value at p ≤ 0.05 ** significantly different from the indomethacin value at p ≤ 0.01, *** significantly different from the indomethacin value at p ≤ 0.001 ,results are means of five experiments ± S.E.

Percentage of NO released(n=2) relative to a theoretical maximum release of 1 mol NO/mol of tested compound; determined by Griess reagent in the presence of 5m M L- cysteine at PH 7.4

## 4. Conclusion

Oral dosage forms of NSAIDs suffer from the limitation of gastric injuries caused by their free carboxylic group. Therefore in this work we found that it is interesting to modify NSAIDs structure in a way that would lead to great reduction in acidic characters by converting the free carboxylic acid group to ester. Also we intended to retain the benefits of presence of NO-NSAIDs in the same structure.

### Anti-inflammatory activity

Acute inflammation induced by formaldehyde results from cell damage, which provokes the production of endogenous mediators, such as, histamine, serotonin, prostaglandins, and bradykinin. It is well known that inhibition of edema induced by formalin in rats is one of the most suitable test procedures to screen anti-arthritic and anti-inflammatory agents as it closely resembles human arthritis. Compound **4a** possessed significant anti-inflammatory activity beginning after 30 min of formalin injection and increased stepwise reaching to 88.64 % inhibition of edema after 24hrs . On the other hand this activity was significantly lesser than the standard drug at 3hrs after formalin injection which may be attributed to lake of a good kinetic profile for this compound. Compound **4b** showed good anti-inflammatory activity beginning after 30 min with edema inhibition of 67.93 % which increased to 74.14 % after 3hrs. Percent inhibition of this compound after 30 min and 1hr was more potent than the reference indomethacin, as it resulted in a significant more reduction in paw edema thickness compared to the reference drug. Also it possessed nearly equal activity with 73.68% inhibition of edema after 2hrs.

Compound **4c** showed significant anti-inflammatory activity compared to the control group. It induced significant more reduction in paw edema thickness compared to the reference drug after 30 min and equal activity after 1 hr, its maximum effect was achieved after 24hrs with 80.00% edema inhibition. All the tested compounds showed good anti-inflammatory activity confirming that NO-NSAIDs retain the anti-inflammatory activity of original NSAIDs. From these results, it is clear that all the tested compounds exhibited their activity starting from 30 minutes which increased till reach maximum at 3 or 24hrs after formalin injection. All compounds were found to release NO which may contribute to their low ulcerogenic effect (Table 4).

### Analgesic activity

Analgesic effects were assessed in two models of nociception, chemical model using acetic acid induced writhing method and thermal model using hot plate test. Th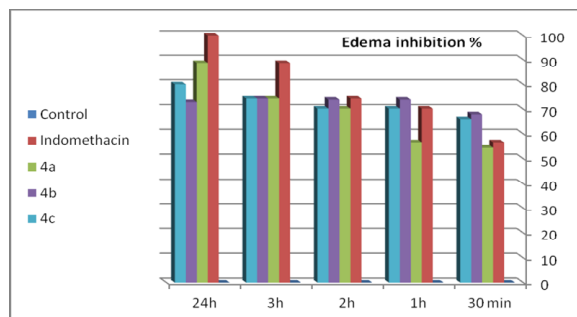ese methods were selected to evaluate both peripherally and centrally mediated effects of the tested compounds respectively.  In writhing test the results elucidated that oral doses of the tested compounds induced significant reduction in the number of abdominal contractions in treated mice compared to indomethacin. Compound **4b** showed the most potent analgesic activity among the tested compounds, with 67.88% inhibition in writhing response. It has been postulated that acetic acid acts indirectly by inducing the release of endogenous mediators, such as PGE2 and PGE2α in peritoneal fluids as well as lipooxygenase products, which stimulate the nociceptive neurons sensitive to NSAIDs. Therefore, the results of the acetic acid induced writhing strongly suggest the inhibition of these compounds to lipooxygenase and cyclooxygenase in peripheral tissues. In hot plate test significant increase in latency time against heat stimuli suggests contribution of central mechanism in the anti-nociceptive effect for these compounds. Compound **4a** showed promising analgesic activity after 30min (101.46% inhibition) and 1hr (150.34%) which was nearly equivalent to the reference indomethacin at the same time interval. Meanwhile its activity was promptly lowered to 95.24% after 2hrs which might be correlated to its kinetic pathway. Compound **4b** exhibited considerable long lasting activity beginning from 58.03% inhibition after 30min then increased to 130.00% and 162.27% after 1 and 2hrs, respectively. Compound **4c** exhibited remarked activity only after 30min (101.46%) which lowered to 40.66 and 31.03% after 1 and 2hrs respectively.

The results of the present study demonstrated that the tested compounds possessed analgesic activity in both nociceptive models suggesting the involvement of both central and peripheral mediated activities. As these compounds are NO- NSAIDs esters, nitric oxide shares a part of this activity as it was previously reported to diminish hyperalgesia via acting at peripheral nociceptors as well as in the spinal pain perception pathway. In this concern nitric oxide has been shown to interact with and reduce transmission via NMDA receptor in the spinal cord. Stimulation of this receptor with some excitatory neurotransmitters like glutamate was found to promote spinal pain perception so inhibition of transmission through this NMDA receptor would be expected to reduce hyperalgesia. In addition all the tested compounds although possess anti-inflammatory and analgesic activities but yet they

are less irritant to GIT than their parent NSAIDs as shown by ulcer index.

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# Splenic Irradiation in the Treatment of Hypersplenism from Congestive Splenomegaly

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**Abstract: Background:** The aim of this study was to evaluate the efficacy of splenic irradiation in relieving symptoms and hematological disorders that accompanying hypersplenism from congestive splenomegaly in cirrhotic patients secondary to chronic viral hepatitis and if the presence of platelet-associated immunoglobulins (AIgs ) can affect the degree of thrombocytopenic recovery in these patients.**Patients, Methods**: Forty patients with hypersplenism from congestive splenomegaly subjected to splenic irradiation 20 Gy, 1 Gy / fraction biweekly using 3D conformal irradiation to protect surround structure. All patients were evaluated as regard clinical response, hematological parameters and splenic size before, during and after splenic irradiation. Quantitative assay of Platelet associated immunoglobulins ( PAIgs ) by flowcytometry was done before beginning of radiotherapy. **Results:** The radiation dose which used in this study induced a remarkable improvement as regard pain and thrombocytopenia,especially in cases with negative PAIgs, slight reduction of splenic size occurred. No considerable effect on anemia or leucopenia, there was no serious complications due to radiotherapy during treatment or follow up periods. **Conclusion:** Splenic irradiation could alleviate some symptoms and hematological disorders and that associate congestive hypersplenism in cirrhotic patients secondary to chronic viral hepatitis.
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**Key words:** Splenic Irradiation, Hypersplenism, Platelet associated immunoglobulins ( PAIgs), Congestive splenomegaly

## 1. Introduction

Pancytopenia in chronic liver disease can be due to hypersplenism, megaloblastic anaemia and primary bone marrow suppression. Hypersplenism is most common cause of pancytopenia in chronic liver disease. (1). Hypersplenism may occur as a primary disease or 2ry disease resulting from underlying disease or disorder (2).Hypersplenism is a clinical syndrome characterized by enlargement of spleen, reduction of at least one cell line in the blood in the presence of normal marrow function and evidence of increased release of premature cells such as reticulocytes or immature Platelets from the bone marrow into the blood. Hypersplenism is a treatable cause of pancytopenia.(1) Hypersplenism resulting from portal hypertension associated with congestive splenomegaly is frequently due to liver cirrhosis.The 5-year survival rate of untreated hypersplenism is only 50% and the usual treatment for hypersplenism is splenectomy or splenic embolization (3). However such modalities may be risky as they carry a high morbidity and mortality rate (4). Splenic irradiation is a non-invasive and alternative treatment for splenectomy and splenic embolization for patients with hypersplenism due to infilterative diseases (5).Thrombocytopenia due to hypersplenism is usually a serious condition in cirrhotic patients who have undergone invasive procedures(6).

Thrombocytopenia typically worsens with the progression of liver disease and can become a major clinical complication. Several mechanisms that contribute to thrombocytopenia have been proposed, including hypersplenism accompanied by increased platelet sequestration, platelet destruction mediated by platelet-associated immunoglobulins (PAIgs), and diminished platelet production stimulated by thrombopoietin (TPO). Serum TPO level may not be directly associated with thrombocytopenia in patients with chronic hepatitis and liver cirrhosis. In contrast, spleen volume and PAIgs are associated with thrombocytopenia in such patients, suggesting that hypersplenism and immune-mediated processes are predominant thrombocytopenic mechanisms (7).

Only few reports are available to evaluate the role of radiotherapy in management of hypersplenism from congestive splenomegaly (8).

The aim of this study was to evaluate the efficacy of splenic irradiation in relieving symptoms and hematological disorders that accompanying hypersplenism from congestive splenomegaly in cirrhotic patients secondary to chronic viral hepatitis and if the presence of platelet-associated immunoglobulins ( PAIgs ) can affect the degree of thrombocytopenic recovery in these patients.

## 2. Patients and Methods

Forty patients with hypersplenism due to congestive splenomegaly were referred to Clinical Oncology Department, Zagazig University Hospitals from July 2008 to August 2009. All patients were subjected to:-

-Thorough clinical examination,
-Abdominal ultrasound to evaluate the cases before starting treatment.
-Routine Laboratory investigations including:
- Complete blood count (SYSMEX K1000).
-Liver and Kidney function (ADVIA1650 Autoanalyzer )
-B.M marrow Aspiration to exclude other causes of thrombocytopenia.
-Detection of HCV Ab and HBsAg by using third generation ELISA technique.
-Detection of HCV -RNA by using qualitative reverse transcriptase PCR (RT-PCR) by Roche **Diagnostics.**

-Quantitative assay of PAIgs % by flowcytometry ( FACS Calibur, Becton Dickinson,,SA ) as follows: 3ml of venous blood were collected aseptically from each patient by veinipuncture into a sterile tube containing EDTA-2Na as anticoagulant. Platelet rich plasma was made by centrifugation( 100 x g ) for 15 min. the isolated platelets was washed twice by centrifugation (700xg)with 10 ml of phosphate buffer saline (PBS) containing 0.5%bovine albumin and 10 mM EDTA-2Na (PBS/EDTA) as 2.5 ml of PBS used for each time of wash. The suspension was adjusted to a platlet concentration of $50 \times 10^9$/L ml of platelets. Fluorescein isothiocyanate (FITC)-conjugated F (ab)2 fragments of rabbit anti-human total Ig, IgG, IgM and IgA (Dako, Glostrup, Denmark) were used to detect PAIg. Pyroerythrin (PE)-conjugated CD41 monoclonal antibody (Becton-Dickinson, Franklin) was used to identify the platelet population. Platelets were dually stained with FITC conjugated antibody and PE-conjugated CD41 monoclonal antibody. Detection of PAIg by flow cytometry is an effective and highly specific method that quantify PAIg and determine the class of Ig (9).

### Radiotherapy (RT):

Patients underwent CT simulation in a supine position for RT planning, with both arms raised above the head to facilitate use of lateral radiation ports. CT data were transferred to a 3D-CRT planning system (Precise). The spleen, liver, kidneys, stomach, and spinal cord contoured on each slice and reconstructed 3-D. The planning target volume (PTV) included a 1.5 to 2 cm margin around the spleen, An extra margin of 1 to 1.5 cm

was added in the craniocaudal direction to account for respiratory spleen motion and all patients were asked to perform shallow respiration to minimize this motion. RT planning aimed to minimize exposure of normal critical organs (normal liver tissue, spinal cord, stomach, etc.). RT was delivered using a linear accelerator (ELEKTA with 6 MV or 15 MV x-rays, depending on depth.

-Informed consent was obtained from the **patients.**

The patients were evaluated weekly during treatment and monthly thereafter for one year results were assessed by comparing physical findings, blood indices, abdominal ultrasound before and after radiotherapy to evaluate the response to splenic irradiation.

### Statistical analysis

Data were entered, checked and analyzed using SPSS version 10.0 (Statistical Package for the Social science, Chicago, IL). Data were expressed as number and percentage for qualitative variables, and mean (X) $\pm$ standard deviation (SD) for quantitative variables. paired "t" test and Chi-square ($X^2$) were used when indicated to assess significance $P$ <0.05 was considered significant.

### 3. Results

This study included forty patients, 25 males, 15 females, their ages ranged from 25 up to 66 years (mean 45 years). All patients gave history of liver cirrhosis. History of chronic hepatitis C presented in 65% of cases, chronic hepatitis B in 35% of cases, 60% of cases presented with mild to moderate degree of ascitis. Left upper abdominal pain was present in all cases but of variable degree. Epistaxis, bleeding gum, hemorrhoidal bleeding and ecchymosis, one or more of them were present in 80% of cases **(Table 1).**

As regard blood indices all patients presented with thrombocytopenia 65% had got platelets count less than $50 \times 10^3$/cmm while the rest of patients 35% had got platelets count from $80 \times 10^3$ up to 100 $\times 10^3$/cmm, hemoglobin was less than 10 gm / dl in 65% of cases while the rest of cases had more than 10 gm/dl, total leucocytic count was less than $3 \times 10^9$/L in 40% of cases.

Follow up of cases during treatment period revealed improvement of upper abdominal pain as 60% of cases showed improvement of pain after the $7^{th}$ sitting, 40% of cases showed pain improvement after the $10^{th}$ sitting of radiotherapy. Pelvi-abdominal ultrasound after the $10^{th}$ sitting of Rth showed reduction of splenic size 10-30% compared with pretreatment size and this reduction occurred in pretreated mildly enlarged spleen. Slight

improvement of platelets count without considerable improvement in WBCs or hemoglobin levels.

Post treatment follow up revealed that left upper abdominal pain as a subjective response relieved completely in 40% of cases where all cases of mild enlarged spleen showed complete pain relieve while cases with moderate and huge spleen enlargement showed lesser response as regard pain improvement **(Table 2)**

Cases of mild enlarged spleen showed 50% reduction of pretreatment size. Cases of moderate enlargement showed 50% size reduction in 40% of cases, and from 50% to 20% size reduction was found in 50% of cases and 10% of cases showed less than 20% reduction in size. As regard cases of huge splenomegaly no cases showed more than 50% size reduction while half of the cases showed less than 20% reduction in size and the other half gave less than 50% reduction in pretreatment size **(Table 3)**. Positive platlet associated immunoglobulins was found in 65% of total cases - 70% of them has viral C hepatitis **(Table 4).**

Follow up of blood indices after treatment revealed that platelets count increase in all cases (statistically significant $P < 0.001$ ) the mean value of improvement was 40% (range 1% to 60%) this improvement continued through the months of follow up period Leucopenia and anemia didn't show the same improvement ratio and some cases deteriorated **(Table 5)**. Cases of leucopenia was managed medically without inetrruption of the treatment. Hemoglobin reaches less than 8 gm/dl in 12 cases (30%) which were managed with blood transfusion packed RBCs It was noticed that all cases of thrombocytopenia, which became more than $100x10^9$/L after irradiation was negative as regards PAIgs while all cases of thrombocytopenia which deteriorated or not increased above $100x10^9$/L was positive as regards PAIgs. In all cases of positive PAIgs the mean ± SD of PAIgs was $71.2 \pm 9.2$ for total Ig, $58.3 \pm 8.3$ for IgG, $21.4 \pm 2.1$ for IgM, $23.5 \pm 5.6$ for IgA.

Epistaxis, gum bleeding, hemorrhoidal bleeding and ecchymosis improved in 90% of cases complaining of such symptoms before starting treatment.

No acute complications due to radiotherapy was found during treatment period or during the follow up period after splenic irradiation.

**Table (1):** Patients Characteristics.

| Characteristics | NO | % |
|---|---|---|
| **Age** | | |
| <50 | 26 | 65 |
| ≥50 | 14 | 35 |
| **Sex** | | |
| Male | 25 | 62.5 |
| Female | 15 | 37.5 |
| **Abdominal pain** | | |
| Mild | 10 | 25 |
| Moderate | 20 | 50 |
| Severe | 10 | 25 |
| **Spleen size** | | |
| Mild | 12 | 30 |
| Moderate | 20 | 50 |
| Huge | 8 | 20 |
| **Child –pugh classification** | | |
| A | 24 | 60 |
| B | 16 | 40 |
| **Hepatitis virus type** | | |
| B | 14 | 35 |
| C | 26 | 65 |

**Table (2):** Pain evaluation pre and post treatment.

| Pain severity | Pre-treatment | | Post-treatment | |
|---|---|---|---|---|
| | **No.** | **%** | **No.** | **%** |
| No pain | - | - | 16 | 40 |
| Mild | 10 | 25 | 10 | 25 |
| Moderate | 20 | 50 | 9 | 22.5 |
| severe | 10 | 25 | 5 | 12.5 |

**Table (3):** Degree of splenic size reduction after treatment

| Splenic size reduction | Huge 8 (20%) | | Moderate 20 (50%) | | Mild 12 (30%) | |
|---|---|---|---|---|---|---|
| 20 % | 4 | 50 % | 2 | 10% | - | - |
| 20 – 50 % | 4 | 50 % | 10 | 50% | - | - |
| > 50% | - | - | 8 | 40% | 12 | 100 % |

**Table (4):** Prevalence of platelet associated immunoglobulin (PAIg) in patients

| | Platelet associated Ig | | | |
|---|---|---|---|---|
| | Negative | | Positive | |
| | No. | % | No. | % |
| HCV      26 | 8 | 30.8 | 18 | 69.2 |
| HBV      14 | 6 | 42.9 | 8 | 57.1 |
| Total     40 | 14 | | 26 | |

$X^2 = 3.5$ ($P<0.05$)

**Table (5):** Blood indices before and after radiotherapy

| Blood indices | Before treatment | After treatment | P |
|---|---|---|---|
| Hemoglobin (g/dl) | $10.3 \pm 1.2$ | $10.8 \pm 1.4$ | >0.05 |
| WBCs $(x10^9/l)$ | $4.36 \pm 2.3$ | $4.65 \pm 2.01$ | >0.05 |
| Platlets Count        $(x10^9/l)$ | $76.8 \pm 23.5$ | $93.5 \pm 16.1$ | <0.001 |

**\*** All parameters are expressed as $X \pm SD$

## 4. Discussion

Hypersplenism represents the increased pooling and / or destruction of the corpuscular elements of the blood by the enlarged spleen(10). Liver cirrhosis or portal hypertension is frequently associated with congestive splenomegaly resulting in hypersplenism (11).We focused our study on hypersplenism from congestive splenomegaly due to liver cirrhosis. Thrombocytopenia and leucopenia are probably the most common hematological disorders due to hypersplenism from congestive splenomegaly resulting from liver cirrhosis.(12). Peck-Radosavljevic's observed that, 15-70% of patients with liver cirrhosis have got thrombocytopenia, most commonly due to pooling of platelets in the enlarged spleen induced by portal hypertension(10).Thrombocytopenia in patients with liver cirrhosis has been reported to be caused by an increased platelet pool in the enlarged spleen (13), impaired platelet production in the bone marrow (14), decreased platelet function(15), and abnormalities in the platelet membranes(16).An article(17) reported that decreased production of thrombopoietin (TPO) might also promote the development of thrombocytopenia in liver cirrhosis. But TPO level may not be directly associated with thrombocytopenia in patients with chronic hepatitis and liver cirrhosis. In contrast, spleen volume and PAIgG are associated with thrombocytopenia in such patients, suggesting that

hypersplenism and immune-mediated processes are predominant thrombocytopenic mechanisms ( 7 ). Autoimmune mechanism plays an important role in the HCV-associated thrombocytopenia and spleen is a major source of PAIgs (1) So, autoimmune mechanism mediated by PAIg may play an important role in thrombocytopenia associated with chronic liver diseases ( 18 ).

In addition to thrombocytopenia anemia and Leucopenia are constitutes a common clinical signs of hypersplenism(19).

Hypersplenism can be treated with splenectomy or splenic embolization (4),but splenectomy in patients with huge splenomegaly and hematological disorders results in an uncommon high morbidity and mortality rate due to technical challenges and problems of hemostasis(20).

Thrombocytopenia which associates hypersplenism has been accompanied with an increased risk of bleeding when undergoing major surgery(8).

Splenectomy, could be associated with peri-operative complications such as post-splenectomy sepsis and a mortality rate as high as 14% (21)

Splenic embolization is an option for treatment of hypersplenism however splenic embolization may cause side effects, such as bacterial peritonitis, splenic abscess and acute or chronic liver failure, patients with uncompensated cirrhosis (19). Tarazov's study reported a high

mortality rate of 18% after splenic artery embolization for hypersplenism from liver cirrhosis.

Splenic irradiation is a non-invasive treatment option in managing hypersplenism (5).

Studies with chromium – 51 indicate that there is decreased red cell breakdown and increased red cell survival following splenic irradiation for chronic leukemia (22).

In our study, all patients showed improvement in thrombocytopenia during follow up period after splenic irradiation with a range (2% - 70%) (mean 36%) this improvement manifested clinically as an improvement in bleeding and ecchymosis in 90% of cases. It was noticed that cases with positive antiplatelet antibody showed lower degree of platelet count improvement after treatment. In contrast RBC'S and WBC'S didn't return to normal range which may be explained by the myelosuppressive activity of hepatitis viruses, and bleeding which associate liver diseases(5).

As regard splenic size only 10% of cases showed > 60% reduction of pretreatment size and 60% of cases showed 20% reduction of pretreatment size. Complete relief of pain was observed in 62.5% of cases. No acute complications (skin reaction, nephritis and enteritis) due to radiotherapy was found during treatment period or during the follow up period after splenic radiation.

Our results in this study coincide with the results reported by Mu, et al. who treated 5 patients with congestive hypersplenism with splenic irradiation, with a mean increase of 31% in platelet count with no considerable change in other hematological parameter. They reported reduction of splenic size in two patients and splenic pain improved in all patients (23 ).

Kenawi, et al.,(4) performed a study on 8 patients with congestive hypersplenism where they treated them with splenic irradiation daily up to 20 Gy, they observed no correlation between response and change in splenic size, with relief of splenic pain in all patients with variable degree,two of eight patients achieved a complete hematological response while three showed partial response.

Comparing the results of our study and the available results treating congestive hypersplenism with radiotherapy, it seems that splenic irradiation considered to be effective for thromocytopenias, splenomegaly and splenic pain associated with hypersplenism from congestive splenomegaly. This approach is non-invasive and may be alternative for splenectomy and splenic embolization for cases with hypersplenism due to congestive splenomegaly. Pretreatment assay of PAIgs can

detect the immunological mechanism of thrombocytopenia in hypersplenism and give picture about response to irradiation therapy as negative PAIgs cases induced a remarkable improvement of thrombocytopenia after irradiation.

Further studies with a larger number of cases, may be with alteration of treatment schedules, as regard fraction size, total dose of radiation with longer follow up period are needed for better definition of the optimal and most effective dose of splenic irradiation which is needed for management of hypersplenism due to congestive splenomegaly.

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## Fuzzy F-ideals in QS-algebras

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**Abstract:** The aim of this paper is to introduce the notion of fuzzy F-ideals in QS-algebras and study their properties. I also define the F-ideals of QS-algebra. **2000 Mathematics subject classification:** 06F35, 03G25, 03B52.
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## 1. Introduction

Y. Imai and K. Iseki introduced two classes of abstract algebras: BCK-algebras and BCI- algebras [5,6]. It is known that the class of BCK-algebras is proper subclass of the class of BCI-algebras. In [3, 4] Q. P. Hu and X. Li introduce a wide class of abstract algebras: BCH-algebras. They have shown that the class of BCI-algebras is a proper subclass of the class of BCH-algebras. J. Neggers and H. S. Kim [8] introduced the notion of d-algebras, which is another useful generalization of BCK-algebras and investigated several relations between d-algebras and oriented diagraphs. On the while Y. B. Jun, E. H. Roh and H. S. Kim [7] introduced a new notion, called a BH-algebra, which is a generalization of BCH / BCI / BCK-algebras. J. Neggers, S. S. Ahn and H. S. Kim [9] introduced a new notion, called Q-algebra, which is a generalization of BCH / BCI / BCK-algebras and generalize some theorems discussed in BCI-algebras. Moreover, they introduced the notion of "quadratic Q-algebras". In [1], Ahn and Kim introduced the notion of QS-algebra which is a generalization of Q-algebras. The concept of fuzzy set was introduced by L. A. Zadeh in [12]. P. S. Das [2] and A. Rosenfeld [10] applied it to the fundamental theory of groups. O. G. Xi [11] applied the concept of fuzzy set to BCK-algebras. In this paper, I introduce the notion of fuzzy F-ideals of QS-algebras and then I investigate several basic properties which are related to fuzzy Q-ideals.

## 2  Preliminaries

### Definition 2.1 [1]:

A QS-algebra is a non-empty set $X$ with a constant 0 and a binary
operation $*$ satisfying axioms:

  (I)    $x * x = 0$,
  (II)   $x * 0 = x$,

  (III)   $(x * y) * z = (x * z) * y$,
  (IV)   $(x * y) * (x * z) = z * y$.

for all $x, y, z \in X$ .

In $X$ we can define a binary relation $\leq$ by $x \leq y$ if and only if $x * y = 0$ .

## 3.  Ideals and Fuzzy ideals in QS-algebras:

### Definition 3.1 [12]:

A non empty subset $I$ of a BCK-algebra $X$ is called a BCK-ideal ideal of $X$ if it satisfies

  (I$_1$)    $0 \in I$,
  (I$_2$)
$x \in I$ *and* $y * x \in I$ implies y$\in I$ *for all* $x, y \in X$.

### Definition 3.2:

A non empty subset $A$ of a QS-algebra $X$ is called a F-ideal of $X$ if

  (F$_1$)    $0 \in I$,
  (F$_2$)   $(x * y) * z \in A$, $y \in A$ imply $x * z \in I$,
  *for all x, y, z* $\in X$ .

### Example 3.3:

Let $X = \{0, 1, 2, 3, 4\}$ be a set with a binary operation $*$ defined by:

| * | 0 | 1 | 2 | 3 | 4 |
|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 4 |
| 1 | 1 | 0 | 0 | 1 | 4 |
| 2 | 2 | 2 | 0 | 0 | 4 |
| 3 | 3 | 0 | 3 | 0 | 4 |
| 4 | 4 | 4 | 4 | 4 | 0 |

Then $(X;*,0)$ is QS-algebra, let $A = \{0,1,2,3\}$ it is easy to see that $A$ is F-ideal of $X$ .

## 4. Fuzzy F-ideal in QS-ideal

**Definition 4.1** [12]:

Let $X$ be a set. A fuzzy set $\mu$ in $X$ is a function $\mu : X \to [0,1]$.

**Definition 4.2** [11]:

Let $X$ be a BCK-algebra. A fuzzy set $\mu$ in $X$ is called a fuzzy BCK-ideal of X if it satisfies

(F$_1$)   $\mu(0) \ge \mu(x) \; \forall \, x \in X$ ,

(F$_2$)   $\mu(x) \ge \min\{\mu(x*y), \mu(x)\} \; \forall \, x, y \in X$ .

**Definition 4.3:**

Let $X$ be a QS-algebra. A fuzzy set $\mu$ in $X$ is called a fuzzy F-ideal of $X$ if it satisfies

(F$_1$)        $\mu(0) \ge \mu(x) \quad \forall \, x \in X$ ,

(FS)

$\mu(x*z) \ge \min\{\mu((x*y)*z), \mu(y)\} \quad \forall \, x, y, z \in X$ .

**Example 4.4:**

Let $X = \{0,1,2,3,4\}$ as in (example 3.3). Let $t_0, \; t_1, \; t_2, \in [0,1]$ be such that $t_0 > t_1 > t_2$. Define a mapping $\mu : X \to [0,1]$ by $\mu(0) = t_0$, $\mu(1) = t_1$, $\mu(2) = \mu(3) = \mu(4) = t_2$. Routine calculation gives that $\mu$ is a fuzzy F-ideal of $X$ .

**Theorem 4.5:**

Any fuzzy F-ideal of QS-algebra $X$ is a fuzzy BCK-ideal of $X$ .

**Proof.** In definition 5.3, let $z = 0$. Hence, (FS) gives that $\mu(x*0) \ge \min\{\mu((x*y)*0), \mu(y)\} = \min\{\mu(x*y), \mu(y)\}$ By the fact $x*0 = x$ , we obtain (F$_2$).

**Lemma 4.6:**

Let $\mu$ be a fuzzy F-ideal of QS-algebra $X$ if the inequality $x*y \le z$ holds in $X$, then $\mu(x) \ge \min\{\mu(y), \mu(z)\}$ .

**Proof.** Assume the inequality $x*y \le z$ holds in $X$, then            $(x*y)*z = 0$          ,           then

$\mu(x*y) \ge \min\{\mu((x*z)*y), \mu(z)\}$

$= \min\{\mu((x*y)*z), \mu(z)\}$   by   (III)   $=$ $\min\{\mu(0), \mu(z)\} = \mu(z)$ but,

$\mu(x*z) \ge \min\{\mu((x*y)*z), \mu(y)\}$

put $z = 0$

$\mu(x) \ge \min\{\mu(x*y), \mu(y)\}$

$\mu(x) \ge \min\{\mu(z), \mu(y)\}$

This completes the proof.

**Lemma 4.7:**

If $(X;*,0)$ is a QS-algebra, then $((x*z)*((x*z)*y))*y = 0$.

**Proof.**       By       (I)       and       (III), $((x*z)*y)*((x*z)*y) = 0$.

**Lemma 4.8:**

If $\mu$ is a fuzzy F-ideal of QS-algebra $X$ , then $x \le y$ implies $\mu(y) \le \mu(x)$.

**Proof.** If $x \le y$ then $x*y = 0$, this together with $x*0 = x$ and $\mu(0) \ge \mu(x)$, gives

$\mu(x*0) = \mu(x) \ge \min\{\mu((x*y)*0), \mu(y)\}$
$\ge \min\{\mu(0*0), \mu(y)\}$
$\ge \min\{\mu(0), \mu(y)\}$
$\ge \mu(y)$.

This complete the proof

**Theorem 4.9:**

The intersection of any set of fuzzy F-ideal in QS-algebra $X$ is also a fuzzy F-ideal.

**Proof.** Let $\{\mu_i\}$ be a family of fuzzy F-ideals in QS-algebra $X$ . then for any $x, y, z \in X$,

$(\bigcap \mu_i)(0) = \inf(\mu_i(0)) \ge \inf(\mu_i(x)) = (\bigcap \mu_i)(x)$

and

$(\bigcap \mu_i)(x*z) = \inf(\mu_i(x*z)) \ge \inf(\min\{\mu_i((x*y)*z), \mu_i(y)\})$

$= \min\{\inf(\mu_i((x*y)*z)), \inf(\mu_i(y))\} = \min\{(\bigcap \mu_i)((x*y)*z), (\bigcap \mu_i)(y)\}$.

this complete the proof.

**Definition 4.10** [9]:

Let $\mu$ be a fuzzy subset of a set $X$ , for $t \in [0,1]$, the set $\mu_t = \{x \in X ; \ \mu(x) \geq t\}$ is called a level subset of $\mu$ .

**Definition 4.11:**

Let $\mu$ be a fuzzy F-ideal of QS-algebra $X$ . The F-ideal $\mu_t$ , $t \in [0,1]$, is called a level F-ideal of $\mu$ .

**Corollary 4.12:**

If a fuzzy subset $\mu$ of a QS-algebra $X$ is a fuzzy F-ideal, then for every $l \in \text{Im}(\mu)$ , µ is F-ideal of $X$ when $\mu_l \neq \phi$ .

**Remark 4.13:**

The union of two fuzzy QS-ideals may not be a fuzzy F-ideal.

**Theorem 4.14:**

Let A be a F-ideal of QS-algebra $X$ . Then for any fixed number t in an open interval (0, 1), there exist a fuzzy F-ideal $\mu$ of $X$ such that $\mu_t = A$ .

**Proof.** Define $\mu : X \to [0,1]$ by

$$\mu(x) = \begin{cases} t & if \ x \in A, \\ 0 & if \ x \notin A, \end{cases}$$

Where t is a fixed number in (0, 1). Clearly, $\mu(0) \geq \mu(x)$ for all $x \in X$ .

Let $x, y, z \in X$. If $y \notin X$ , then $\mu(y) = 0$ and so $\mu(x) \geq 0 = \min\{\mu((x*y)*z), \mu(y)\}$.

If $x \in A$ , then clearly $\mu(x*z) \geq \min\{\mu((x*y)*z), \mu(y)\}$. If $x*z \notin A$, $y \in A$, then $(x*y)*z \notin A$, because $A$ is F-ideal. Thus $\mu(x*z) = 0 = \min\{\mu((x*y)*z), \mu(y)\}$.

Hence $\mu$ is a fuzzy F-ideal of $X$ . It is clear that $\mu_t = A$ .

**Theorem 4.15:**

Let $A$ be a non empty subset of a QS-algebra $X$ and $\mu$ be a fuzzy subset of $X$ such that $\mu$ is into {0, 1}, so that $\mu$ is the characteristic function of $A$ . Then $\mu$ is a fuzzy F-ideal of $X$ iff $A$ is a F-ideal of $X$ .

**Proof.** Assume that $\mu$ is a fuzzy F-ideal of $X$ . Since $\mu(0) \geq \mu(x)$ for all $x \in X$ . Clearly we have $\mu(0) = 1,$ and so $0 \in A$ . Let $(x*y)*z \in A$, and $y \in A$, then Since $\mu$ is a fuzzy F-ideal of $X$ , it follows that $\mu(x*z) \geq \min\{\mu((x*y)*z), \mu(y)\} = 1,$ and that $\mu(x*z) = 1$. This means that $(x*z) \in A$, so that $A$ is F-ideal of $X$ .

Conversely suppose $A$ is a F-ideal of $X$ . Since $0 \in A$, $\mu(0) = 1 \geq \mu(x)$ for all $x \in X$ . Let $x, y, z \in X$ . If $y \notin A$, then $\mu(y) = 0$, and so $\mu(x*z) \geq 0 = \min\{\mu((x*y)*z), \mu(y)\}$, if $x*z \notin A$, and $y \in A$, then $(x*y)*z \notin A$ because $A$ is F-ideal. Thus $\mu(x*z) = 0 = \min\{\mu((x*y)*z), \mu(y)\}$.

Therefore $\mu$ is a fuzzy F-ideal of $X$ .

**Theorem 4.16:**

Let $\mu$ be a fuzzy F-ideal of a QS-algebra $X$ and let $\mu_{t_1}, \mu_{t_2}$ be level QS-ideals of $\mu$ , where $t_1 < t_2$, then the following are equivalent.

(i) $\mu_{t_1} = \mu_{t_2}$ .

(ii) There is no $x \in X$ such that $t_1 \leq \mu(x) < t_2$ .

**Proof.** Assume that $\mu_{t_1} = \mu_{t_2}$ for $t_1 < t_2$ and that there exist $x \in X$ such that $t_1 \leq \mu(x) < t_2$ . Then $\mu_{t_2}$ is proper subset of $\mu_{t_1}$ , a contradiction. Conversely suppose that there is no $x \in X$ such that $t_1 \leq \mu(x) < t_2$ . It follows from $t_1 < t_2$ that $\mu_{t_1} \subset \mu_{t_2}$ . Let $x \in \mu_{t_1}$ . Then $\mu(x) \geq t_1$ , and hence $\mu(x) \geq t_2$, because $\mu(x)$ does not lie between $t_1$ and $t_2$ . Hence $x \in \mu_{t_2}$ , this implies that $\mu_{t_2} \subset \mu_{t_1}$ . Therefore $\mu_{t_1} = \mu_{t_2}$ .

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# Evidence for Persisting with Treatment with Paracetamol in Patients with Mild to Moderate Osteoarthritis of the Knees

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**Abstract:** Although paracetamol is recommended as first line pharmacological therapy for mild to moderate osteoarthritis (OA) of the knees, it is deemed to be not as efficacious as other pharmacological agents. One of the reasons could be due to poor adherence and persistence to therapy. This study examines the efficacy of the early response and the response after four weeks to paracetamol in mild to moderate OA of the knees in daily clinical practice. This is an open label study. Consecutive patients with mild to moderate OA of the knees were given 1.3 grams extended-release paracetamol three times per day for 4 weeks. Pain based on the Western Ontario and McMaster Universities (WOMAC) v3 VAS osteoathritis index was used as a measure of efficacy. Serial liver and renal profiles were done for safety monitoring. An early assessment of efficacy was done at week 1 and a later at the end of 4 weeks of therapy. The primary efficacy endpoint was a 30% reduction in global pain score at week 4 compared to baseline Analysis was done using the SPSS Version 18. Thirty patients entered the study. 73.3% were females. Mean age, BMI and duration of OA was 58.5years (SD±6.9), 28.1 kg/m2 (SD±6.4) 22.8 (SD±32.2) months respectively. The mean VAS WOMAC at baseline for pain was 35.4mm (SD±17.5). At the end of the first week of therapy, there was no difference in the WOMAC pain score compared to baseline. (95% CI -0.54-12.1, p=0.07). However by the end of 4 weeks there was a statistically significant 46.6% (95% CI 27.6-72.6, p<0.001) reduction in global pain compared to baseline. An absolute reduction of 16.5mm in global pain (95% CI 9.9-23.0, p<0.001) compared to baseline was also seen. No serious adverse events were encountered. Paracetamol used to treat OA of the knees is not efficacious in the first week of therapy. However persistence with therapy for a further three weeks results in significant reduction in pain. Therefore every effort should be made to ensure persistence with the recommended full four weeks of treatment.

## 1. Introduction

Osteoarthritis (OA) of the knees is a common disorder amongst older individuals in the community.[1-2] Many present to primary care doctors with complaints of pain.[1-2] and are often prescribed non-steroidal anti-inflammatory agents (NSAIDs) or cyclo-oxygenase2 inhibitors (COX-2).[2] While these agents are efficacious, they are associated with serious adverse events especially when used for longer duration in conditions like OA of the knees.[3-4] Elderly patients tend to have more comorbidities and therefore require multiple medications. Therefore, drug interactions are more likely to occur in this group of patients.[5]

Recent studies have reported that the use of NSAIDs and COX-2 inhibitors is associated with increased cardiovascular events.[4-6] Furthermore, although paracetamol is recommended as first line treatment by various guidelines for the management of OA of the knees, it is often under-prescribed.[7-8]

Various reasons have been cited as to why paracetamol is not efficacious.[9-11] One of the reasons could be the poor adherence.[12] Regular paracetamol has to be taken four times a day and it is well known that frequent medication dosing is inversely related to adherence to therapy.[13-14] Furthermore, patients frequently do not persist with the recommended 4 weeks therapy as they tend to give up when they do not appreciate any significant reduction in pain within the first few days of taking medication, rather than persisting longer with the therapy.

A literature search produced very few studies that looked at the effect of paracetamol after the first week of therapy in the treatment of OA knees compared to the effects seen later with persistence of therapy. Two studies study examined efficacy of paracetamol compared to placebo at one week [15-16] but these studies were not extended beyond one week and thus do not allow comparisons with prolonged use. One other study did look at the efficacy of paracetamol compared to placebo at one week and six weeks but unfortunately did not report on paracetamol at week one and at week six compared to baseline.[17]

Yet another study compared efficacy of paracetamol at 2 weeks and 12 weeks and found no significant reduction in pain compared to baseline at any of these two time intervals.[18] Of note is that all

these studies used regular paracetamol that requires four times a day dosing.

We thus examined the early response and compared it to the response after 4 weeks of extended-release paracetamol in treating mild to moderate OA of the knees.

## 2. Materials and Methods

We conducted an open label study using extended-release paracetamol amongst patients presenting with osteoarthritis of the knees at a university based primary care clinic. The reason for using an open label study was to emulate a real life clinical practice scenario. Furthermore, a placebo controlled trial would be deemed to be unethical in the light of available and efficacious therapy for OA knees, especially as the patients who present to our clinic which is located in a tertiary teaching hospital are usually patients who either have more severe or of longer duration illnesses and would have had received previous treatment by other primary care doctors without much improvement. An extended-release formulation was chosen as it needs to be taken only three times daily and this in itself may enhance adherence.

Consecutive patients with mild to moderate unilateral or bilateral OA of the knees based on the American College of Rheumatology diagnostic criteria[19] were eligible for the study.

Those with inflammatory arthritis, contraindication to use of paracetamol, chronic liver disease, trauma, surgery or corticosteroid injection of knee within past 3 months, psychiatric illness, pregnancy, inability to walk unassisted or with knee effusion were excluded from the study.

This was a 4-week active treatment study in concordance with the recommendations of rheumatology societies of treatment with paracetamol for 4 weeks in mild to moderate OA knees.[19-21] However neither the guidelines nor the clinical trials for OA knees have assessed efficacy in the early stages of treatment. As we wanted to compare efficacy at early to late stage of therapy, we evaluated the patients at baseline, at the end of one week of therapy and at a final visit in week 4.

Also because of the concern of safety of prolonged use at full dose of paracetamol in the background of a high prevalence of Hepatitis B carrier in the country, liver and renal biochemistries were done after one week for safety monitoring and again at the end of 4 weeks of therapy. For those with biochemistry abnormalities, further follow-up was done one month after the active treatment had ended.

Demographic data and physical examination were done at baseline. The Western Ontario and McMaster Universities WOMAC[22] v3 VAS

osteoarthritis index from 0-100 mm was applied at baseline, week 1 and week 4 for pain, function and stiffness.

Weight loss was emphasised to all overweight and obese patients. All patients were also taught knee exercise by the trained research assistant. This was provided as part of the care recommended by the various guidelines.

All patients were prescribed 1.3 Grams of extended-release paracetamol (Panadol Extend[TM]) three times daily for 4 weeks. Efficacy of treatment was assessed by change in the WOMAC pain score at week 1 and week 4 compared to baseline.

The primary end point chosen was a 30% decrease in global pain intensity between baseline and week 4 in accordance to recommendations of a report by the Osteoarthritis Research Society International (OARSI).[23] The secondary efficacy end point was a reduction of 10mm on the WOMAC pain score between baseline and week 1, week 1 and week 4 and baseline and week 4. This is the consensus level of response for efficacy studies of OA knees.[23] Based on a power of 80% and a two-sided $\alpha$ value of 5%, and a defaulter rate of 20%, the number of patients needed is 30.

Compliance was measured by a daily diary and pill count.

Analysis was done using SPSS version18 and was done on an intention to treat analysis. Written informed consent was obtained from all patients and approval for the study was granted by the institution's University of Malaya Medical Centre Ethics Subcommittee.

## 3. Results

A total of 30 patients entered the study and 25 (83.3%) completed the study. Four patients attended the week 1 visit, said they felt better and did not want to continue with the study. One had diarrhoea and voluntarily withdrew from the study at week 1, although the investigators deemed that she could continue with the study. In the 25 patients who completed the study, both at week 1 and week 4, less than 4% of each outcome variable of the pain WOMAC v3 VAS score was missing.

Table 1 shows the baseline characteristics of the study patients. Majority of the patients were females and two thirds were overweight or obese. Bilateral OA was common too seen in nearly three quarters of the patients.

The results presented here are the intention to treat analysis. There was no difference in the intention to treat and per protocol analysis on the primary outcome and liver toxicity.

Table 2 shows the percentage change and Table 3 the absolute change in global WOMAC

Score in pain, stiffness and difficulty in function at week 1 and week 4 compared to baseline.

**Efficacy of early and late response to paracetamol**

Although an early reduction in pain of 5.8mm was seen after one week of therapy, this was not statistically significant (95% CI -0.54-12.1, p=0.07). Furthermore the magnitude of pain reduction did not meet the primary efficacy end point either.

However at the end of 4 weeks of treatment, the reduction in pain was nearly 50% (CI 27.6-72.6, p<0.001) when compared to baseline. There was also a statistically significant reduction of 16.5mm (95% CI 9.9-23.0, p<0.001) on the WOMAC pain score at the end of 4 weeks compared to baseline.

Furthermore the reduction in WOMAC pain score of 10.7mm was also significant between week 1 and week 4 (95% CI 2.8-18.6, p=0.01).

A reduction in stiffness of nearly 30% and in difficulty in function of 34.9% was also seen between week 4 and baseline. There was also a statistically significant reduction of 12.3mm and 15.2mm in stiffness and difficulty in function respectively at the end of the study when compared to baseline.

Table 1: Baseline Characteristics of Study Patients (N=30)

| Variable | Mean ±SD |
|---|---|
| Age (years) | 58.5 (6.9) |
| BMI kg/m$^2$ | 28.1 (6.4) |
| Duration of OA (months) | 22.8 (32.2) |
| | |
| Variable | N (%) |
| Females | 22 (73.3%) |
| Overweight and Obese (BMI ≥25 kg/m2) | 19 (63.3%) |
| Obesity (BMI ≥30 kg/m2) | 8 (26.7%) |
| Bilateral OA | 21 (70%) |

Table 2: Percentage Reduction in WOMAC Score in pain, stiffness and difficulty in function at week 1 and week 4 compared to baseline

| | % change in WOMAC VAS (95% CI) | | | | | |
|---|---|---|---|---|---|---|
| | Wk0-Wk1 | p | Wk1-W4 | p | Wk0-Wk4 | p |
| **Pain** | 16.4 (-2.4-43.3) | 0.071 | 35.8 (1.9-59.2) | 0.001 | 46.6 (27.6-72.6) | <0.001 |
| **Stiffness** | 6.8 (-13.9-30.0) | 0.47 | 23.7 (-12.8-41.2) | 0.09 | 28.9 (15.0-53.4) | 0.03 |
| **Difficulty in Function** | 18.2 (1.5-37.7) | 0.02 | 20.5 (-2.6-49.5) | 0.06 | 34.9 (20.5-62.5) | <0.001 |

Table 3: Absolute Change in WOMAC pain, stiffness and difficulty in function score at baseline, week 1 and week 4

| Global WOMAC Score (0-100 mm VAS) | | | | | | |
|---|---|---|---|---|---|---|
| Mean Score (mm) | | | Absolute Reduction in mm ( 95% CI), (p value) | | | |
| | Wk 0 | Wk 1 | Wk 4 | Wk 0-1 | Wk 1-4 | Wk 0-4 |
| **Pain** | 35.4 | 29.6 | 18.9 | 5.8 (-0.54-12.1) (p=0.07) | 10.7 (2.8-18.6) (p=0.01) | 16.5 (9.9-23.0) (p<0.001) |
| **Stiffness** | 42.5 | 39.6 | 30.2 | 2.9 (-6.5-12.2) (p=0.48) | 9.4 (-1.8-20.6) (p=0.09) | 12.3 (2.2-20.6) (p=0.03) |
| **Difficulty in Function** | 43.5 | 35.6 | 28.3 | 7.9 (1.3-15.1) (p=0.02) | 7.3 (-0.3-14.4) (p=0.06) | 15.2 (7.3-23.2 ) (p<0.001) |

**Safety and Tolerability**

There were no serious adverse events encountered. Minor adverse events included dizziness (two) and diarrhoea (one).

There were also no clinically significant changes in the liver enzymes. Although there was some elevation in liver enzymes seen between baseline and at the end of week 4, none of it was raised more than twice the upper limit of normal. For those with raised liver enzymes, a follow-up was done a month after the study ended and repeat blood tests showed their enzymes had reverted to their baseline. There were also no significant changes in renal function.

Compliance was very good with all the 25 completers achieving a compliance of between 96-98% at week 1 and 94- 96% at week 4 based on the patient's daily diary and pill count. In four of the defaulters, the compliance was between 80-86% at week 1, after which they did not wish to continue with the study as they said they felt their pain was very much reduced. The defaulter who had diarrhea took the medication for 3 days only and voluntarily withdrew from the study when reviewed at week 1

**4. Discussions**

Paracetamol is recommended as first line pharmacotherapy by various guidelines on the management of OA of the knees.[19-21] This study, done to reflect daily clinical practice, shows that with persistence, extended-release paracetamol given at a dose of 1.3 gram three times daily for four weeks is effective in reducing pain in patients with mild to moderate OA of the knees. It is also effective in reducing stiffness and in improving function and is safe and well tolerated. This safety and tolerability has since been confirmed in other studies when paracetamol was given for six weeks or longer.[17, 24]

Our study does not have a placebo or control arm for comparison and it can be argued that paracetamol may be no better than a placebo.[18] While it is acknowledged that the lack of a placebo or control arm is one of the limitations of our study, several randomized control trials have shown greater efficacy of paracetamol compared to placebo.[15-16,25] However, a meta-analysis[26] has shown that it is less efficacious than NSAIDs[26] providing greater support for the use of NSAIDs instead of paracetamol for OA of the knees. But many of the studies which show NSAIDs to be more effective than acetaminophen[26-28] were usually done in patients with more severe pain and longer duration of symptoms.[26-28] On the other hand, several studies have shown that there is no difference when acetaminophen, either regular or the extended formulation is compared against an NSAID.[29-30] Furthermore, the effect size seen in

NSAIDs versus placebo studies is only 0.34, (95% CI 0.14-0.54) and this is not much greater than the effect size of paracetamol versus placebo[26] (effect size 0.21, 95% CI 0.02-0.41). Hence, based on our study which was done in a primary care setting and emulating daily clinical practice, there is still a case for using paracetmaol as first line pharmacotherapy especially in mild to moderate OA of the knees.

Most of the above mentioned studies compared therapies at the end of 4 weeks or longer.[17-18, 24-25, 27-29] Very few have been done to compare the effect of short term therapy.[15-16] Even fewer compared early response to response with persistent drug usage. A randomized short term study of one week[15] found significant reduction in pain with paracetamol over placebo. But another randomized short term study, also of one week, found that while paracetamol was superior to placebo, NSAIDS was superior to paracetamol.[16] Unfortunately these two studies were only for a week and thus it was not possible to examine the efficacy with longer use. A possible outcome, if there was a comparison of longer use, could be a narrowing of the differences in efficacy between NSAIDs and paracetamol. One study did examine the efficacy of paracetamol at 2 weeks and 12 weeks compared to baseline but found no difference in efficacy with prolonged use.[18] In this same study the reduction in pain was significant and seen early at 2 weeks with the use of diclofenac, suggesting an earlier onset of pain relief with NSAIDs compared with paracetamol. Because there were very few studies that compared early response to response after four weeks of paracetamol use, our study aimed to do this. Our results did show that there is significant benefit with persistent use, unlike that of one study[18] that showed that there was no significant response at 2 nor at 12 weeks compared to baseline.

Our study also shows that while there was some early reduction in pain and stiffness, this was not statistically significant. This finding does not suggest that there is no effect but that the lack of statistical significance could have been due to the small number of patients. However with persistent use of paracetamol, the improvement became greater and significant. While we studied the response after one week of therapy, this time point was an arbitrary choice. We decided to see the patient earlier rather than at the end of 4 weeks as recommended by guidelines was because we were concerned about the safety of full dosing for four weeks. This was because at the time of our study there was no available data about safety of paracetamol of longer than 2 weeks duration of use. While our study showed a statistically significant reduction in pain at the end of 4 weeks but not after one week, the

response at the end of 2 weeks or even at the end of three weeks remain unknown. In fact a meta-analysis of short term efficacy of pharmacotherapeutic interventions concluded that there was not enough data to identify a time point for maximum effect of paracetamol within a 4 week time frame for treatment of OA knees.[31] This being the case, our study helps to support the recommendation of using paracetamol for a full four weeks.

A limitation of our study was that it was conducted for four weeks only and efficacy for a longer duration of therapy was not evaluated. However our purpose was to emulate daily clinical practice. To be in accordance with the OA guidelines recommendations, patients are to be reviewed after four weeks of paracetamol therapy and a decision made then on further management at this time point depending on the response of the patients. Hence we did not proceed beyond the 4 weeks. It is likely that a longer study may show a continued persistence but not necessarily a further improvement in the benefit. In fact one study which compared paracetamol against placebo did not show any significant improvement at 2 weeks compared to baseline and it also did not show any further improvement at 12 weeks compared to baseline.[18]. This suggests that no further improvement can be seen after the maximum efficacy seen at four weeks is already attained.

It has to be acknowledged that the response seen in our study could have been a result of a regression to the mean or to a response shift. [32-33] However, the mean duration of OA symptoms of our study patients was nearly 2 years and not new onset OA, and it is unlikely that a regression to the mean or a response shift alone could have accounted for the response seen.

Another confounding factor would be that the reduction in pain seen in our patients could have been due to the knee exercise given to all of them. While this may be the case, we wanted to emulate best clinical practice and to be in accordance with guideline recommendations of combining non-pharmacological with pharmacological therapy. Hence we proceeded to provide knee exercise. We acknowledge that the presence of a control arm of exercise but without paracetamol, may have helped to eliminate this confounding issue. But again as these are not patients with newly diagnosed OA, it is unlikely that knee exercise alone would have accounted for the response seen. As such, inspite of all the above limitations there is still a sound reason to use paracetamol as first line as recommended by the various guidelines.

Our finding thus has implications as it adds to the dearth of data supporting persistence with paracetamol use. Our finding also suggests that it is important to remember that patients should persist and stay on treatment with paracetamol for longer, and that doctors should resist the pressure to change to another medication too soon.[34-35]

Effectiveness of paracetamol is related to adequate dosage. Doctors and other health care providers often do not use paracetamol adequately and thus paracetamol is perceived by doctors as well as patients not to be effective[7,9] Furthermore, compliance to a four times daily dosing is usually poorer than a less frequent daily dosing. Compliance to a three times a day extended preparation is excellent here. While our study shows that the treatment of OA of the knees with paracetamol is significantly efficacious, several other studies failed to show this.[17-18]One of the reasons for this difference could be the better compliance with an extended preparation seen in our study as for example versus 72% seen in another study[17]. Furthermore, many of the other studies used the regular four times a day dosing paracetamol and the studies were of a longer duration.[17-18]These factors could have contributed to the poorer compliance[12-13] and hence may have contributed to their lack of positive findings. Although it is recognized that patients in studies tend to be more compliant because of close supervision, doctors, nevertheless, should try to prescribe extended preparations in full doses as far as possible [12-13] and patients should be encouraged to take medication regularly according to the directions to reduce pain episodes.[34-35]

Given that more adverse events are associated with NSAIDs use[3-4] and that patients would forgo some degree of effectiveness for safety[36] NSAIDS are thus not necessarily superior to paracetamol, especially in patients presenting to a primary care clinic with mild to moderate OA knees. Together with the excellent safety and tolerability of using paracetamol in full dose for 4 weeks and its good safety/benefit ratio, there is still a case for advocating the use of paracetamol as first line therapy in OA of the knees.

The aim of management of OA is not to cure as this is not realistically possible, but to relieve pain, improve function and improve quality of life. This study has shown a reduction in pain severity and this is achieved with minimal adverse events with 1.3 grams of extended release paracetamol given three times daily and persisted for a full four weeks.

## 5. Conclusion

Paracetamol used to treat OA of the knees is not efficacious in the first week of therapy. However persistence with therapy for a further three weeks results in significant reduction in pain. Therefore

every effort should be made to ensure persistence with the recommended full four weeks of treatment.

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**Competing Interests:**
YCC: has received honorarium as speakers' fee from GSK Healthcare Malaysia
All the other authors declare that they have no competing interests.

**Author's Information:**
YCC: conceived, designed and obtained the research funding for the study. She also coordinated the study, collected and analysed the data and wrote the manuscript.
RB: participated in data collection
MM: participated in the study design
NSH: participated in conception of the study
CJN: participated in conception of the study

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# Use Gold Nanoparticles To product Plastic timber recycling waste plastics and Fibers palm Fronds

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**Abstract:** Saudi Arabia has plenty of agricultural waste products such as fiber palm fronds. Among the advantages of these fibers are: renewable, nonabrasive, cheaper, abundance and show less health and safety concern during handling and processing. Also Saudi Arabia has a lot of industrial waste such as plastic. Recently, the interest has increased to recycle plastic materials accordingly, the composite industry has begun investigating the possibility of increasing the proportion of recycled composites. This leaded to search about environment eco-friendly reinforcement and resins systems while providing the same performance as their man made counterparts**,** and if we want to enhance the performance recycled composites we can use gold nanoparticles.

Key word: Gold nanoparticles; plastic timber; waste plastic; fibres palm; fronds

## 1. Introduction

The trend to add value to products and that is environmentally friend has encouraged transformation industries to work with waste recovery. Discarded post-consumer plastics are generally considered a problem due to the damage they cause to the environment. Most come from disposable food packages, which, after being discarded in landfills, pile up and increase the volume of waste and the visual pollution(1-3).

One of the alternatives to reduce the amount of material currently treated as urban solid waste is to recycle it(4).

The traditional process for producing thermoplastic materials is the mechanical one(5), involving the use of the equipment's.

Recycling plastic waste with vegetable fibers, plentiful in the middle East region, would increase its value, and this process has aroused interest in studying the production and application of such composites(6).

In general, vegetable fibers, when adequately combined with polymers, can provide better flexibility and improve mechanical resistance and toughness (7-9). However composites reinforced with natural fibers and gold nanoparticles tend to show low mechanical resistance due to poor interfacial adhesion caused by the low chemical interaction of the fibers (10)and gold Nano particles.

Dates have been a staple food of the Middle East for thousands of years.

The date palm trunks are used as beams and rafters, leaves are used as a raw material for many of the industries. Furthermore, rachis and leaves can be viewed as sources of reinforcing fibers for polymeric matrices in composite materials (11).

The valorization for fiber production of eight Saudi lignocelluloses were investigated. Fiber length, specific gravity and chemical composition: total extractives, lignin, holocellulose and ash contents of the eight lignocelluloses materials were determined. All the characteristics examined varied significantly due to the natural resource effect. The three lignocelluloses materials of date palm had higher contents of total extractives, lignin and ash; and lower holocellulose content compared to those from timber trees. Although the date palm leaflet possessed the longest fibers (1.31mm), followed by rachis (1.19mm). Their fiber manufacturing needs more chemicals and time and some problems arise upon chemical recovery process due to their chemical composition(12).

Date palm leaves were compounded with plastic and gold nanoparticles stabilizers to form composite materials. The stability of the composites in natural weathering conditions of Saudi Arabia and in accelerated weathering conditions was investigated.

The composites were found to be much more stable than Plastic under the severe natural weathering conditions of Saudi Arabia and in accelerated weathering trials. Compatibilized samples are generally less stable than uncompatibilized ones as a result of the lower stability of the plastic.

In addition to enhanced stability imparted by the presence of the fibres in the composites, enhanced interfacial adhesion resulting.

From add gold nanoparticles can be the source of retention of mechanical strength.fibers have a high potential to be used in many different area particularly as reinforcement in development of composites. Many studies have been done on isolation and characterization of fibers from various sources. fibers can be extracted from simple

mechanical methods or a combination of both chemical and mechanical methods(13). This study investigated the influence of add gold nanoparticles to fiber as an element of reinforcement for post consumption package materials, using simplified and low cost methodology.

## 2. Experimental

### Synthesis of gold nanoparticles

Add 20 mL of 1.0 mM $HAuCl_4$ to a 50 mL beaker or Erlenmeyer flask on a stirring hot plate. Add a magnetic stir bar and bring the solution to a rolling boil.To the rapidly-stirred boiling solution, quickly add 2 mL of a 1% solution of trisodium citrate dehydrate, $Na_3C_6H_5O_7.2H_2O$. The gold sol gradually forms as the citrate reduces the gold(III). Remove from heat when the solution has turned deep red .

### Fibre preparation

Branches obtained from palm trees were cut intopieces about 8 inches long. Thereafter, they were air dried for 48 hrs at room temperature. The material brought to room temperature and specimens were prepared and tested according to ASTM standards (Specific Gravity, ASTM D792-91.Water Absorption, ASTM D570-95).

### Preparation of Waste palm leaves and fiber material

The pieces of branches were then granulated to a small size using a Granulator (Rapid Granulator Inc., USA, Type 79-C,No. 201544). The fibers were then size separated by using a sieving machine. Only the large fraction of fibers was used in this study. The fibers size distribution was characterized using a digital vernier caliper. The average length of the fibers was 6.2 mm with a standard deviation of 2.8 mm and an aspect ratio of 10.8. The fibers obtained were then cleaned to remove the volatile organic compounds. The chemicals used for cleaning were ethanol and toluene in the ratio of 1:2 (V/V). The mixture of these two chemicals was prepared in a large container. The fibers were soaked in the mixture for 24hrs. The fibers were then washed with water and dried in a vacuum oven (Blue M Electric Company, Model OV-490A-2) at 105 °C for 24 hrs to remove residual moisture, and stored in suitable bags at dry place.

### Preparation of plastic wastes

A random collection of different mixed plastic waste was shredded followed by washing with detergent and rinsed twice and excess of water was drained allowed for complete dry in open air. The clean and dry bits of mixed plastics were fractionated in to different size particles by passing through size selective meshes and stored in containers.

### Composite sample

Fiber material + Waste Plastic + gold nanoparticles + PVC= new Composite

## 3. Results and Discussion

### Characterization of gold nanoparticles

The UV–visible spectra of the samples were recorded for the wavelength 520 nm at 25 °C. Figure (1) on a Hewlett-Packard 8452A diode array spectrophotometer.

The gold nanoparticles obtained were characterized by atomic force microscope (AFM). Transmission electron microscopy (TEM). Figures (2,3)

### Characteristics of composite samples

The composite samples (A) with gold nanoparticles prepared in this project have properties comparable with those of the same composite(B) with out gold nanoparticles. It noted that most of the characteristics of composite samples (A),could be enhanced by putting gold nanoparticles to increase the density, by increasing the compression before the material solidification in the mold. Surface modification leaf material/fibers with chemical reagent and gold nanoparticles in order to develop strong adhesiveness between plastic, leaf fiber materials as it is one of the important step in the process for the improvement of mechanical properties of composites. The properties of composites depend on the matrix, the fibers and their interfacial compatibility. Natural fibers because of hydrophilic nature reduce their compatibility with polymer matrix. Surface modification of fibers and their compatibility development is considered to be a challenging area of research for the development of composites.

### Density

The density of prepared composite samples with gold nanoparticles(A), (1.A.6; 1.A.8; 1.A.10; 1.A.12 and 1.A.14), were recoded, it was ranged between 1.29 and 1.99 with an average of 1.59 g/cm³ in comparison to composite sample without gold nanoparticles(B) where its density recorded 1.1g/cm³.(Figure 4). Density is a crucial factor for wood-plastic composites or fiber reinforced plastic composites with gold nanoparticles, which primarily depend on the specific gravities of its ingredients and their proportional formulation. Moisture in natural cellulose fibers create steam and vapor during processing due to plastic decomposition produces volatile organic compound at hot melt temperatures, hence, porosity. To overcome this constraint using gold nanoparticles to vented extruder is the best option in terms of removing the trace gases and steam which subsequently decreasing porosity and bring the density close to the maximum one.
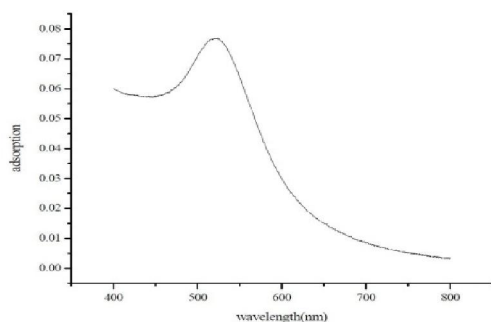
Figure (1) UV-vis spectroscopy of colloids gold nanoparticels
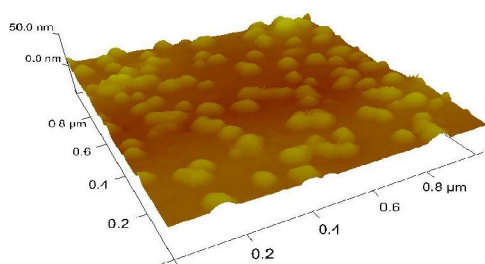


Figure(2)atomic force microscope (AFM)
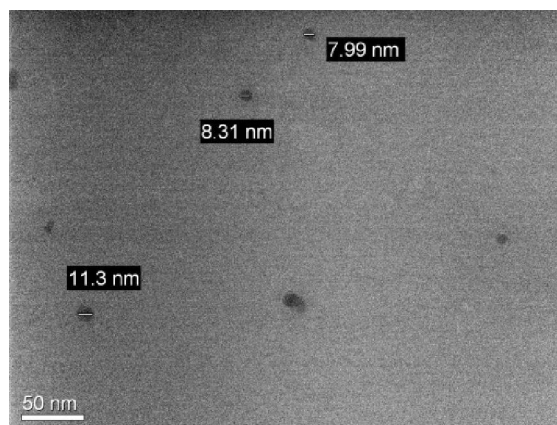


Figure(3)(TEM) images of gold nanoparticles

Table 1. Density and Water Absorption of some prepared wood composites

| samples | Density(g\cm3) | Water Absorption % |
|---------|----------------|--------------------|
| 1.A.6   | 1.29           | 5.4                |
| 1.A.8   | 1.44           | 6.6                |
| 1.A.10  | 1.55           | 4.5                |
| 1.A.12  | 1.71           | 3.06               |
| 1.A.14  | 1.99           | 2.2                |
| 2B      | 1.1            | 8.47               |

**Table 2.Tensile properties of some prepared wood composites**

| samples | Modulus of Elasticity at yielding point (MPa) | Strain at yielding point | Stress at Max. load )MPa( |
|---------|-----------------------------------------------|--------------------------|---------------------------|
| 1.A.6   | 576.2                                         | 0.0023                   | 1.89                      |
| 1.A.8   | 690.8                                         | 0.0025                   | 3.25                      |
| 1.A.10  | 599.1                                         | 0.0009                   | 3.5                       |
| 1.A.12  | 773.4                                         | 0.0004                   | 3.2                       |
| 1.A.14  | 918.8                                         | 0.0034                   | 3.9                       |
| Mean    | 711.66                                        | 0.0019                   | 3.18                      |

**Water Absorption**

Water uptake or swelling ratio of a sample is determined by measuring the change of weight percent due to water absorption within certain period of time. The prepared samples with gold nanoparticles(A), in addition to a sample without gold nanoparticles(B) were immersed in water, for 24 hours, and then reweighed after surface drying. The change of mass due to swelling (water absorption) is determined.(Figure 4) shows the swelling ratio of different samples(A,B). It is, clearly, indicated that swelling ratio is inversely proportional to the sample(A) density as compared to the sample(B). Least swelling was recorded in sample number 1- A - 14, which has density 1.99 g/cm³.(Table 1).

Ability of water absorption by the composites containing natural fiber and plastic polymer mixture with gold nanoparticles (A)depends on their porosity, amount of fiber content and their availability to incoming water. Composite materials are typically porous, and their degree of porosity is determined by moisture of the incoming raw materials, as well as, processing conditions, mainly heat treatment. The water uptake ability of composite depends on the level of moisture content in the initial formulation leading to develop elevated value of porosity during the processing and lowers the density of composite sample consequently, higher the water absorption (8).

**Tensile property**

The tensile property in terms of modulus of elasticity at yielding point of prepared composite samples tested. Stress at maximum load ranging from 1.89 to 3.9 with an average of 3.18MPa and corresponding modulus elasticity at yielding point were recorded 576.2; 690.8; 599.1; 773.4;918.8 and711.66MPa for samples 1.A.6; 1.A.8; 1.A.10; 1.A.12; 1.A.14 respectively (Table 2). The average value for all samples were recorded 643.48 MPa. The variations in elasticity at yielding point attributed to modifications of conditions to improve the quality of composites such as proportional mixing of raw

materials, heat treatments, compression and addition of gold nanoparticles etc. Further improvements in the strength of composites are in progress.
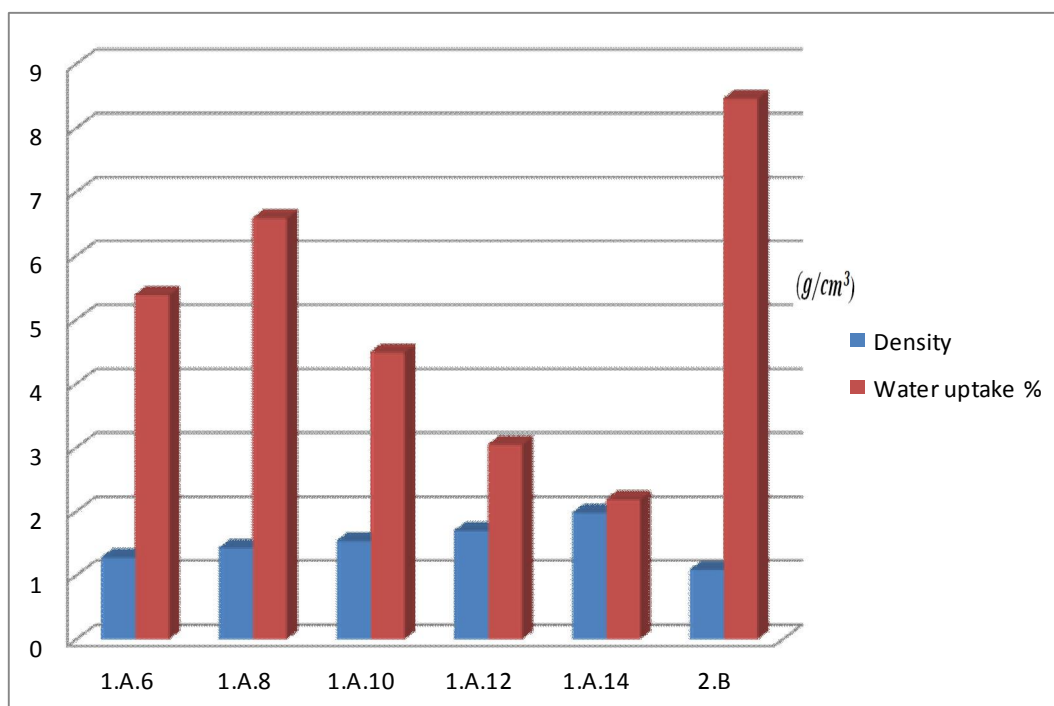


**Figure 4. Comparison of Density and Water Absorption of composite**

**Conclusion**

Recycling of plastic wastes is scientifically good practical solution for plastic disposal. This research work aims to use Gold Nanoparticles to enhance performance composites from plastic wastes and fibers obtained from waste date palm leaves as wood alternative. It is an approach of vital interest, which provides the solution for two environmental problems. From the economic point of view, date palm leaf fiber plastic composite have many benefits: They use low cost and plentiful raw materials like plastic palm leaves waste become assists instead of liabilities. They are competitively priced and are competitive with traditional materials such as timber and MDF. They are true hybrid materials, and combine the best properties of both wood and plastics and can be produced in a broad range of finishes and appearances, also easily recycled after their useful life. They are environmentally friendly contains no toxic or volatile organic components. These composites are suitable for many indoors and outdoors applications. Also, they are not suitable as insect's shelter. Therefore, the industrial production and further development of such composites are an excellent solution to get rid of a waste of agricultural origin and plastics from solid municipal waste. The waste recycling issues considered in this research project is the problem of waste palm leaves, which localized, together with the problem of plastic wastes, which is international one. This approach can be followed in other countries, middle-east countries in particular, using the available wastes as renewable resource for the production of value added building material as wood alternative, which in turn save forests and green zones contribute to environmental sustainability.

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# Spectral and Kinetic Studies of Thermal Decomposition of Ni$^{II}$ hexanoate Complex Ni$_2$(cap)$_4$

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**Abstract:** Nickel(II) hexanoate complex, Ni$_2$(cap)$_4$, (where cap is the hexanoate anion = CH$_3$(CH$_2$)$_4$COO$^-$) was prepared and discussed using elemental analysis, infrared spectra, thermogravimetric analysis (TGA), differential thermal analysis (DTA), UV-vis spectra, and X-ray powder diffraction (XRD) studies. Using the non-isothermal, Horowitz-Metzger (HM) and Coats-Redfern methods, and the kinetic parameters for the non-isothermal degradation of the respective complex was calculated by using TG data. The infrared data are in agreement with coordination through carboxylate-to-metal, with cap acting as a bridging bidentate ligand. Thermogravimetric analysis of the Ni$^{II}$ complex shows that the first degradation step is associated with the release of terminal methyl groups followed by the decomposition of the hexanoate molecules to form nickel carbonate salt and then give nickel(II) oxide as residual product.
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**Keyword:** Infrared spectra, Hexanoic acid, Thermal analysis, Nickel oxide.

## 1. Introduction

n- Hexanoic acid (n- hexanoic acid) Scheme 1, C$_6$H$_{12}$O$_2$, occurs in milk fats (about 2%), in coconut oil (< 1%). Such fatty acid is employed in the manufacture of pharmaceuticals and flavorings [1]. It is slightly soluble in water and readily soluble in ethanol and ether [2]. The binding of metal ions to carboxylic acids has been a subject of intense research investigation in view of its diverse applications, such as from the relevance of metal-carboxylate complexes as model systems for the metalloactive sites in bioinorganic chemistry [3, 4]. The structural diversity encountered in metal-carboxylate complexes can be attributed to the versatile bonding behavior of the carboxylate group which can act as a bidentate ligand or a bridging ligand [5, 6]. Compounds of transition and non-transition elements with hexanoic acid are not so common. A literature survey reveals that there are some papers on the preparation of hexanoates of some rare earth elements [7, 8] and the preparation of anhydrous copper(II) hexanoate from cuprous and cupric oxides [9]. Pietsch [10] extracted hexanoates of thorium, lead and iron hexanoates into CHCl$_3$. From the point of view of analytical chemistry, hexanoic acid is a good extracting agent for many elements [11-13] such as rare earths, zirconium, chromium, manganese, iron, gallium as well as aluminum with catechol violet by a mixture containing CHCl$_3$, hexanoic and propionic acids. The aim of the present work is to enhance the knowledge about metal-fatty acid (mono carboxylate) compounds. For such purpose, the synthesis, characterization and TG-DTA analysis of Ni(II)- hexanoate are reported. By using non-isothermal TG data, kinetic parameters for the thermal degradation processes were calculated, through Horowitz Metzger (HM) and Coats-Redfern (CR) methods.
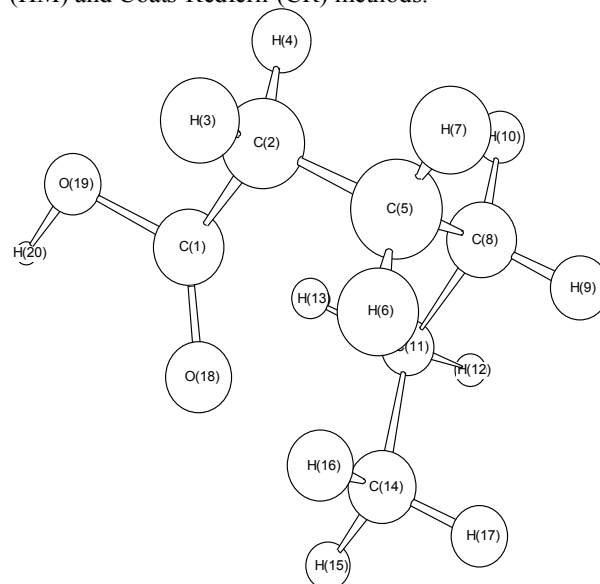


**Scheme 1**: Structure of hexanoic acid

## 2- Experimental

All used reagents were of analytical grade and were employed without further purifications. Nickel(II) chloride anhydrous (1 mmol, Aldrich Company) were dissolved in 25 cm$^3$ of methanol and then the prepared solutions were slowly added to 25 cm$^3$ of an methanolic solution with 1 mmol of hexanoic acid (Fluka) under magnetic stirring. The

pH of each solution was adjusted to 8-9 by addition of ammonium hydroxide. The resulting mixture was heated at $60^{o}C$ and left to evaporate slowly at room temperature overnight. The Turquoise precipitate was filtered off, washes with hot methanol and dried at $60^{o}C$. The elemental analysis data of carbon and hydrogen were performed in a CHN 2400 Perkin Elmer analyzer. The metal content was found gravimetrically by converting the resulted complex into its corresponding stable oxide. FTIR spectra were recorded on a Genesis II FT IR spectrometer in the 4000-400 $cm^{-1}$ range with 40 scans in KBr discs. The electronic spectra were recorded in dimethylsulphoxide (DMSO) using a Shimadzu model 1601 PC UV spectrophotometer with quartz cells of 1 cm path length. The X-ray diffraction patterns (XRD) were obtained on a Rikagu diffractometer using $Cu/K_{\alpha}$ radiation. The thermal studies TG/DTA–50H were carried out on a Shimadzu thermogravimetric analyzer under nitrogen till 800 $^{o}C$.

### 3- Results and Discussion

Nickel hexanoate complex was obtained as green solid product. The elemental analysis results summarized as: Calc. %C= 54.42; %H= 8.52; %Ni= 17.73, Found %C= 53.95; %H= 8.47; %Ni= 17.75, these data are compatible with TGA and in a good agreement with the proposed formulas. The main infrared spectral data are summarized in Table 1. The carboxylate group is able to coordinate to metal ions by three different modes, as shown in Scheme 2 [14].
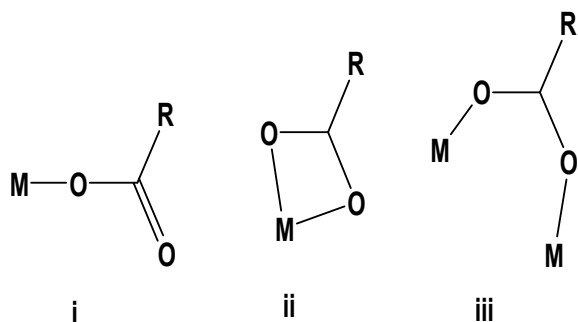


**Scheme 2:** Mode of carboxylate chelation

Type I: When the carboxylate group coordinates the metal ion in a monodentate manner, the difference between the wave numbers of the asymmetric and symmetric carboxylate stretching bands, $\Delta\nu = \nu_{as}COO^{-} - \nu_{s}COO^{-}$), is larger than that observed for ionic compounds. Type II: When the ligand chelates, $\Delta\nu$ is considerably smaller than that for ionic compounds, while on the asymmetric bidentate coordination, the values is in the range characteristic of monodentate coordination [15].

Type III: The characteristic wave numbers difference, $\Delta\nu$, is larger than that for chelated ions and nearly the same as observed for ionic compounds. Based on these facts it is possible to distinguish the coordination mode of the – $COO^{-}$ group.

**Table 1a**: Main infrared data for $Ni_2(cap)_4$ (values in $cm^{-1}$).

| $Ni_2(cap)_4$ | Assignments |
|---|---|
| 3410 br | $\nu$ (OH); $H_2O$ |
| 3135 br | $\nu$ CH; $CH_3$ |
| 2952 m | $\nu_{as}$ (CH) |
| 2922 m | |
| 2864 ms | $\nu_s$ (CH) |
| 1580 vs | $\nu_{as}$ (OCO) |
| 1510 m | |
| 1440 w | $\delta(CH_2)$ |
| 1412 ms | $\nu_s$ (OCO) |
| 1366 s | |
| 1340 s | |
| 1312 w | |
| 1253 mw | $^{\rho}_w$ ($CH_2$) |
| 1223 mw | $\nu_{as}$ (CC) |
| 1202 s | |
| 1110 ms | |
| 965 vw | $\nu_s$ (CC) |
| 902 mw | |
| 849 mw | $\delta$ (CC) |
| 804 w | |
| 729 s | $\delta$ (OCO) |
| 674 s | $^{\rho}_r$ ($H_2O$) |
| 543 w | $\delta$ (CCO) |
| | $^{\rho}_w$ (OCO) |
| 454 mw | $\nu$ (M-O) |
| 427 mw | |

vs: very strong, s: strong, m: medium, w: weak, vw: very weak, br: broad. $\nu_{as}$: asymmetric stretching; $\nu_s$ : symmetric stretching; $\delta$: angle deformation; $^{\rho}_w$: wagging mode; $^{\rho}_r$: rocking mode.

**Table 1b:** Asymmetric and symmetric stretching vibrations of the carboxylate group, and their difference (in $cm^{-1}$) [$\Delta\nu = \nu_{as} - \nu_s$].

| Compounds | $\nu_{as}$ (COO) | $\nu_s$ (COO) | $\Delta\nu = \nu_{as} - \nu_s$ | Bonding mode |
|---|---|---|---|---|
| $Ni_2(cap)_4$ | 1580 | 1366 | 214 | Bridge Bidentate |

The hexanoic acid exhibits a strong absorption band around 1700 $cm^{-1}$ due to the C=O group. For the prepared complexes, the difference between the asymmetrical and symmetrical vibrations, summarized in Table 1b, when compared with those data for sodium hexanoates (the $(\nu_{as}-\nu_s)$ values of the

COO⁻ groups are smaller than the value of sodium salt), strongly, suggest that COO⁻ groups are acting as bridge bidentate chelating ligand (type III) [16]. Synthesized nickel hexanoate compound exhibit a strong absorption band around 260 nm, furthermore, the Ni(II) hexanoate exhibits a peak at 660 nm which assigned to d-d transition. The molar absorptivities ($\varepsilon_{max}$) of the nickel(II) hexanoate is 9783 l.mol$^{-1}$.cm$^{-1}$. These values are almost twice the value found for hexanoic acid (5068), in agreement with the fact that two ligand molecules of the ligand are present. The TG and DTA results are summarized in Table 2. The final product of thermal decompositions is the respective NiO.

**Table 2:** Main TGA and DTA data for the nickel (II) hexanoate complex

| Compounds | DTA results T/K peak | | TG results | |
|---|---|---|---|---|
| | | T range (K) | Losses | Residue |
| $Ni_2(cap)_4$ | 375 endo 550 exo 570 exo 665 exo | 353-538 538-550 563-870 | $4C_2H_4$ Organic matter $2CO_2$ | NiO |

The TGA and DTA curves of the compound $Ni_2(cap)_4$ shown that this compound is thermally stable up to 350 K, when the slow decomposition to NiO begins. The TG curve shows that the first mass loss between 350-540 K corresponds to the release of terminal four ethylene molecules, followed by the release of organic moiety. Hence the hexanoate of Ni(II) decompose to oxide (NiO) with intermediate formation of basic carbonate, $NiCO_3.Ni(OH)_2$, at 665 K. The most probable thermal decomposition Scheme can be shown as below:

$$Ni_2(cap)_4 \xrightarrow{350-540K} NiCO_3.Ni(OH)_2$$
$$\xrightarrow{>770K} NiO$$
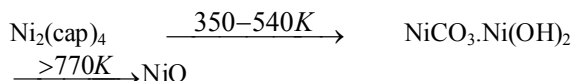
The DTA curve for Ni(II)-hexanoate displays two spaced endothermic and exothermic peaks, respectively at 375 and 550 K. The inflexion points at 375 and 550 K can be attributed to the loss water molecules. The exothermic signal at 665 K can be attributed to the decomposition reaction of the intermediate formed: $NiCO_3.Cu(OH)_2$, involving the loss of $CO_2$ and hydroxyl group with simultaneous formation of NiO.

The previous studies showed an increase in the use of non-isothermal TG data to the calculation of

rate-dependent parameters of solid-state decomposition has occurred, and several equations [19-26] have been employed for such purpose. Many authors [19-23] have discussed the advantages of the non-isothermal methods in comparison with the isothermal ones. The rate of a decomposition process can be described as the product of two separate functions of temperature and conversion rate [20]:

$$d\alpha/dt = k(T)f(\alpha) \qquad (1)$$

Where $\alpha$ is the fraction decomposed at time t, k(T) is the temperature dependent function and f($\alpha$) is the conversion function dependent on the mechanism of decomposition. It has been established that the temperature dependent function k(T) is of the Arrhenius type and can be considered as the rate constant k.

$$k = A\,e^{-E*/RT} \qquad (2)$$

Where, R is the gas constant in (Jmol$^{-1}$K$^{-1}$). Substituting equation (2) into equation (1), we get,

$$d\alpha/dT = (A/\varphi\,e^{-E*/RT})f(\alpha)$$

Where $\varphi$ is the linear heating rate dT/dt. On integration and approximation, this equation can be obtained in the following form

$$\ln g(\alpha) = -E*/RT + \ln[AR/\varphi E*]$$

Where g($\alpha$) is a function of $\alpha$ dependent on the reaction mechanism. Several techniques have been used for the evaluation of temperature integral. Most commonly used methods for this purpose are the differential method of Freeman and Carroll [19] integral method of Coat and Redfern [21] and the approximation method of Horowitz and Metzger [24]. The thermodynamic parameters obtained for the nickel hexanoate complex are summarized in Table 3, in terms of stability ranges, peak temperatures and values of kinetic parameters.

The Coats-Redfern equation, which is a typical integral method, can be represented as:

$$\int_0^\infty d\alpha/(1-\alpha)^n = (A/\varphi)\int_{T1}^{T2} e^{-E*/RT}\,dT$$

For convenience of integration the lower limit $T_1$ is usually taken as zero. This equation on integration gives;

$$Ln[-\ln(1-\alpha)/T^2] = -E*/RT + \ln[AR/\varphi E*]$$

A plot of left-hand side (LHS) against 1/T was drawn. $E*$ is the energy of activation in kJ mol$^{-1}$ and calculated from the slop and A in (s$^{-1}$) from the intercept value. The entropy of activation $\Delta S*$ in (JK$^{-1}$mol$^{-1}$) was calculated by using the equation:

$$\Delta S* = R\,\ln(Ah/k_B T_s) \qquad (3)$$

where $k_B$ is the Boltzmann constant, h is the Plank's constant and $T_s$ is the DTG peak temperature [27].

The Horowitz-Metzger equation is a good illustration of the approximation methods. These authors derived the relation:

$$\log[\{1-(1-\alpha)^{1-n}\}/(1-n)] = E*\theta/2.303RT_s^2 \quad \text{for } n\neq1 \quad (4)$$

Where $\theta = T - T_s$ , $w_\gamma = w_\alpha - w$, $w_\alpha$ = mass loss at the completion of the reaction; w = mass loss up to time t. The plot of $\log[\log(w_\alpha / w_\gamma)]$ vs $\theta$ was drawn and found to be linear from the slope of which $E^*$ was calculated. The pre-exponential factor, A, was calculated from the equation:

$$E^* /RT_s^2 = A/[ \varphi \exp(-E^*/RT_s)]$$

The entropy of activation, $\Delta S^*$, was calculated from equation 3. The enthalpy of activation, $\Delta H^*$, and Gibbs free energy, $\Delta G^*$, were calculated from $\Delta H^* = E^* - RT$ and $\Delta G^* = \Delta H^* - T \Delta S^*$, respectively.

**Table 3:** Kinetic parameters of the studied nickel hexanoate complex from Coats-Redfern (CR) and Horowitz-Metzger (HM)

| Parameters | E/kJmol$^{-1}$ | Z/s$^{-1}$ | $\Delta$S/Jmol$^{-1}$K$^{-1}$ | $\Delta$H/kJmol$^{-1}$ | $\Delta$G/kJmol$^{-1}$ | r |
|---|---|---|---|---|---|---|
| Horowitz-Metzer | 250 | 3.20E+21 | 162 | 245 | 155 | 0.99 |
| Coats-Redfen | 226 | 1.30E+19 | 116 | 222 | 160 | 0.97 |

From the point of view of TG analysis, the most important and reliable kinetic parameter is the activation energy, which can be related with the thermal stability of the compounds and, in some cases, with some IR data. As can be verified by inspection of Table 3 data, the nickel compound is the one with the higher value of $E_a$, suggesting a stronger metal-to-ligand interaction for this compound. Since Ni(II) exhibits a [Ar] $3d^8$ configuration, it is possible to suppose that the interaction with the ligand molecules has promoted a higher stabilization to this cation. Significantly, the Ni(II) complex is the only one to exhibits a positive $\Delta S$ for the thermal degradation process. This fact is probably related with the fact that this compound exhibits the higher $\Delta H$ value. We mean, if it is most difficult to remove the ligands from this compound, the degree of disorder introduced into the system by such process could be positive. In this kind of process it is always necessary to take into account that under heating a solid (the compound) is producing a new solid and a gaseous product. So, the $\Delta S$ value is for this "large system", and not only to the main decomposition process product. Hence, the overall $\Delta S$ value can be positive, as consequence of the entropy changes in the gaseous and solid products (in this last case, the formation of a new crystalline lattice) [28]. X-ray powder diffraction study of nickel hexanoate complex was carried in order to obtain an idea about the lattice dynamics of the compound. The obtained X-ray powder diffraction patterns exhibit a diffraction peak in the range 11-13º. On the basis of above physiochemical data in conjunction with consideration we can suggest the pentadentate geometry Fig. 1.
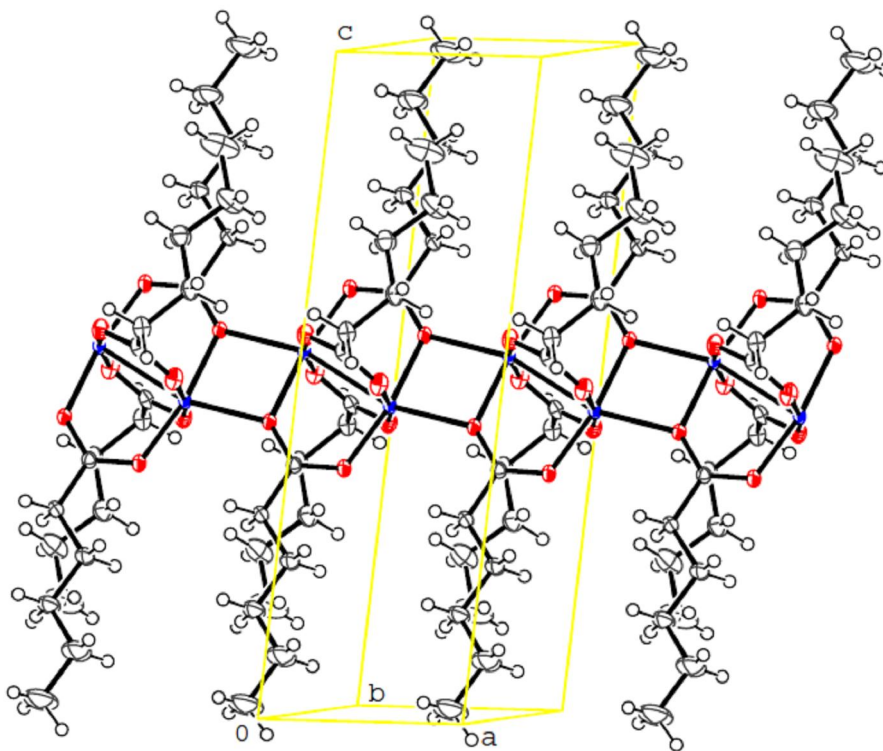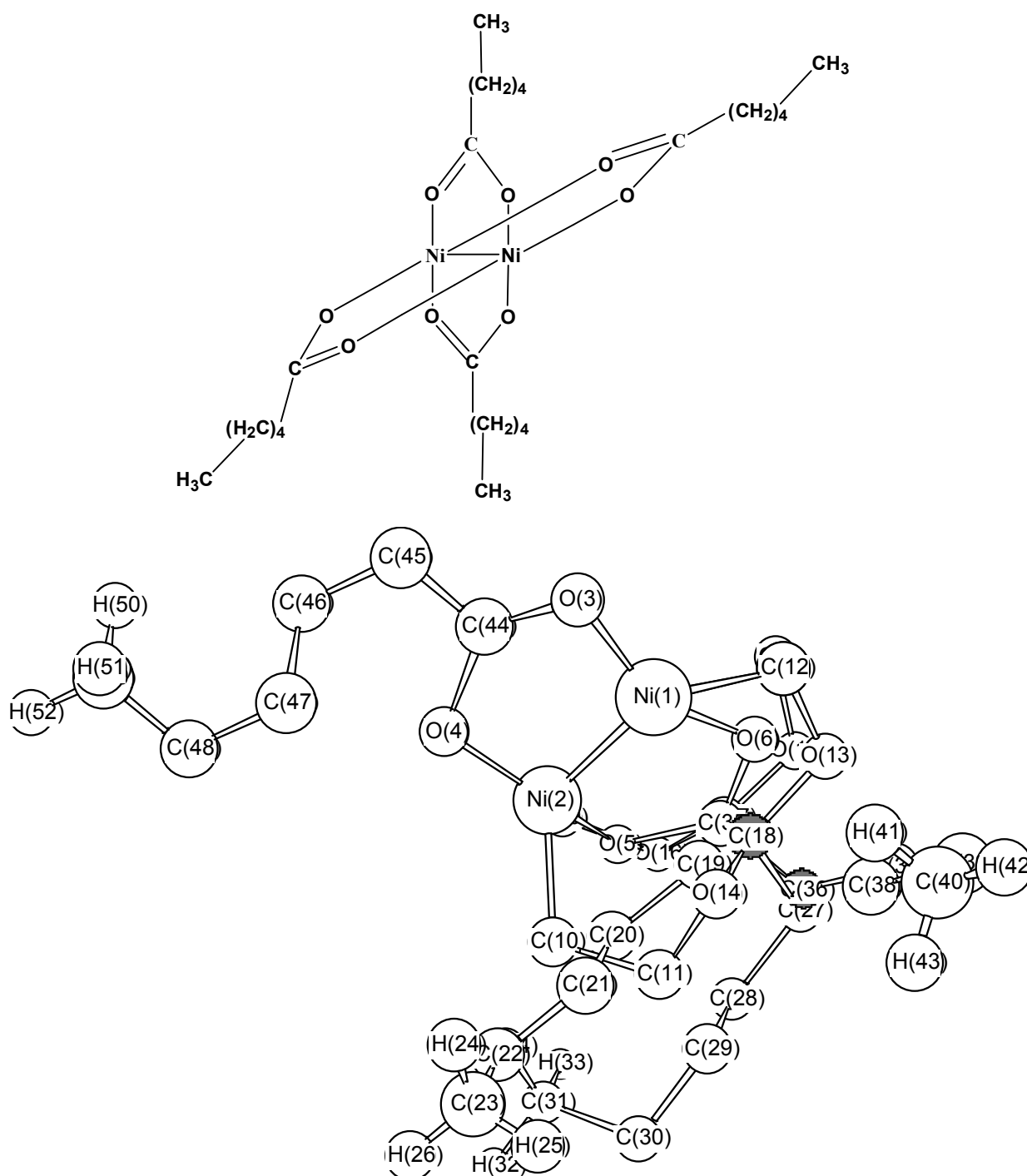
**Fig. 1**: Suggested structure of nickel (II) hexanoate complex

Molecular modeling had been successfully used to detect three dimensional arrangements of atoms in free hexanoic acid ligand and its nickel (II) complex. The bond lengths and bond angles values of the chelation complex were summarized and refereed in Table 4 and Fig. 1. This calculation for $Ni_2(cap)_4$ complex was obtained by using the commercial available molecular modeling software Chem Office Ultra–7. These statistical data have a good agreement with Fig. 1 confirmed the place of coordination towards cobalt(II) ions.

**Table 4:** The values of bond lengths and bond angles of hexanoic acid and its nickel complex

| Atoms | Actual | Optimal |
|---|---|---|
| C(1)-C(2) | 1.509 | 1.509 |
| C(1)-O(18) | 1.208 | 1.208 |
| C(1)-O(19) | 1.338 | 1.338 |
| C(2)-C(5) | 1.523 | 1.523 |
| C(2)-H(3) | 1.113 | 1.113 |
| C(2)-H(4) | 1.113 | 1.113 |
| C(5)-C(8) | 1.523 | 1.523 |
| C(5)-H(6) | 1.113 | 1.113 |
| C(5)-H(7) | 1.113 | 1.113 |
| C(8)-C(11) | 1.523 | 1.523 |
| C(8)-H(9) | 1.113 | 1.113 |
| C(8)-H(10) | 1.113 | 1.113 |
| C(11)-C(14) | 1.523 | 1.523 |
| C(11)-H(12) | 1.113 | 1.113 |
| C(11)-H(13) | 1.113 | 1.113 |
| C(14)-H(15) | 1.113 | 1.113 |
| C(14)-H(16) | 1.113 | 1.113 |
| C(14)-H(17) | 1.113 | 1.113 |
| O(19)-H(20) | 0.972 | 0.972 |
| C(2)-C(1)-O(18) | 122.5 | 122.5 |
| C(2)-C(1)-O(19) | 107.099 | 107.1 |
| O(18)-C(1)-O(19) | 122.002 | 122 |
| C(1)-C(2)-C(5) | 109.998 | 110 |
| C(1)-C(2)-H(3) | 108.8 | 108.8 |
| C(1)-C(2)-H(4) | 108.8 | 108.8 |
| H(3)-C(2)-C(5) | 109.409 | 109.41 |
| H(3)-C(2)-H(4) | 110.411 | 109.4 |
| H(4)-C(2)-C(5) | 109.409 | 109.41 |
| C(2)-C(5)-C(8) | 109.5 | 109.5 |
| C(2)-C(5)-H(6) | 109.411 | 109.41 |
| C(2)-C(5)-H(7) | 109.411 | 109.41 |
| H(6)-C(5)-C(8) | 109.409 | 109.41 |
| H(6)-C(5)-H(7) | 109.687 | 109.4 |
| H(7)-C(5)-C(8) | 109.409 | 109.41 |
| C(5)-C(8)-C(11) | 109.5 | 109.5 |
| C(5)-C(8)-H(9) | 109.409 | 109.41 |
| C(5)-C(8)-H(10) | 109.411 | 109.41 |
| H(9)-C(8)-C(11) | 109.411 | 109.41 |
| H(9)-C(8)-H(10) | 109.689 | 109.4 |
| H(10)-C(8)-C(11) | 109.409 | 109.41 |
| C(8)-C(11)-C(14) | 109.498 | 109.5 |
| C(8)-C(11)-H(12) | 109.409 | 109.41 |
| C(8)-C(11)-H(13) | 109.411 | 109.41 |
| H(12)-C(11)-C(14) | 109.409 | 109.41 |
| H(12)-C(11)-H(13) | 109.69 | 109.4 |
| H(13)-C(11)-C(14) | 109.409 | 109.41 |
| C(11)-C(14)-H(15) | 109.998 | 110 |
| C(11)-C(14)-H(16) | 110 | 110 |
| C(11)-C(14)-H(17) | 110 | 110 |
| H(15)-C(14)-H(16) | 108.998 | 109 |
| H(15)-C(14)-H(17) | 109.002 | 109 |
| H(16)-C(14)-H(17) | 108.811 | 109 |
| C(1)-O(19)-H(20) | 106.099 | 106.1 |
| Ni(1)-Ni(2) | 2.3 | |
| Ni(1)-O(3) | 1.79 | |
| Ni(1)-O(6) | 1.79 | |
| Ni(1)-C(7) | 1.92 | |
| Ni(1)-C(12) | 1.92 | |
| Ni(2)-O(4) | 1.79 | |
| Ni(2)-O(5) | 1.79 | |
| Ni(2)-C(9) | 1.92 | |
| Ni(2)-C(10) | 1.92 | |
| O(3)-C(44) | 1.355 | 1.355 |
| O(4)-C(44) | 1.694 | 1.421 |
| O(5)-C(35) | 1.664 | 1.421 |
| O(6)-C(35) | 1.355 | 1.355 |
| C(7)-C(8) | 1.514 | 1.514 |
| C(7)-H(95) | 1.113 | 1.113 |
| C(7)-H(96) | 1.113 | 1.113 |
| C(8)-O(15) | 1.402 | 1.402 |
| C(8)-H(87) | 1.111 | 1.111 |
| C(8)-H(88) | 1.111 | 1.111 |
| C(9)-O(16) | 1.402 | 1.402 |
| C(9)-H(91) | 1.111 | 1.111 |
| C(9)-H(92) | 1.111 | 1.111 |
| C(10)-C(11) | 1.514 | 1.514 |
| C(10)-H(89) | 1.113 | 1.113 |
| C(10)-H(90) | 1.113 | 1.113 |
| C(11)-O(14) | 1.402 | 1.402 |
| C(11)-H(85) | 1.111 | 1.111 |
| C(11)-H(86) | 1.111 | 1.111 |
| C(12)-O(13) | 1.402 | 1.402 |
| C(12)-H(93) | 1.111 | 1.111 |
| C(12)-H(94) | 1.111 | 1.111 |
| O(13)-C(18) | 1.502 | 1.355 |
| O(14)-C(18) | 1.355 | 1.355 |
| O(15)-C(17) | 1.355 | 1.355 |
| O(16)-C(17) | 1.353 | 1.355 |
| C(17)-C(19) | 1.497 | 1.497 |
| C(18)-C(27) | 1.497 | 1.497 |
| C(19)-C(20) | 1.523 | 1.523 |
| C(19)-H(83) | 1.113 | 1.113 |
| C(19)-H(84) | 1.113 | 1.113 |
| C(20)-C(21) | 1.523 | 1.523 |
| C(20)-H(73) | 1.113 | 1.113 |
| C(20)-H(74) | 1.113 | 1.113 |
| C(21)-C(22) | 1.523 | 1.523 |
| C(21)-H(71) | 1.113 | 1.113 |
| C(21)-H(72) | 1.113 | 1.113 |
| C(22)-C(23) | 1.523 | 1.523 |
| C(22)-H(69) | 1.113 | 1.113 |
| C(22)-H(70) | 1.113 | 1.113 |
| C(23)-H(24) | 1.113 | 1.113 |
| C(23)-H(25) | 1.113 | 1.113 |
| C(23)-H(26) | 1.113 | 1.113 |
| C(27)-C(28) | 1.523 | 1.523 |
| C(27)-H(81) | 1.113 | 1.113 |
| C(27)-H(82) | 1.113 | 1.113 |
| C(28)-C(29) | 1.523 | 1.523 |
| C(28)-H(67) | 1.113 | 1.113 |
| C(28)-H(68) | 1.113 | 1.113 |
| C(29)-C(30) | 1.523 | 1.523 |
| C(29)-H(65) | 1.113 | 1.113 |
| C(29)-H(66) | 1.113 | 1.113 |
| C(30)-C(31) | 1.523 | 1.523 |

| | | | | | |
|---|---|---|---|---|---|
| C(30)-H(63) | 1.113 | 1.113 | Ni(2)-O(5)-C(35) | 87.692 | |
| C(30)-H(64) | 1.113 | 1.113 | Ni(1)-O(6)-C(35) | 104.499 | |
| C(31)-H(32) | 1.113 | 1.113 | Ni(1)-C(7)-C(8) | 109.468 | |
| C(31)-H(33) | 1.113 | 1.113 | Ni(1)-C(7)-H(95) | 109.474 | |
| C(31)-H(34) | 1.113 | 1.113 | Ni(1)-C(7)-H(96) | 109.468 | |
| C(35)-C(36) | 1.497 | 1.497 | C(8)-C(7)-H(95) | 109.409 | 109.41 |
| C(36)-C(37) | 1.523 | 1.523 | C(8)-C(7)-H(96) | 109.409 | 109.41 |
| C(36)-H(79) | 1.113 | 1.113 | H(95)-C(7)-H(96) | 109.596 | 109.4 |
| C(36)-H(80) | 1.113 | 1.113 | C(7)-C(8)-O(15) | 107.398 | 107.4 |
| C(37)-C(38) | 1.523 | 1.523 | C(7)-C(8)-H(87) | 109.409 | 109.41 |
| C(37)-H(75) | 1.113 | 1.113 | C(7)-C(8)-H(88) | 109.411 | 109.41 |
| C(37)-H(76) | 1.113 | 1.113 | O(15)-C(8)-H(87) | 106.697 | 106.7 |
| C(38)-C(39) | 1.523 | 1.523 | O(15)-C(8)-H(88) | 106.704 | 106.7 |
| C(38)-H(61) | 1.113 | 1.113 | H(87)-C(8)-H(88) | 116.784 | 109.4 |
| C(38)-H(62) | 1.113 | 1.113 | Ni(2)-C(9)-O(16) | 109.47 | |
| C(39)-C(40) | 1.523 | 1.523 | Ni(2)-C(9)-H(91) | 109.468 | |
| C(39)-H(59) | 1.113 | 1.113 | Ni(2)-C(9)-H(92) | 109.472 | |
| C(39)-H(60) | 1.113 | 1.113 | O(16)-C(9)-H(91) | 106.702 | 106.7 |
| C(40)-H(41) | 1.113 | 1.113 | O(16)-C(9)-H(92) | 106.702 | 106.7 |
| C(40)-H(42) | 1.113 | 1.113 | H(91)-C(9)-H(92) | 114.866 | 109.4 |
| C(40)-H(43) | 1.113 | 1.113 | Ni(2)-C(10)-C(11) | 109.47 | |
| C(44)-C(45) | 1.497 | 1.497 | Ni(2)-C(10)-H(89) | 109.47 | |
| C(45)-C(46) | 1.523 | 1.523 | Ni(2)-C(10)-H(90) | 109.47 | |
| C(45)-H(77) | 1.113 | 1.113 | C(11)-C(10)-H(89) | 109.412 | 109.41 |
| C(45)-H(78) | 1.113 | 1.113 | C(11)-C(10)-H(90) | 109.407 | 109.41 |
| C(46)-C(47) | 1.523 | 1.523 | H(89)-C(10)-H(90) | 109.594 | 109.4 |
| C(46)-H(57) | 1.113 | 1.113 | C(10)-C(11)-O(14) | 107.398 | 107.4 |
| C(46)-H(58) | 1.113 | 1.113 | C(10)-C(11)-H(85) | 109.409 | 109.41 |
| C(47)-C(48) | 1.523 | 1.523 | C(10)-C(11)-H(86) | 109.409 | 109.41 |
| C(47)-H(55) | 1.113 | 1.113 | O(14)-C(11)-H(85) | 106.697 | 106.7 |
| C(47)-H(56) | 1.113 | 1.113 | O(14)-C(11)-H(86) | 106.699 | 106.7 |
| C(48)-C(49) | 1.523 | 1.523 | H(85)-C(11)-H(86) | 116.789 | 109.4 |
| C(48)-H(53) | 1.113 | 1.113 | Ni(1)-C(12)-O(13) | 109.472 | |
| C(48)-H(54) | 1.113 | 1.113 | Ni(1)-C(12)-H(93) | 109.474 | |
| C(49)-H(50) | 1.113 | 1.113 | Ni(1)-C(12)-H(94) | 109.47 | |
| C(49)-H(51) | 1.113 | 1.113 | O(13)-C(12)-H(93) | 106.7 | 106.7 |
| C(49)-H(52) | 1.113 | 1.113 | O(13)-C(12)-H(94) | 106.697 | 106.7 |
| Ni(2)-Ni(1)-O(3) | 104.503 | | H(93)-C(12)-H(94) | 114.868 | 109.4 |
| Ni(2)-Ni(1)-O(6) | 90 | | C(12)-O(13)-C(18) | 112.035 | 110.8 |
| Ni(2)-Ni(1)-C(7) | 119.998 | | C(11)-O(14)-C(18) | 110.799 | 110.8 |
| Ni(2)-Ni(1)-C(12) | 119.998 | | C(8)-O(15)-C(17) | 110.799 | 110.8 |
| O(3)-Ni(1)-O(6) | 149.999 | | C(9)-O(16)-C(17) | 110.608 | 110.8 |
| O(3)-Ni(1)-C(7) | 120 | | O(15)-C(17)-O(16) | 120.241 | |
| O(3)-Ni(1)-C(12) | 120 | | O(15)-C(17)-C(19) | 133.047 | 120 |
| O(6)-Ni(1)-C(7) | 33.32 | | O(16)-C(17)-C(19) | 106.707 | 120 |
| O(6)-Ni(1)-C(12) | 33.32 | | O(13)-C(18)-O(14) | 124.245 | |
| C(7)-Ni(1)-C(12) | 0 | | O(13)-C(18)-C(27) | 103.663 | 120 |
| Ni(1)-Ni(2)-O(4) | 89.997 | | O(14)-C(18)-C(27) | 103.667 | 120 |
| Ni(1)-Ni(2)-O(5) | 104.501 | | C(17)-C(19)-C(20) | 109.5 | 109.5 |
| Ni(1)-Ni(2)-C(9) | 120.001 | | C(17)-C(19)-H(83) | 109.407 | 109.41 |
| Ni(1)-Ni(2)-C(10) | 120.001 | | C(17)-C(19)-H(84) | 109.411 | 109.41 |
| O(4)-Ni(2)-O(5) | 149.999 | | C(20)-C(19)-H(83) | 109.411 | 109.41 |
| O(4)-Ni(2)-C(9) | 120.001 | | C(20)-C(19)-H(84) | 109.409 | 109.41 |
| O(4)-Ni(2)-C(10) | 119.998 | | H(83)-C(19)-H(84) | 109.69 | 109.4 |
| O(5)-Ni(2)-C(9) | 30.204 | | C(19)-C(20)-C(21) | 109.5 | 109.5 |
| O(5)-Ni(2)-C(10) | 75.398 | | C(19)-C(20)-H(73) | 109.409 | 109.41 |
| C(9)-Ni(2)-C(10) | 90.002 | | C(19)-C(20)-H(74) | 109.409 | 109.41 |
| Ni(1)-O(3)-C(44) | 104.499 | | C(21)-C(20)-H(73) | 109.409 | 109.41 |
| Ni(2)-O(4)-C(44) | 110.329 | | C(21)-C(20)-H(74) | 109.412 | 109.41 |

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|---|---|---|---|---|---|---|
| H(73)-C(20)-H(74) | 109.689 | 109.4 | C(36)-C(37)-H(75) | 109.409 | 109.41 |
| C(20)-C(21)-C(22) | 109.498 | 109.5 | C(36)-C(37)-H(76) | 109.407 | 109.41 |
| C(20)-C(21)-H(71) | 109.405 | 109.41 | C(38)-C(37)-H(75) | 109.411 | 109.41 |
| C(20)-C(21)-H(72) | 109.411 | 109.41 | C(38)-C(37)-H(76) | 109.411 | 109.41 |
| C(22)-C(21)-H(71) | 109.407 | 109.41 | H(75)-C(37)-H(76) | 109.689 | 109.4 |
| C(22)-C(21)-H(72) | 109.412 | 109.41 | C(37)-C(38)-C(39) | 109.498 | 109.5 |
| H(71)-C(21)-H(72) | 109.69 | 109.4 | C(37)-C(38)-H(61) | 109.411 | 109.41 |
| C(21)-C(22)-C(23) | 109.5 | 109.5 | C(37)-C(38)-H(62) | 109.407 | 109.41 |
| C(21)-C(22)-H(69) | 109.407 | 109.41 | C(39)-C(38)-H(61) | 109.412 | 109.41 |
| C(21)-C(22)-H(70) | 109.414 | 109.41 | C(39)-C(38)-H(62) | 109.411 | 109.41 |
| C(23)-C(22)-H(69) | 109.409 | 109.41 | H(61)-C(38)-H(62) | 109.687 | 109.4 |
| C(23)-C(22)-H(70) | 109.409 | 109.41 | C(38)-C(39)-C(40) | 109.498 | 109.5 |
| H(69)-C(22)-H(70) | 109.687 | 109.4 | C(38)-C(39)-H(59) | 109.409 | 109.41 |
| C(22)-C(23)-H(24) | 109.998 | 110 | C(38)-C(39)-H(60) | 109.407 | 109.41 |
| C(22)-C(23)-H(25) | 110 | 110 | C(40)-C(39)-H(59) | 109.412 | 109.41 |
| C(22)-C(23)-H(26) | 110 | 110 | C(40)-C(39)-H(60) | 109.409 | 109.41 |
| H(24)-C(23)-H(25) | 109 | 109 | H(59)-C(39)-H(60) | 109.69 | 109.4 |
| H(24)-C(23)-H(26) | 109.002 | 109 | C(39)-C(40)-H(41) | 109.996 | 110 |
| H(25)-C(23)-H(26) | 108.813 | 109 | C(39)-C(40)-H(42) | 109.998 | 110 |
| C(18)-C(27)-C(28) | 109.498 | 109.5 | C(39)-C(40)-H(43) | 110 | 110 |
| C(18)-C(27)-H(81) | 109.409 | 109.41 | H(41)-C(40)-H(42) | 109.003 | 109 |
| C(18)-C(27)-H(82) | 109.411 | 109.41 | H(41)-C(40)-H(43) | 109.003 | 109 |
| C(28)-C(27)-H(81) | 109.412 | 109.41 | H(42)-C(40)-H(43) | 108.814 | 109 |
| C(28)-C(27)-H(82) | 109.411 | 109.41 | O(3)-C(44)-O(4) | 129.589 | |
| H(81)-C(27)-H(82) | 109.687 | 109.4 | O(3)-C(44)-C(45) | 118.372 | 120 |
| C(27)-C(28)-C(29) | 109.5 | 109.5 | O(4)-C(44)-C(45) | 112.04 | 120 |
| C(27)-C(28)-H(67) | 109.409 | 109.41 | C(44)-C(45)-C(46) | 109.5 | 109.5 |
| C(27)-C(28)-H(68) | 109.412 | 109.41 | C(44)-C(45)-H(77) | 109.405 | 109.41 |
| C(29)-C(28)-H(67) | 109.412 | 109.41 | C(44)-C(45)-H(78) | 109.412 | 109.41 |
| C(29)-C(28)-H(68) | 109.407 | 109.41 | C(46)-C(45)-H(77) | 109.407 | 109.41 |
| H(67)-C(28)-H(68) | 109.687 | 109.4 | C(46)-C(45)-H(78) | 109.409 | 109.41 |
| C(28)-C(29)-C(30) | 109.5 | 109.5 | H(77)-C(45)-H(78) | 109.692 | 109.4 |
| C(28)-C(29)-H(65) | 109.412 | 109.41 | C(45)-C(46)-C(47) | 109.498 | 109.5 |
| C(28)-C(29)-H(66) | 109.407 | 109.41 | C(45)-C(46)-H(57) | 109.411 | 109.41 |
| C(30)-C(29)-H(65) | 109.409 | 109.41 | C(45)-C(46)-H(58) | 109.409 | 109.41 |
| C(30)-C(29)-H(66) | 109.412 | 109.41 | C(47)-C(46)-H(57) | 109.409 | 109.41 |
| H(65)-C(29)-H(66) | 109.687 | 109.4 | C(47)-C(46)-H(58) | 109.411 | 109.41 |
| C(29)-C(30)-C(31) | 109.498 | 109.5 | H(57)-C(46)-H(58) | 109.69 | 109.4 |
| C(29)-C(30)-H(63) | 109.407 | 109.41 | C(46)-C(47)-C(48) | 109.498 | 109.5 |
| C(29)-C(30)-H(64) | 109.407 | 109.41 | C(46)-C(47)-H(55) | 109.409 | 109.41 |
| C(31)-C(30)-H(63) | 109.412 | 109.41 | C(46)-C(47)-H(56) | 109.409 | 109.41 |
| C(31)-C(30)-H(64) | 109.414 | 109.41 | C(48)-C(47)-H(55) | 109.412 | 109.41 |
| H(63)-C(30)-H(64) | 109.687 | 109.4 | C(48)-C(47)-H(56) | 109.412 | 109.41 |
| C(30)-C(31)-H(32) | 110.002 | 110 | H(55)-C(47)-H(56) | 109.689 | 109.4 |
| C(30)-C(31)-H(33) | 110 | 110 | C(47)-C(48)-C(49) | 109.5 | 109.5 |
| C(30)-C(31)-H(34) | 110.003 | 110 | C(47)-C(48)-H(53) | 109.407 | 109.41 |
| H(32)-C(31)-H(33) | 108.998 | 109 | C(47)-C(48)-H(54) | 109.409 | 109.41 |
| H(32)-C(31)-H(34) | 109 | 109 | C(49)-C(48)-H(53) | 109.412 | 109.41 |
| H(33)-C(31)-H(34) | 108.809 | 109 | C(49)-C(48)-H(54) | 109.412 | 109.41 |
| O(5)-C(35)-O(6) | 132.126 | | H(53)-C(48)-H(54) | 109.687 | 109.4 |
| O(5)-C(35)-C(36) | 110.976 | 120 | C(48)-C(49)-H(50) | 109.998 | 110 |
| O(6)-C(35)-C(36) | 110.977 | 120 | C(48)-C(49)-H(51) | 110 | 110 |
| C(35)-C(36)-C(37) | 109.498 | 109.5 | C(48)-C(49)-H(52) | 109.996 | 110 |
| C(35)-C(36)-H(79) | 109.412 | 109.41 | H(50)-C(49)-H(51) | 109.002 | 109 |
| C(35)-C(36)-H(80) | 109.411 | 109.41 | H(50)-C(49)-H(52) | 108.998 | 109 |
| C(37)-C(36)-H(79) | 109.412 | 109.41 | H(51)-C(49)-H(52) | 108.814 | 109 |
| C(37)-C(36)-H(80) | 109.412 | 109.41 | | | |
| H(79)-C(36)-H(80) | 109.685 | 109.4 | | | |
| C(36)-C(37)-C(38) | 109.498 | 109.5 | | | |

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# Studies on liquid agitation fashion, oxygen transfer rate and *E. coli* growth in the triangular prism shaped flexible bioreactor

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**Abstract:** Traditional suspension culture vessels for microorganism and mammalian cell growth at laboratory scale are usually made of rigid materials and possess either a conical body or bottom, such as Erlenmeyer flasks usually made of glass with a conical body and spin tubes usually made of rigid plastic with an inverted conical shaped bottom. The designed conical structure facilitates the liquid inside to generate swirling agitation so as to achieve mixing and aeration when shaken on an orbital shaker. Due to their non-disposability, the glass Erlenmeyer flasks have to be cleaned, packed and sterilized before use, which are time, labor and energy consuming. Whereas the rigid plastic culture vessels, despite possible for single use, are not economically effective and produce more wastes. In this article, we described a triangular prism shaped bioreactor, which was made of medical application film, and studied its fluid motion fashion, oxygen transfer rate and *E. coli* growth in a conventional orbital shaker under different shaking speeds. The results showed that significant higher oxygen transfer efficiencies and *E. coli* growth rates were achieved in the flexible bioreactors at much lower speeds than that in the conventional flasks, indicating the flexible bioreactor is an ideal disposable culture vessel for laboratory scale suspension growth of bacteria.
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## 1. Introduction

The conventional Erlenmeyer flasks and spin tubes are common used suspension culture vessels for microorganism and mammalian cell growth at laboratory scale, which are usually made of rigid materials and possess either a conical body or a conical bottom, such as the Erlenmeyer flasks usually made of glass with a conical body (Sambrook J and Russell D, 2001) and spin tubes usually made of rigid plastic with an inverted conical shaped bottom (Strnad J *et al.*, 2010). The designed conical structure facilitates the liquid inside to generate swirling agitation so as to achieve mixing and aeration when shaken on an orbital shaker (Maier U *et al.*, 2001). Due to the non-disposability of glass materials, the glass flasks have to be cleaned, packed and sterilized before use, which are time, labor and energy consuming. Whereas the rigid plastic culture vessels, despite possible for single use, are not economically effective and produce more wastes. During the past decade, the infusion bags and transfusion blood bags have increasingly replaced the glass bottles and rigid plastic ones in clinical application, thus the medical film is believed to be an ideal material for making disposable flexible bioreactors, which could reduce cost and waste production, thus representing a trend in the bioreactor development future. WAVE bag, as the first flexible bioreactor, was made of plastic film and used mainly for production scale culture of mammalian cells (Okonkowski J *et al*., 2007; Vijay Singh, 1999), though it could be used for small scale suspension culture of microorganism (Mahajan E *et al*., 2010), it was rarely employed as it required complicated aeration system and a specific rocker. Therefore, the further research should be focused on the development of a simpler disposable flexible bioreactor that could be used in small scale culture and utilized the commercially available orbital shaker. Due to the film with feature of flexibility, it will be difficult to make a flexible reactor in conical shape and maintain its independent three-dimensional internal space without air inflation and support. To solve this issue, we created a triangular prism shaped bioreactor with medical application film, and herein for the first time studied its fluid mixing fashion, oxygen transfer rate and *E. coli* growth in an orbital shaker under different shaking speeds.

## 2. Material and Methods
### 2.1. Culture vessels

The flexible bioreactors, named Celloom, were provided by Viri Biotechnology Limited Company (Zhengzhou, China). They were made of a three-layer co-extruded non-polyvinyl chloride plastic film approved by sFDA as the class I medical solution packaging material, which consist of polypropylene (PP) and styrene-ethylene-butene-styrene-copolymer (SEBS) in the inner layer, in the middle layer SEBS and in the outer layer PP, respectively. As shown in the Fig.1, a triangular prism-shaped flexible bioreactor was designed and prepared through folding and fusing methods following the indicated lines by utilizing a heat-sealing machine (Thermocompressor 4V210-08, Meizhidian Electronic Equipment Factory, Wuxi, China). On the upper part of one of the triangle side walls, a hole with a diameter 3cm was punched and a rigid plastic (PP) pipe (diameter 3cm) was sealed onto the surrounding film of the hole. The distal port of the pipe was designed to have a pair of notches and screwed matched with a screw cap (NEST Biotech Co., LTD, Wuxi, China), so that to keep air exchange, even when the cap was tightly screwed up. The triangular prism reactors (short side = 120mm, long side = 200mm) were matched to the wide-necked glass flasks with a nominal volume of 1000ml (Spark, Chengdu Hongqi Glass Works, Sichuan, China, Figure.2). Before use, all the flasks were cleaned and loosely covered with aluminum foil before autoclaving, and the flexible bioreactors were sterilized by gamma irradiation (Dose: 20 kGy, the Irradiation Engineering Research Center, Henan Academy of Science Institute of Isotope, Zhengzhou, China).
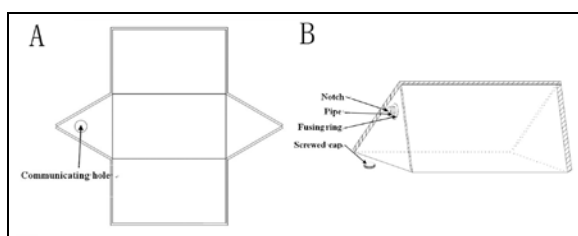

Figure 1. Schematic diagram of the flexible reactor.


Figure 2. The flexible Celloom reactor vs glass flask

## 2.2. Bacterial strain and culture medium

*Escherichia coli* Top 10 (Tiangen biotechnology Co. Ltd, Beijing, China) transformed with plasmid vector pENTR-MCS (Promega, Madison, USA) with kanamycin resistance gene was used for all the experiments of bacteria culture and Luria Bertani (LB) medium was used for *E. coli* growth ,and would be autoclaved at 121°C and 15 psi for 30 minutes before use.

## 2.3. Culture procedure

The seed culture was prepared by growing 1% inoculum overnight in 10ml LB in a 50 ml culture tube at 37°C and 150 revolutions per minute (rpm) in the orbital shaker with an orbit 28mm (THZ-312, Jing Hong Co. Ltd, Shanghai, China). Next day, a total 800 ml of LB medium with 50 mg/L kanamycin was inoculated with 8ml of the overnight culture (1%, v/v) and aliquot 200ml (25% of the vessel volume) into each vessel in duplicate was continuously cultured in the shaker at 37°C under 40rpm. Then the cultures at 60rpm, 80rpm, and 100rpm were performed as above described, respectively. Cultures in the conical flask at a high speed 250rpm were also performed. The conical flasks were fixed in the shaker platform by conventional spring clamps, whereas the Celloom reactor, which possessed a large rectangle bottom and a low center of gravity, were placed directly on the orbital shaker platform tray matted with a silicone gel pad, which is adhesive and enables the Celloom reactor to sit on it steadily during the culture process. The key parameters of bacteria growth, optical density (OD), and dissolved oxygen (DO) in the culture samples were analyzed at 2-hour intervals. The measurements were performed within 5 minutes after the culture samples were taken out.

## 2.4. Measurement of cell density, dissolved oxygen

The optical density of the bacteria culture was measured at a 600 nm wave-length ($OD_{600nm}$) with a Spectrophotometer (Eppendorf AG 22331, Hamburg, Germany) and used to plot the growth curves of *E. coli*. The DO was determined by using a dissolved oxygen meter (JPB-607A, INESA, Shanghai, China).

## 2.5. Determination of oxygen transfer coefficients

Oxygen transfer rates (OTR) in the vessels were determined in duplicate measurements by an applied sodium sulfite ($Na_2SO_3$) method described in detail by Hermann R *et al.* (2001). In brief, tap water was filled into each vessels and saturated with open access to air, and then added with sodium sulfite at an concentration 7.9mg per mg dissolved oxygen ($Na_2SO_3 + \frac{1}{2}O_2 \rightarrow Na_2SO_4$) to reduce the dissolved oxygen level of the water to zero, and then measure the DO changes of the water every minute until it was saturated again.

## 2.6. Observation of medium mixing fashion and foam production

Different configuration of the culture vessels would produce different medium motion type in the shaker, and then influence the efficiency of mixing and aeration. We observed the mixing fashions and extent of foam generation at different agitation speeds in both Celloom reactors and glass flasks so as to find out the optimal shaking speed for the Celloom reactors to achieve adequate mixing and dissolved oxygen without evident foam formation.

**2.7. Statistic analysis**

All the experiments were repeated three times, and the statistic analysis was carried out by SPSS 11.0 (SPSS, Inc., Chicago, Illinois, USA). The data were shown in mean ± standard deviation of the three sets of experiments. $p < 0.05$ was considered as statistically significance.

**3. Results and discussion**

**3.1. Observation of bacteria growth and dissolved oxygen changes**

In the Celloom reactors and the glass flasks the bacteria growth both showed typical bacterial growth curves (Gupta A and Rao G, 2003) and the maximum OD value was higher as the speed increased (McDaniel LE and Bailey EG, 1969). But the peak OD in Celloom reactors were significant higher at any agitation speeds below 100rpm ($p < 0.01$) than that in conical flasks, and at speed more than 80rpm was compatible with or higher than that in conical flasks at 250rpm (5.2 or 5.8 vs. 5.6). At speeds below 100rpm, we observed the medium in glass flasks without obvious swirling formed, which is the main way to generate mixing and aeration by increasing the gas-liquid interface, it was inferred that a limited supply of oxygen and inadequate mixing was caused and then led an inadequate bacterial growth with a low level of OD values below 4.
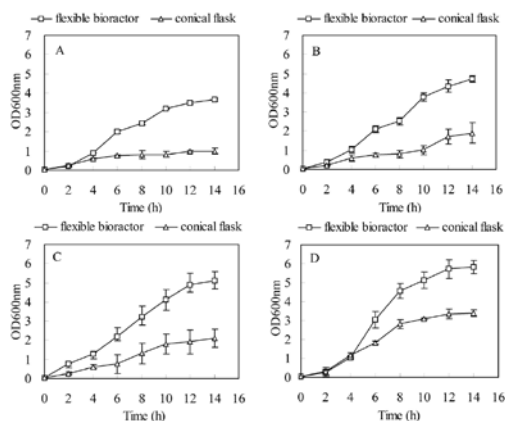


Figure 3. Growth curves of *E. coli* in the two vessels under different speeds. A. 40rpm, B. 60rpm, C. 80rpm, D. 100rpm.

Since dissolved oxygen was a key factor for bacteria growth (Losen M *et al.*, 2004), it was measured in the meantime. As shown in Figure.4, the profiles of DO in both of the two vessels were exhibited similar "U" shape curves, The start point was a DO concentration about 6-7 mg/l, then showed a sharply decrease to a lower level, even zero-level, which was caused by oxygen consumption of bacteria growth with an increasing rate in the medium, and finally went up to a higher level which meant the bacterial growth entered into the stationary phase (Namdev PK *et al.*, 1993). Therefore, the DO concentration was a balanced result of oxygen supply by agitation and oxygen consumption by bacteria growth. In comparison of the DO concentrations, the main differences were seen in the stationary phase, at which, the rising rate of DO of the culture in the Celloom bioreactors were a little quicker than that in the flasks, indirectly reflecting a higher aeration rate in the former than that in the latter and explaining the higher bacterial growth in the Celloom.
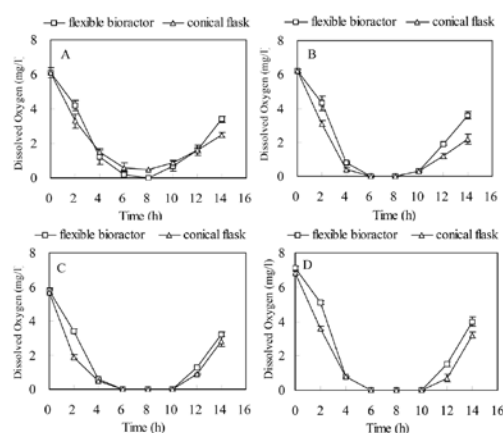


Figure 4. Changes of dissolved oxygen in the culture of the two vessels under different speeds. A. 40rpm, B. 60rpm, C. 80rpm, D. 100rpm.

**3.2 Oxygen transfer rate**

In order to study the oxygen transfer of the Celloom reactor, we performed cell free experiments and measured changes of DO concentration by sulfite sodium method under the shaking speeds of 40rpm, 60rpm, 80rpm, and 100rpm, respectively. The results showed that a much higher oxygen transfer efficiency in Celloom reactor was achieved than that in conical flask ($p < 0.01$, Figure.5). At any of these speeds, the DO concentrations in the flexible reactors increased from zero to the saturation level about 8.2 mg/l in no more than 6 minutes, however it took more than 8 minutes to reach the saturation level in the glass flasks.
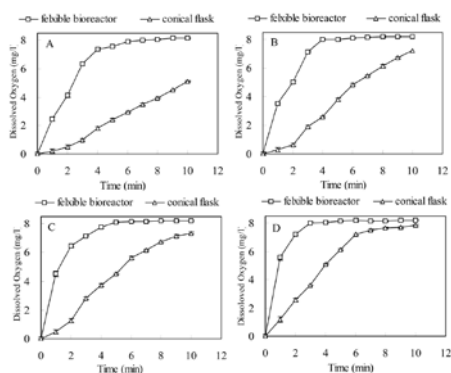
Figure 5. Comparison of oxygen transfer rates.
A. 40rpm, B. 60rpm, C. 80rpm, D. 100rpm.

　　　Though the method of timely sampling coupled with offline measurement couldn't reflect the real time condition of the culture medium, the flask as the control and the Celloom reactors were under the same conditions, and reproducible results were got, so the indirect measurement of these parameters would be good for the comparison of the culture vessels.

**3.3. Observation of liquid mixing fashion and the foam formation**

　　　Due to the specific triangular prism-shaped configuration, different from the conical shape of the glass flasks, the Celloom reactor generated much different mixing fashion from that the glass flasks did even under the same conditions. Its high efficient mixing and oxygen transfer was achieved through a wave involved liquid agitation and aeration mechanism in a conventional orbital shaker. As schematically diagram shown in Figure.6, the liquid movement in the Celloom reactors varied in different directions and resulted four different wave patterns with speed increasing from 40rpm to 100rpm, including stripe-like waves along with long axis, oval shaped waves, stripe-like waves along with short axis, and double circular waves in sequence. Whereas the glass flasks generated mixing and oxygen transfer just through forming swirling to increase gas-liquid interface for air diffusion. At speed below 100rpm, obvious waves were formed in Celloom reactors but no visible swirling was generated in glass flasks yet.
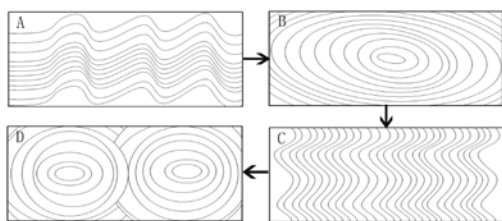


Figure 6. A schematic diagram of liquid mixing fashion and wave patterns. A. 40rpm, B. 60rpm, C. 80rpm, D. 100rpm.

　　　When shaking speed increases, more foam would be formed in the medium, then might reduce some biomass yield and increase risk of contamination if the foam escapes (Junker B, 2007), thus we took a comparative observation on foam production in the two vessels under different agitation speeds to find out the optimal agitation speed for generating adequate mixing without evident foam formation. Figure.7 showed almost no foam were generated in the conical flasks below 100rpm, however, a small amount of foam was observed at 80rpm in Celloom reactors; at 100rpm, much more foam was generated in Celloom reactors than that in flasks. Considering that the bacteria growth and oxygen transfer at 80rpm in the Celloom reactor was compatible with that in glass flask at 250rpm, and no evident foam was formed, the shaking speed of 80rpm was demonstrated to be the optimal speed for bacteria culture in Celloom reactor.
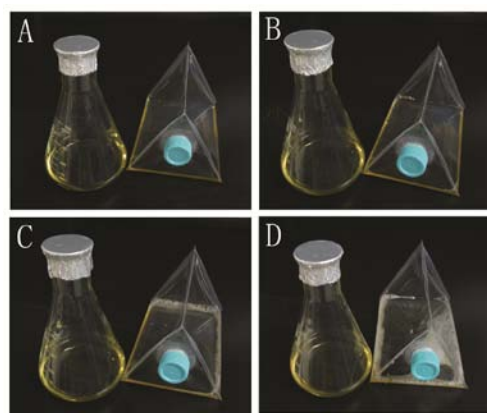


Figure 7. Observation of the foam generation in the two culture vessels at different shaking speeds. A. 40rpm, B. 60rpm, C. 80rpm, D. 100rpm.

**4. Conclusion**

　　　We for the first time developed a novel disposable flexible Celloom reactor, which possessed a unique triangular prism configuration and enabled to keep its three-dimension internal space independently and generated different liquid mixing fashions under different shaking speeds. In comparison with the conventional rigid conical culture vessels, such as the glass flasks, significant higher efficient aeration and *E. coli* growth were obtained in the flexible bioreactors at much low shaking speeds. In addition, the flexible bioreactors also have some other advantages, such as no need of fixation, low cost in production and transportation. In conclusion, the innovative flexible bioreactors are suitable for laboratory scale bacteria culture and hold a promising potential to replace rigid conical culture vessels.

**Competing interests**

The authors declare that they have no competing interests.

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# Land Evaluation and Ranking with Using an Incorporate Vision of Parametric Method and Analytic Hierarchy Process

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**Abstract:** Land use planning as a solution for many of present problems, emphasizes on land evaluation and possible land use types. Land suitability evaluation is a logical basic for making decisions to determine Land use types. The goal of this paper is presenting the combined methodology of parametric method and AHP to rank lands in general aspect. In this method first lands were evaluated by parametric methods and then AHP method was used for general ranking of lands. With using the combined methodology in shahriar, akhtarabad, results such: determining 17 land units and classifying them using second square method and then ranking lands with AHP method are catched, these results show that the land unit number 5 specified the best preference Of selection to itself and after that land units number 10 and 17 were in second rank And land unit number 6 was in third rank subsequently and …. And the last rank was belonged to land unit number 8. In this research the focus was on the physical aspect and proposed that this method extended in other aspects as environmental, social, economic and political factors.

## 1- Introduction

Indiscriminate exploitation of agricultural land and emphasizing the importance of land for human and the world by scientists have led to great attention to land resources (Drohan & Farnham, 2006). Also along with economic development, modification and conversion rate of agricultural land to non-agricultural land has increased over the last 20 years and the necessity for an approach to use land resources for agricultural products is being felt. This approach should be accompanied by determination of the appropriate land use (based on land resources) (Waithaka et. al, 2006). In fact, land suitability assessment estimates the land efficiency for specific uses that are determined in advance and provides a basis for making decisions about land use. Also, it estimates the predicted inputs and outputs. Land suitability deals with two major aspects of land: first, land's physical resources such as soil, topography, climate, etc., second, economic

resources such as farm size, availability of labor, management level, marketing conditions, etc., and the amount of each aspect's interference in the study results depends on quality and/or quantity assessment method. Land quality assessment method has been used in this study. It should be noted that the assessment techniques determine the amount of land suitability based on each product and the product's type is considered in selecting the land.

Decision-making support systems have been making progress in recent years. Many practices have facilitated the decision process (Gomez-Ruiz et. al, 2010). Multi-criteria decision-making issues are a dynamic and complex process between two levels of management and engineering (Duckstein & Opricovic, 1980). The management's level determines goals and selects the final optimum option (Jahanshahloo et. al, 2006). One of the applicable decision-making practices is hierarchical analysis in which various options are compared based on a set of criteria and sub criteria and is classified in a hierarchical structure. At

each level of hierarchy, the criteria are compared in pairs and their relative priority is achieved. The compatibility of paired comparison matrix is a related factor in the hierarchical analysis and the paired comparison matrix should be completed to calculate it (Gomez-Ruiz et. al, 2010).

The purpose of this study is to provide a compound approach of parametric techniques in land assessment and hierarchical analysis in order that the lands will be ranked and the preferences of land selection will be determined from a wide perspective. The study of ecological security and food supply on the one hand and research on the relationship between the land and the crop production on the other hand are matters of concern. Zhang et al have used Remote Sensing techniques in combination with Geographical Information System (Zhang et. al, 2005), in a research. Using this methodology and FAO manual in land assessment has increased the rate and accuracy of land suitability assessment (Zhang et. al, 2003; Chen et. al, 2002).

## 2- Literature review

Foley et al, (2005), studied land uses and emphasized that although modern land use practices have increased materials and goods supply in the short term, it may destroy ecosystems in the long term (Foley et.al, 2005). Thus, the land suitability assessment to determine optimal areas for food production and forest lands is essential. Appropriate solutions to solve complicated issues associated with the overuse of land resources for agricultural production and their management does not come from a single policy and designing an advanced technique to use land resources for agricultural productions appears to be essential. This technique should be accompanied by determination of appropriate land use (based on land resources) (Waithaka et. al, 2006).

After over 30 years of land assessment analysis, progress in the development of this method has been disappointing (Samranpong et. al, 2009). Johnson and Gramb stated that failure in predicting crops production and inability to reflect technological changes and economic climate are due to weakness in land assessment techniques (Johnson & Cramb, 1996). In addition, the systems are not able to provide information on production risk and price (which are crucial and important factors for farmers). For this purpose, product-centric models are used to forecast the production. In Thailand, rice models (Jintrawet, 1995), sugar beet models (Promrit & Jintrawet, 2001) and peanut models (Banterng et. al, 2004), have been used and therefore, the relationship between soil characteristics, climate and crop production should be carefully studied to predict crops production (Olson & Olson, 1986; De La Rosa et. al, 1981).

Mandal et al found relationships between cotton production and agricultural-environmental factors (e.g. soil's physiographic conditions, periods of growth, evaporation perspiration and rainfall) in their study. The FAO's soil quality indicator was used to obtain the amount of product in this study (Mandal et. al, 2005). Since most land units are not suitable for all types of land uses, the amount of land unit's suitability for various uses is specified using land assessment, and different suitability cases are determined (Rossiter, 1995).

Land assessment has several stages and it becomes more complex based on the different requirements of users. In local scale, land assessment is facilitated with GIS. Today, many decision-making systems have been developed for land assessment. Hierarchical analysis technique uses the experts' judgment as an input for criteria and solutions. Today, multi-criteria assessment methods are used to solve three-dimensional problems. Malczewski's method used the combination of Multi-Attribute Utility Theory and GIS (Geographical Information System) for three-dimensional expression of issue and set up a background for many studies (Strager & Rosenberger, 2006; Neaupane & Piantanakulchai, 2006; Ayalew et. al, 2005; Thirumalaivasan et. al, 2003; Tseng et. al 2001; Store & Kangas, 2001; Hoctor et. al, 2000).

Above-mentioned studies deal with different views of assessment. Anticipating areas which are exposed to the risk of contamination (due to agricultural activities) is an example of using Analytic Hierarchy Process (AHP), in three-dimensional problems. AHP calculates the weight of each criterion and the three-dimensional image of the optimal solution is shown by GIS software (Thirumalaivasan et. al, 2003). In another research, Ayalew et al predicted the risk of falling with the combination of Analytic network process (ANP) and logical regression (Ayalew et. al, 2005). Strager and Rosenberger studied the prioritization of land protection and used hierarchical analysis to combine the experts' judgment with the geographic display of soil loss (Strager & Rosenberger, 2006).

In Bahadur Thapa and Murayama's paper a combination method of hierarchical analysis and GIS for agriculture is presented (Rajesh & Yuji, 2008). Studying the suitability of olive plantation in natural areas of Spain is one of the researches which have used the combination of hierarchical analysis and GIS (Olexandr et. al, 2009). Regardless of the functional scope of these papers, all of them are a combination of GIS and hierarchical analysis.

### 3- Methodology

In this study, first land assessment has been done based on predominant products using parametric methods and then the land has been ranked to be selected from a wide perspective using analytical hierarchy analysis. Briefly, next part will discuss the above mentioned methods.

### 3-1- Analytical hierarchy process

Analytical hierarchy process is used in decision-making to rank options based on a huge goal. The basic idea of hierarchical analysis is to sort goals, standards and issues in a hierarchical structure and achieve two goals: obtaining a complete insight of main relationships in the issue and providing a comparison mechanism with the same method at each level (Saaty, 1990). Paired comparison matrices are used in hierarchical analysis to determine the preference in which the decision maker fills the high elements of the diameter using numerical quantity from comparing variables (equal, more, a bit more, much more, so much more, infinitely more). This comparison is converted to numerical quantities (1; 3; De La Rosa et. al, 1981; Duckstein & Opricovic, 1980; Gomez-Ruiz et. al, 2010) based on Likert scale and the numbers between these numerical quantities (2; Chen et. al, 2002; Drohan & Farnham, 2006; Foley et.al, 2005) are used to explain the preferences which lie between the numerical judgment. The elements of triangle below the diameter matrix are completed with reversed judgment values (the principal of mutuality) (Saaty, 1991). The weight of standards is calculated through paired comparison matrix and the specific vector of criteria weight is obtained. Then, paired comparison matrix is completed for options' levels and the main specific vector is calculated and normalized for each matrix. These normalized specific vectors are combined with paired comparison matrix of options and a column is created in a new matrix which is used to determine the final weight of each option. This particular normalized vector and the matrix are multiplied by paired matrix of standards and final ranking of options is obtained. Although the overall process implies algebraic calculations of simple matrix, the compatibility of matrix is notable. It is essential to make sure that the judgment of decision makers' is compatible in hierarchical analysis. There are different mathematical ways to measure the compatibility of paired comparison matrix. The compatibility index should be less than 0.1 (Gomez-Ruiz et. al, 2010), for determination of the compatibility of paired matrix.

### 3-2- Land assessment method

Defining various land productivity types and classifying land according to current and potential land suitability for a particular use is the first step in land assessment in FAO method. Qualitative land suitability assessment method consists of three studying phases as follows: 1- Gathering information about land characteristics 2- Determination of vegetative requirements of land productivity types 3- qualitative land suitability classification. In the third step, land qualities are compared with vegetative requirements of various land productivity types and finally land suitability class is determined using one of the limitation or parametric (Sys et. al, 1991), methods. In this study, land suitability classes are determined using parametric method.

Parametric method in land characteristics assessment includes numerical ranking of the different limitation levels of land characteristics in a numerical scale from maximum (usually 100) to minimum number. If land characteristics are optimum for productivity type, it will be attributed to the maximum number in rating (usually 100). However, if some of land characteristics are undesirable, they'll get less number. Then, the assigned grades will be used to calculate the land index. In this method, at first climate assessment is carried out. Climatic characteristics are divided into four groups: Radiation characteristics, Temperature characteristics, Precipitation characteristics and Air relative humidity. Climate index is calculated using rates of each group and is used in land assessment (Table 1) (Sys et. al, 1991).

*Table 1; Climate index and classification relationship*

| Climate class | Class index | amount of Limitation | Related degree |
|---|---|---|---|
| $S_1$ | 75-100 | No- low limitation | 85-100 |
| S2 | 50-75 | Moderate limitation | 60-85 |
| S3 | 25-50 | High limitation | 40-60 |
| $N_1$ | 12.5-25 | Extremely High limitation (corrigible) | 20-40 |
| $N_2$ | 0-12.5 | Extremely High limitation (Incorrigible) | 0-20 |

Climate and land indexes are calculable with both Storie and Square Root Methods. In Storie method index is obtained using the formula below:

$$I = A \times \frac{B}{100} \times \frac{C}{100} \times \cdots$$

Where "I" is index and "A, B, C…" are specific rates for different characteristics.

In square root method the index is derived from the formula below:

$$I = R_{min} \times \sqrt{\frac{A}{100} \times \frac{B}{100} \times \cdots}$$

Where "I" is index, "$R_{min}$" is the minimum rate and "A, B…" is Other rates which are allotted to different characteristics (except minimum rate).

Suitability classes are defined according to index's values in Table 2.

*Table 2; The amount of indexes for various suitability classes (25)*

| Index | Land Suitability class |
|-------|------------------------|
| 75-100 | $S_1$ : (Very Suitable) |
| 50-75 | $S2$ : (Moderately Suitable) |
| 25-50 | $S3$ : (Marginally Suitable) |
| 0-25 | N : (unsuitable) |

**3-3- The research model and collecting data**

The area which has been studied is 7110 ha wide and located in Akhtarabad (shahriar). The lowest point is at altitude of 1188 meters and the highest part is at altitude of 1340 meters. The purpose of this study is to promote optimum use of lands and process satellite images digitally. And, GIS are used to determine land suitability. During the field survey, 19 profiles have been drilled in the area and the different layers of soil profiles were sampled. Then, soil samples were tested both physically and chemically. Next, using RS, Digital elevation model (DEM) and other available maps of region and studying soil's tests results, soil units were separated and 17 land units were designated in the area. After that, vegetative requirements of productivity types were reviewed and matched with land characteristics. And finally, land suitability classes of each unit of lands were determined using FAO framework and Sys method for different uses. The results of above mentioned method were used as input to GIS software for a schematic display of the results of land assessment with parametric method (land maps). Also, they're used as input for hierarchical analysis technique to rank land from a wide perspective. Figure 1 depicts the research model based on its stages.
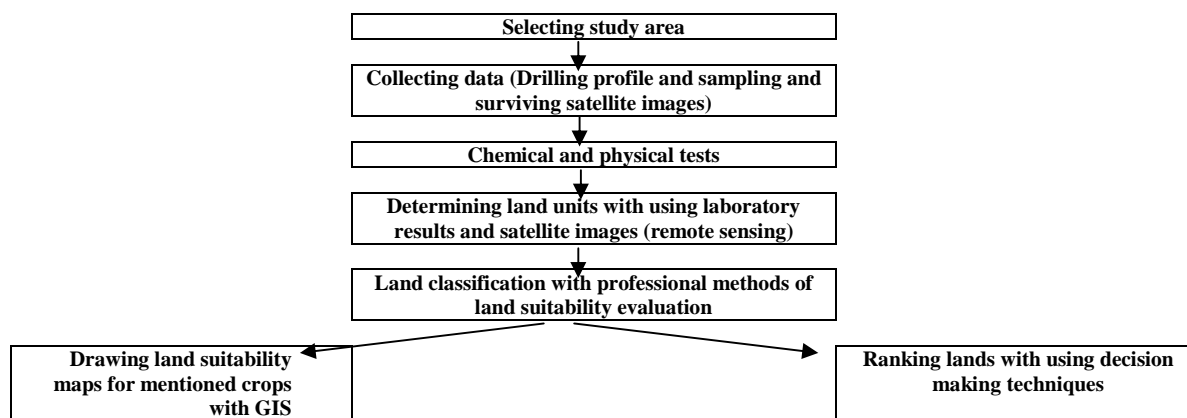


**Figure -1 Research stage**

**4- Finding**

**4-1- Mapping and physical and chemical analysis of soil samples**

After classification and interpretation of satellite images (LANDSAT ETM+), and combination of data from height digital elevation model (DEM), slope maps and soil maps of the area which has been studied, also reviewing the results of physical, chemical and fertility analysis of soil samples, soil unit map were prepared for the area. Soils in this area are placed in Aridisols category. The map of land units was drawn through overlapping slope map and soil unit's map in the area.

following results were obtained through collecting and analyzing laboratory results, data from interpretation

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of satellite images and climatic data and topography maps: 1-the mapping of slope, aspect and height layers of area in GIS 2- soil units and land units mapping 3- land suitability mapping for wheat, barley, canola, corn and cotton 4- ranking lands for cultivation of dominant products in area. The maps mentioned above are represented in Appendix III.

Land index and land suitability classes for one of the products (canola) are presented in Table-3 using both

Storie and square root methods (product's land suitability maps and the results of parametric method for other products are given in Appendix I). Table 4 depicts land suitability classes for all products in research using square root method.

*Table 3; Parametric methods for canola's data*

| Land unit | Storie | Suitability class | Square root | Suitability class | Land unit | Storie | Suitability class | Square root | Suitability class |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 26.76 | S3 | 48.32 | S3 | 11 | 50.74 | S2 | 50.61 | S2 |
| 2 | 25.78 | S3 | 41.27 | S3 | 12 | 27.88 | S3 | 62.5 | S2 |
| 3 | 25.8 | S3 | 33.74 | S3 | 13 | 26.41 | S3 | 48.32 | 3S3 |
| 4 | 25.25 | S3 | 28.49 | S3 | 14 | 25.49 | S3 | 30.52 | S3 |
| 5 | 28.63 | S3 | 65.1 | S2 | 15 | 25.19 | S3 | 59.7 | S2 |
| 6 | 26.83 | S3 | 52.66 | S2 | 16 | 26.95 | S3 | 53.99 | S2 |
| 7 | 26.02 | S3 | 40.22 | S3 | 17 | 27.27 | S3 | 49.8 | S3 |
| 8 | 0.21 | N2 | 0.81 | N2 | 18 | 27.85 | S3 | 62.8 | S2 |
| 9 | 27.51 | S3 | 58.14 | S2 | | | | | |

*Table 4; Matrix of land suitability classes based on the square root method*

| Land unit | wheat | Barley | Corn | Cotton | Canola |
|---|---|---|---|---|---|
| Unit 1 | S2 | S2 | S2 | S2 | S3 |
| Unit 2 | S3 | S3 | S3 | S2 | S3 |
| Unit 3 | S3 | S3 | S3 | S2 | S3 |
| Unit 4 | S3 | S2 | S3 | S3 | S3 |
| Unit 5 | S2 | S2 | S2 | S2 | S2 |
| Unit 6 | S2 | S2 | S2 | S3 | S2 |
| Unit 7 | S2 | S3 | S2 | S2 | S3 |
| Unit 8 | N2 | N2 | N2 | N2 | N2 |
| Unit 9 | S2 | S3 | S3 | S2 | S2 |
| Unit 10 | S2 | S2 | S2 | S2 | S2 |
| Unit 11 | S3 | S2 | S2 | S2 | S2 |
| Unit 12 | S2 | S2 | S2 | S2 | S3 |
| Unit 13 | S3 | S3 | S3 | S3 | S3 |
| Unit 14 | S2 | S2 | S2 | S3 | S2 |
| Unit 15 | S3 | S2 | S2 | S2 | S2 |
| Unit 16 | S2 | S3 | S3 | S3 | S3 |
| Unit 17 | S2 | S2 | S2 | S2 | S2 |

**4-2- Ranking land suitability classes using hierarchical decision-making method**

Considering what mentioned previously, hierarchical tree is made as figure-2 so that crops are criteria and options are land divisions which are obtained through agricultural specialized techniques. Regarding the qualitative assessment of lands and the lack of social

and economic factors, in this structure the same preference will be considered for different products. On the other hand, based on land classification with parametric method and using Likert, priority grades are assigned to classes. For example, there are two land units: A and B. If these two units have the same class, the priority grade of units compared with each other will be 1. And, if A is one class different from

B, the priority grade of A compared with B will be 3. If the difference is two classes, the priority grade of A compared with B will be 5. And, if there is three classes' difference, the priority grade will be 7.

Finally, if it reaches four classes' differences, the priority grade will be 9.
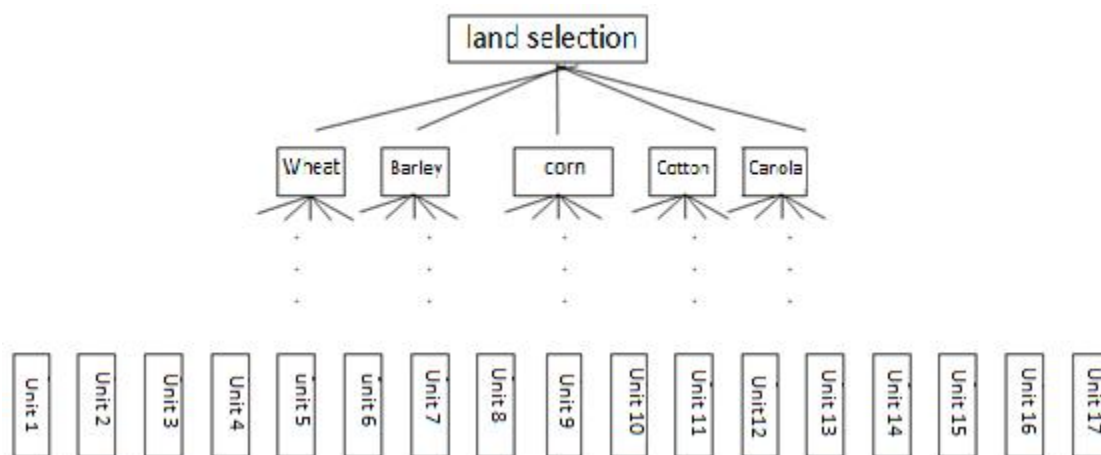


**Figure 2; AHP Tree for Selecting Lands**

In these modes, the preference of B land unit to A land unit will be 1, 1.3, 1.5, 1.7, 1.9 respectively. The method that has been used in forming paired comparison matrices will adjust all of matrices and the amount of their adjustment will be complete. Products are of equal weight in decision tree due to a lack of social and economic factors, so it is no need to form a paired comparison matrices and weight of each of them is 0.2. Tables of the lands paired comparison matrices are represented in Appendix II based on the criteria. Then, land selection preferences are identified using EXCEL software (Table 5).

*Table 5; Ranking lands with hierarchical method*

| Final weight | Lands ranking | Land unit |
|---|---|---|
| 0.0707259 | 6 | 1 |
| 0.0407683 | 10 | 2 |
| 0.0407683 | 10 | 3 |
| 0.0394987 | 11 | 4 |
| 0.0826423 | 1 | 5 |
| 0.0725989 | 3 | 6 |
| 0.0619521 | 9 | 7 |
| 0.0099980 | 14 | 8 |
| 0.0629787 | 8 | 9 |
| 0.0823444 | 2 | 10 |
| 0.0717525 | 5 | 11 |
| 0.0704281 | 7 | 12 |
| 0.0276709 | 13 | 13 |
| 0.0723010 | 4 | 14 |
| 0.0717525 | 5 | 15 |
| 0.0394751 | 12 | 16 |
| 0.0823444 | 2 | 17 |

**5- Discussion and conclusion**

Making decision is a dynamic process that involves two levels of management and engineering and is used for the best options selection among those that are

possible. In these issues, many criteria affect options selection ((Duckstein & Opricovic, 1980)). There are combination practices of decision-making methods. Hierarchical analysis method calculates the weight of each criterion. Then, GIS software displays three-dimensional picture of optimal solution (Thirumalaivasan et. al, 2003).

Unlike this study, the output of parametric method is input for GIS - in this research- to draw the maps mentioned above. And, it is also input for hierarchical analysis method. Ayalew et al also predicted the risk of falling using combination of ANP and logical regression (Ayalew et. al, 2005). AHP is also used in this research to rank agricultural land's selection and is a different use of decision-making techniques and farming professional methods. Strager and Rosenberger emphasized on determination of the priority of areas for land conservation and used group hierarchical analysis (Strager & Rosenberger, 2006). However, AHP is used for determination of the priority of land selection in this study. Regardless of type of product, providing a solution for decision makers to select lands with maximum potential in productivity is the main advantage of this paper. The study in this paper is a new combination of two fields: agriculture and resource management that shows which land unit is preferred to be invested in.

This paper can help decision makers with management level. And, using decision-making methods ranks designated land suitability classes for different crops in engineering level from a wide perspective targeting the best land selection for cultivation. And, it defines the part of land that is more desirable for various crops.

Accordingly, best rank is assigned to the $5^{th}$ land unit and this land unit is the first option for cultivating various crops. After that, $10^{th}$ and $17^{th}$ land units are known the best and the $6^{th}$ land unit comes third …, so that the lowest rank is assigned to the $8^{th}$ land unit (considering special outputs for all of the crops, this land unit has $N_2$ suitability class). Finally, using this method decision-making at high-level management is facilitated and this methodology will link professional knowledge and management level.

Land assessment from both physical and economical perspective is recommended for future studies. Because in this paper only physical aspect is considered and other influential items such as environmental and social factors and also economic and political cases are not involved. On the other hand, according to environmental changes Fuzzy view is recommended to cover the facts in issue better.

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# CHALLENGES OF IRANIAN WOMAN FOR ONLINE SOCIAL INTERACTIONS
## (PERSPECTIVES OF FEMALE ACTIVISTS ON THE INTERNET)

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**Abstract:** Separations and limitations of women on the basis of social attitudes, in the area of information and knowledge, have come to challenge with interactive attitudes. The relations of pc and human beings are increasingly growing. The computers are connecting to each other through local and global networks and wireless technologies. Computer technology provides a vast new opportunity for interaction of human being and machine. The most important point is interaction of human to the human on internet and on line. Iranian women are also active on this Virtual Space and statistics show that they are using all communicational opportunities .These connections on virtual space, will bring out growths and developments of women. There are, of course, some challenges in the virtual space for women. This essay will study challenges and pathologies of social interactions of women in the virtual space. Study method is on the basis of descriptive and methodology is surveying. 102 activist women in the virtual space were chosen and their opinion collected through questioners. Research findings show that there are opportunities and threats on this space for women and in this field enough information and education are necessary.
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**Keywords:** Internet, Virtual space, Social interaction, Women, Threats, Challenges

## 1. Introduction

There are numeral arguments and researches on communication through computer and internet and it is same as emergences of universal mass media in the past decades. There are many researches that show individual and social effects, short and long effects, positive and negative effects and at last superficial or deep effects. While considering historical, social and cultural records of the different societies, it reveals that women have not effective roles. Thus some people confirm crucially that women have not assigned any fundamental rules during agricultural and individual eras. The most important factor, maybe, patrimonial perspectives during this eras-mass culture, of course is another reason because of its patrimonial approach. 21the century, which have brought about knowledge and information era, has created a ground for sexual approaches and has challenged any action for limiting interactive space for presence of women. Thus, skill and knowledge are the basis for playing any role, and we may call it competence. "Communication on the basis of computer "has created a revolution in the process of communication and it will create a new culture .This kind of communication historically is new media and will relatively empower women and other minority groups. It might be an opportunity for reversing traditional roles of power and authority (Weber Max .1991).As a result, we may say that this new communication tool has created a new

opportunity for new presence .This is an opportunity for people to know themselves as they are willing so.

### 1.1. PROBLEM STATEMENT

Expansion of internet has created in itself a new environment which needs theoretical framework in the field of psychology, recognition and communication (Goslin, M, and Morie, J. F., (1996)).The women also have experienced new social presences through internet opportunities. Iranian women who are considerable parts of users-are willing to be present in the virtual space. There are more than 30000 women blogs and bloggers on the internet.Women are also present in social networks. These networks are increasingly progressive, wide spread and common place; therefore it is necessary to investigate its social consequences. The process for women is more complex and considerable. There are new forms of women participations and interactions on the internet unlike the traditional outlooks toward women. Communication is forming on line and is increasingly growing. Therefore, there are needs to study the social and sociological aspects of the phenomena. Technologies of communication and information have facilitated all kinds of connections and removed geographical barriers of availability on one hand and created some anomies and problems, on the other hand. It seems that using internet has caused isolationism of women, and this will threat their day to day interactions. There are some obstacles on the way of availability to the internet by women such as

digital gap, on-availability of computer, lower level of literacy for women, and lacking other related tools and facilities. These limitations will lead to unsuitable presence of women into virtual space. Some behaviors are not suit able for women and will make them humbles. There are some anomies because of non-availability of enough information. Internet crimes have targeted women and are going to abuse them. It is necessary for women to be aware of these risks and anomies, to avoid anomies. To use internet, education and making culture is necessary .there are many insecurities, crimes in the virtual space. The women should be aware of these risks and dangers and crimes. The women will be able to adapt themselves to the positive aspects of this space, through enough education, knowledge and information, and they will also be able to minimize these risks and anomies. This essay is trying to answer following questions:

1) Is there enough social security for women on virtual space?

2) Is there any threat for women privacy through net?

3) Are there any sexual attitudes toward women on net?

4) Will women family relations be in dangers through virtual relations?

## 2.1. THEORETICAL FRAMEWORKS
### 1.2.1. Digital sexual gap:
Using internet is the most important digital sexual gap, since women have the less usage of internet in spite of their positive approaches toward internet. For example only 38% of users in Latin America are women .Whereas this percent in European Union is 25%, Russia 19%, Japan 18% and it is only 4 % in Middle East. The most users on the global level are men, university graduated or other persons who are wealthy. There is a good development in this respect, in Scandinavia and American countries and the sexual gap has been totally decreased (VALKENBURG, et.al. 2006). As primary conference of ministries for global sessions of global informative society (Whang, S.-M. – Chang, G. (2004)) has emphasized on the lists of special limitations on availability of internet for women, on the basis of digital sexual gap:

1) High costs and expenses for availability of internet

2) Limited availability to the new education and skills (lacking information and lack of necessary motivations for universality of communication and information)

3) Shortages of networks

Meanwhile, there is a man image to the internet.

Someone has pointed out other factors such as geographical families and ages of the users, as obstacles. A research show that women are mostly consumers of virtual space and there are in comparison with men, a less production of content (Rheingold, H. (2000)).

## 3.1. BIGLOBALISM PARADIGMS
This paradigm study related, integrated and parallel worlds and pay attention to the multi globalism into these two worlds. The first world has a geographical traits and its political system is based on nation-state, natural, industrial, concrete and a sense of historical oldness. This world is distinguished from the second one. The second worlds traits are as follow: super industrialization, super place and time, non limited civic law based on nation-states, altered and post modern epistemology, synchronized availability, availabilities of new cultural, economic, political spaces which are relatively separated from the first one, but these two are twins and many individual and group interactions are based on the interactions of these two worlds.

We may expect these two aspects of globalizations for women who are active in the virtual space and major parts of their daily communication are on line.

In addition there are some defects for virtual communication as follow:

1) Self-conscious individualism

2) Provisional connections

3) Abnormalities of internet

4) Decrease of real social relations

5) Disorder

These defects may result in problems for personality and feelings of women.

## 4.1. SELF CONSCIOUS INDIVIDUALISM:
We may say evidently that privacy and individuality has expanded and has gotten a most important situation against public sphere. Individuals on internet are able to hide their identities, so they present on a collective scene but will feel that are separated and isolated from others. This trait resulted in strengthening capacity and power of individual and they may act on their most hidden aspects of their personalities. There are no hierarchical of power on internet, so individuality will not be dissolved in the place of connection and as Rheingold, H. says, a person will learn a respectful way of life and independence action on internet. The basis of individual and identity is so changeable that there will not be any collectiveness on the internet. There will be movements on the basis of strengthened individuality in the society. As Shank, P. (2003), is believed that reversed trends all are expressing that individual has empowered and individual norms are

dominating on collective social norms. This cultural plurality has a meaningful relation with expanding of human communication and the most part of it is caused by sharing in virtual space (Shank, P. (2003)).

**5.1. PROVISIONAL CONNECTIONS**

Everything s are provisional on virtual space. There is no guarantee for continued action and activity on line, therefore, there will not by any sense of liability. Precisions are taken on the basis of feelings and excitements of the moments (Kanuka, H., & Anderson, T. (1998)).

**1.5.1. Breaking Norms on Internet:**

Ambiguity of the identity ,lack of face to face communication and lacking of any power hierarchical, internet is a suitable place for breaking norms, values and for moral and belief misuses. Deviations such as second gap, entering into pornographic sites, creating blogfa and including in it on immoral menu are examples (Gunawardena, C., N., & Zittle, F. J. (1997)).

**2.5.1. Decreasing Real Social Relations:**

Virtual space is so much interesting and attractive; so many people who enter into it will forget their time passing on internet. Grant has investigated and showed that more use of internet results in less social communication.

It is impossible to reproduce a sincere and affective social relation on internet (Wendt, Alexander.1999).

**6.1. Disorder and Anarchy**

Any authorization has a risk of being despotic. Omitting power and authority will also create conflict and challenge .It will resulted in anarchism on internet. Anarchistic structures or at least unstructured networks will not allow any hierarchy. Identity is a common trait which connects public and hierarchy and individual will understand itself and other identities through this connection. Therefore, plural and unreal identities will not allow any power hierarchies. There is a huge volume of online information and it has no management, then on line information encountered with anarchical situation.  On line privacy and security are limited and hackers are able to enter into privacy of other life (Grieco, Josheph.1988).

**2. Material and Methods**

Methodology of this research is descriptive and explanative on the basis of survey method. Descriptive method will describe studying phenomena. It will merely contribute to know existing conditions, or decision making. The most part of behavior science and researches are done on the basis of descriptive method.

**1.2. STATISTICAL POPULATION**

Populations are prominent women on blogfa and virtual spaces. Persian blog held a seminar for the most prominent women on blogfa and virtual space on Oct 2008. The title of seminar was: more prominent blogfa writer's women in Persian blogfa area." Data collecting tools of the research is electronic questioner and to evaluate its credit validity views of some scholars have been used. A site in the name of http:/cybawomen.ir has been designed for placing questioners on it.

**2.2. VALIDITY OF MEASURING TOOLS**

Validity as a concept is to answer this questions that how the tools or methods of data collecting will measure them. Correctly the questioner were considered by some scholars, edited and then distributed. This method is called content or rational validity and is used for measuring constituents of measuring tools. 102 questioners were completed, but statistical population was 110.

**3.2. SAMPLING METHOD**

The target sampling was chosen for this research. Target sampling is a non probable sampling method and researcher will chose a special sample on the basis of targets of research. The sample includes subjects who are compatible with special traits and attributes. Any subjects who are not compatible with these criteria are omitted Sampling method is suitable for this research because of presence of women activists on internet. Through this method we could study about women who are much active on internet. Alfa Kronbakh method was used for assurance of durability and permanency. This method is used to measure one sided believes and attitudes. In fact, we want to know the sameness of answers. The Alfa Kronbakh index was 75% after evaluation and removing any ambiguity and this index achieved through SPSS. This percent is acceptable one in the scientific resources. To analyze all statistical operation needed for such as one variable and two variables khi2, SPSS software was used .This software will facilitate analyzing and will bring assurance toward exactness of calculations. Answers of the questioners were analyzed and encoded and entered into SPSS software for analyzing needed statistical operations.

**3. Results**

The following tables are resulted from questioners of population.

**Table1:** Communication with virtual friends are constituting most parts of women presences on internet

| Communication with virtual friends are constituting most parts of women presences on internet | Observed frequencies | Expecting frequencies | differences |
|---|---|---|---|
| Agree fully | 18 | 20.4 | -2.4 |
| Agree | 53 | 20.4 | 32.6 |
| No opinion | 15 | 20.4 | -5.4 |
| Not agree | 10 | 20.4 | -10.4 |
| Not agree fully | 6 | 20.4 | -14.4 |
| Total | | 102 | |

Table No.1 one variable khi2 table in terms of the degrees of interactions with virtual friends.

$X^2=69.275$   df=4   sig=0.000

In view of khi2 test of one variable and df=4 khi 2 was 69275.We may say by 99% that there are meaningful differences between observed and expected frequencies .Therefore, 53 persons (55%) are agree with this chosen item.

**Table2:** it has shown one variable khi2 in terms of preferring virtual communications on relations with real friends.

| There are not enough security for women on line | Observed frequencies | Expecting frequencies | differences |
|---|---|---|---|
| Agree fully | 7 | 20.4 | -13.4 |
| Agree | 38 | 20.4 | 11.6 |
| No opinion | 18 | 20.4 | -2.4 |
| Not agree | 32 | 20.4 | 17.6 |
| Not agree fully | 7 | 20.4 | -13.4 |
| Total | | 102 | |

One variable khi2, DF=4 is 33.196 - sig=0.000

There is a full meaningful difference between observed and expected frequencies, therefore 38 persons who are majorities in statistical populations are agreeing with chosen case.

**Table3:** it has shown one variable khi2 in terms of security of women in virtual space

| There are not enough security for women on line | Observed frequencies | Expecting frequencies | differences |
|---|---|---|---|
| Agree fully | 7 | 20.4 | -13.4 |
| Agree | 38 | 20.4 | 11.6 |
| No opinion | 18 | 20.4 | -2.4 |
| Not agree | 32 | 20.4 | 17.6 |
| Not agree fully | 7 | 20.4 | -13.4 |
| Total | | 102 | |

The most persons are agree with the chosen case (38 persons=36.3%).  $X^2=33.667$ df=4 sig=0.000

**Table4:** it has shown one variable khi2 in terms of security of "sexual attitudes toward women in the virtual space

| There are no sexual attitudes toward women | Observed frequencies | Expecting frequencies | differences |
|---|---|---|---|
| Agree fully | 5 | 20.4 | -15.4 |
| Agree | 6 | 20.4 | -14.4 |
| No opinion | 7 | 20.4 | -13.4 |
| Not agree | 59 | 20.4 | 38.6 |
| Not agree fully | 25 | 20.4 | 4.6 |
| Total | | 102 | |

There are meaningful differences between observed and expected frequencies (57.8%).

**Table 5:** it has shown one variable khi2 in terms of "weakening family relations in effects of women virtual interactions

| Social interaction of virtual space will weaken women family relations | Observed frequencies | Expecting frequencies | differences |
|---|---|---|---|
| Agree fully | 6 | 20.4 | -14.4 |
| Agree | 58 | 20.4 | 37.6 |
| No opinion | 17 | 20.4 | -3.4 |
| Not agree | 16 | 20.4 | -4.4 |
| Not agree fully | 4 | 20.4 | -15.4 |
| Total | | 102 | |

57.8% agree with chosen case and there are meaningful differences between observed and expected frequencies.

Result of the research reveals that the majority of respondents are agree with this phrase (there are no enough social security for women on internet). And there are also meaningful relations between situations of married or single women and their opinions on security or insecurity. This result is harmonious with results of a research under title of "social problems of women in internet: 2005".

Respondents agree that there is sexual attitude on internet and the real identity will create more problems for women. They do not agree that "there is no sexual attitude on internet." Experiences of women in science and technology historically have been limited and dominated by the men many researches show that internet is men oriented such as other technological grounds. Internet is reproducing Special structure of races, classes and sexual stereotypes. The women need securities both in real life and virtual space, but unfortunately this security is neglected into virtual space. For examples there are oral and written coarseness through chat and internet, using annoying and obscene words against women or even spoiling and attack to women sites. Pornographic scenes and images on line teach men that women are vulnerable people and are entitled to be misused through quarreling sexual torment and aggression .Pornographic activities reveal continuous system of paternalism and men domination. The men show their dominations through sexual misuses of women. This pictures show women as obedient persons. Coarseness and sex are main themes of Pornographic Industry .The most parts of these pictures and movies show that men are dominating on women and the women are showed in the degraded position. There is possibility to violate privacy of people because there are no identified identities and availability of personal information. The most respondents are believed in threats for women privacy and they should learn more about security on internet and pay attention to their interactions to avoid any harm. Emergence of networks ,have created more risks and threats than other technologies .The most evident threats are violating privacy, misusing personal data, and physical threats through on line interactions. Albeit, for following all actions of public networks users are more threatening for people. There are two crimes against women on line .One is sexual exploitations and the second one is torment and aggression toward women. Using women for online pornography and women stowaway are under the first category and internet has facilities these unlawful activities.

One of the conclusions of this research is that many respondents have announced that most parts of their presence are related to their interactions with friends on line and many of them prefer this kind of relations to real communication. Virtual communication in the excessive form will bring about isolation and depression; it will weaken family institution and will create many problems for all people in any old ages. The most respondents have been agreed to this chosen case:"social interaction on virtual space will weaken the family connections". One of the Respondents says that:"the virtual space is an insecure, convulsive and uneasiness, therefore it is necessary for women to learn more about virtual space and its risks and dangers. Respondents often look at blogfa to be more suitable and secure. Activist women on line believe that there is no online desirable availability for women and all layers of women have no opportunities to present on line because of lacking public education about this space, and also lack of software and hardware possibilities. Respondents say that availability to the internet is not desirable, because of high expenses and low quickness .These factors will affect on women too.

And the conclusion is compatible with sexual digital gap theory:
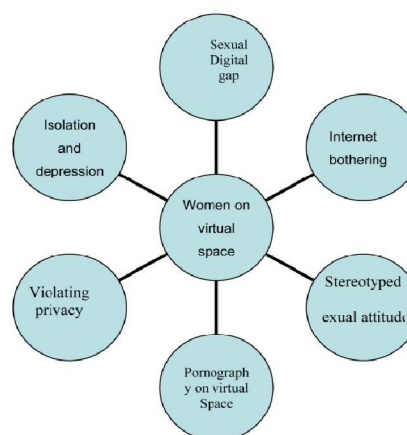


**Fig 1. Challenges of women on virtual space**

### 4. Discussions

Modern communication technologies have created new opportunities for different group of people and it is also so valuable for women .Women in the third world or developing countries are encountered with many obstacles for interactions, because of common traditions and circumstances.

There are many opportunities and threats for women on internet. Following people proposals are put on to develop social interactions of women and meanwhile to decrease the threats and pathologies:

1) Providing public education in the aim of more on line availability of all layers of women.

2) Providing for women desirable availability to internet.

3) Instituting social clubs and networks, in so that members of family (parents and children) may participate and enter – collectively and commonly.

4) Producing useful Persian (Persian) contents online about women problems;

5) Giving necessary education about the way of caring on line privacy.

6) Giving educations to women for on line participations and avoiding side pathologies and so on.

7) Expanding scientific investigations and researches on psychological aspect of internet.

8) Developing necessary and suitable laws and regulation for keeping women security on internet.

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# Azar Barzin Mehr Firetemple, Shining Over the Peaks of Sassanids' Era Architecture

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**Abstract:** The Sassanids' art has been the continuing of Iran, Achaemenids, and Parthian' ancient arts, and is associated with a religious worldview. The structural form of the fire temples has been similar, a dome on the squinches and was situated on a big footstool, which was joined by arcades. Each fire temple, usually had eight doorways, and some eight-corner rooms. Chahar Taq (the four arches) has had four doors or arcades, which was later considered as the basis of great Islamic mosques. Azar Barzin Mehr fire temple is one of the greatest Sassanids' Chahar Taqs, which is situated on the height of the rural highlands of Rivand in fifty kilometers from the west of Khorasan Razavi. The Azar Barzin fire temple has been used only by farmers' class. In the remains, one can see the Tawaf Hall, such of those can be found in most of the Charat Taqs, especially Ghasr-e-Shirin Chahar Taq. Regarding the technical styles and administration methods, it can be stated that Azar Barzin has things in common with Khosrovestan, Ghasr-e-Shirin, and Takht-e-Soleyman Palaces. The building materials have mostly been rubble stone. Moreover, there is some news of finding gypsum mortar inside the outside of the building. The sources of Sassanids' era have known the fire temples of, Azargoshasb, Azarfaranbagh, and Azar Barzin Mehr from the three mythological fires of Zoroastrianism belonging to respectively one social class (priests' fire, worriers' fire, and farmers' fire).

**Keywords:** Fire temple, Barzin Mehr, Chahar Taq, Architecture, Azar, arch, pier, squinches, dome

## 1. Introduction

The Sassanids were people from Fars State. This state was governed by local princes, who claimed to be the Achaemenids' posterity, and knew themselves as the heir and guardian of the mentioned-dynasty traditions. Ardeshir I, the founder of Sassanids' dynasty, and two went to Ctesiphon two years later, after killing the Parthian's king and founded the dynasty bi his coronation, in the year266 AD. His grandfather, Sasan, was the the officer guarding the highly famous temple, Izad, Anahita in Estakhr. His father, was one of the local kings. The Sassanids' art is basically associated with a religious worldview and although it is the continuing of ancient Iranian and Parthian arts, and has been from under the influence of different movements from east and west, owns its specific characteristics. Since from the long-term Sassanids' governance (224-624 AD) many art works and buildings have been left, including: ornaments, buildings, cities, dome-shaped figures, fire temples, and other arts related to architecture (Uphan Pope, (1982)).

### 1.1. Fire Temple

The Sassanids' temples and fire temples that have thousand years practices and traditions were dispersed in all parts of Iran and Sassanids' kingdom. Some of them were in the sight, and were dedicated to public worship, while the others were only used by priests, and were used for keeping the Holy Fire. The temple that was the place specialized for public general ceremonies of fire worshiping was first discussed during the second century AD by Pausania. As it was mentioned there were some fire temples in Iran at that time, and there were religious buildings that did not have anything in common with fire worshiping. Kangavar temple has been one of them that has been dedicated to goddess Anahita (Schmandt-Besserat, 1980). In the modern building that included the place of Holy Fire, and in where the believers participated in religious rituals, the fire has been in a dark and closed room of the related buildings. On the contrary, the altar that was situated in the center of the yard, its significance and extent increased. Then it was situated on a high platform that has mostly decorative aspects, and it was Chahar Taq. Some of these Chahr taqs, are stilled remained in a more or less bad situation in Natanz, Kazeroon, and Firooz Abad; however, the buildings that were surrounding them are destroyed.

### 2.1. The Building Form of Fire Temple

The building form of fire temples was the same everywhere. The fire was situated in the middle of the temple, and Holy Azar was constantly burning in it. Every fire temple has had eight doorways and some eight-corner rooms. One sample of this building exists in Yazd nowadays that has been one

of the ancient fire temples, and has been turned into a mosque when Islamic people conquered the city. Moreover, in the book of [*Ashnaie ba Banahaye-e Tarikhi*] getting acquainted with historical buildings edited by Mirdanesh is written that they had similar forms. "A dome was situated on the squinches, and on the huge footstools, that were joined together by arcades. Sometimes, the internal temple was surrounded by a passageway, which was like a guard for that."

**3.1. Chahar Taq**

Is a dome that is situated on four pillars, which were joined together by arches, and it has been nearly the general form of the Sassanids' architecture or the canopy of numerous fires that were shining on the chest of Iran's mountains. It means the canopy of the fires that have been in the middle of Zoroastrianism fire temples, and it was the basis of Iran's great mosques, which was first unique to this shape and form, and then, has been combined with other factors of that time architecture. The Sassanids' fire temples have been composed of a huge yard, in the middle of which there was, situated a high platform, and on that Chahar Taq, there was the place of fire. Chahar Taq owned four doors or arches that used to be situated in the center of Zoroastrianism temples or the Iran's mountain range as the canopies of fire during the Sassanids' period.

**4.1. The Constituent Elements of Chahar Taqi Buildings**

- A square plan
- Four columns or piers on the above-mentioned plan
- Four arches that join the four piers.
- A dome that is built with the help of four rooms or squinches.
- The four doorways that are created in the form of a rectangle, finally.

Arthur Pope, the American famous orientalist and Iranologist introduces architecture as one of the basic elements of Iran's art and culture. Art is as old as history in Iran, and architecture is one of the most ancient arts. Iran's architecture is the variable identity card of the Iranians since from the old times. The tradition and customs, rituals, spirit, morality, thought, and generations' notions have a clear reflection of Iran's history. Not only in great buildings, but also, in small buildings, one can see these reflections. The fire temples and regality villages that have been created in all parts of Iran, the scattered signs of which are left around, have hidden a lot of Iran's architecture culture in it. In the ancient

Iran, the fire temples and regality villages were built on the hills. In the regality villages, there were temples attributed to Mehr and Nahid (the water's angel) worship. The regions that are not attributed to Pol-e-Dokhtar, or Dokhtar's Castle are the same Nahid's (the water angel) ancient temple. The ancient Mehr worshipers touched the water before entering the temple, and called it Mehrab (the altar; Persian Mehrab, is possibly derived from this word in the Islamic period). Islamic architecture is the result of many year's revolutions, though, our ancestors art talent, and their inspirations from traditions, and other nations' achievements. Although, the Iran's architecture face has accepted some changes and revolutions, its unique spirit and powerful nature have always remained alive and flourishing, and have changed its capacities with time. Regarding the significance of Sassanids' era, and the high impact of this era in the growth of Iran, and other countries culture and art, especially architecture, and its related elements, cities, palaces, fire temples, and other buildings of Sassanids' era, have been referred many times in different sources (Grabar O.1987). As an example, the fire temples of Firooz Abad, Takht-e-Soleyman, Azargoshnasb (Niasar) between Kashan and Delijan, (Baku, Ghasr-e-Shirin in Damghan, Tape Mil fire temples) on the road of Rey-Varamin, (the old fire temple of Estakhr, Masjed Soleyman, have been mentioned frequently, but unfortunately the Azar Barznim Mehr fire temple has been mentioned less, which is going to be explained in this article.

**5.1. Azar Barzin Mehr**

Is one of the greatest Sassanids' Chahar Taqs that is situated on the northern heights of Rivand village in 50 kilometers of the west of Sabzevar in one of the most impassable geographical regions in the forms of few remains with the major stile material? In order to achieve the mentioned building, one is facing with steep valleys and nearly unattainable, above which a massive stone heap with a height of 100 meters has raised its head from the bed of the river, and a famous Chahar Taq in a mood of silence and wonder with illusion and greatness has been based overlooking the river and around the stone heap with an indescribable landscape. The Azar Barzin fire temple has been one of the most important Chahar Taqs in the Sassanids' era, which has been unique and for the workers' class, only.

**6.1. The Explanation of the Building**

In order to strengthen the first pillars, and to coordinate the lower surface of the building with its square plan, the constructors have built clerestory. In fact, it can be stated that nature has helped a lot in

conducting this architectural plan, and the architect has succeeded in creating natural clerestory and a permanent Chahar Taq with little insertion in the southern and eastern part of the heap. In the southern and northern embedded piers, the Tawaf Hall has been guided. Nowadays, a few works of the Hall have been left, and undoubtedly, similar to other Chahar Taqs, especially that of Ghasr-e-Shirin, the existence of the mentioned Hall has been regarded as the necessities of Sassanids' Chahar Taqs. The square dimensions inside the building has been $60/6 \times 60/6$, and the length of quartet doorways, or in other words, the distances between the piers have been 30.4, and their width is different from 2 to 5.2 meters. In the four corners of the building, the four squinches have created four side walls. By the means of these squinches that are all stone the architects could easily change the square plan to a center circle, and they could raise the dome at its top. The parts that have been observed, remind us the designers' work in the buildings of Khosrovestan, and Ghasr-e-Shirin Palaces. The northern arch of Chahar Taqi, is almost safe and sound, and is similar to the horseshoe-shaped arcades of its contemporaneous buildings such as the northern and southern gates of Takht-e-Soleyman; however, it cannot cope with them in terms of dimensions and greatness. This building is seven meters long in the status quo, and due to the falling of ceiling debris, it is not possible to measure the exact size and the height of the dome. Many researchers have similar opinions about the Azar Barzin fire temple, and have named it as the farmers' fire. In Pahlavi texts, it is stated that the Azar Barzin Mehr fire temple has been the farmers' worship place in Rivand Mountains. Regarding the legend of planting a tree by Zarathustra in Khorasan, attributing this fire temple to the farmers in that era, is close to the truth.

About the tree planting in Tarikh-e-Beyhaghi, it is written that Zarathustra, who has been the owner of magus, has chosen two villages and ordered to plant two cypresses to those villages. One in Kashmar, and one in Farivamd village, and the Zarathustra, the fire worshipper had planted those trees. Moreover, it is written in Shahnameh that

*Like Azargosab, Khordad, and Mehr*
*Shining like Bahram, Nahid, and Mehr*

Christine believed that Azarbarzin or the farmers' fire has been situated in the east of Sassanids' country, in Rivand Mountains, Lazar Farapi believed that Rivan village has been the Moghan village, and Jacqes believed that the place of Azar Barzin Mehr fire temple has been in the Mehr village, on Khorasan, near Sabzevar. In another place, Ferdowsi believes that

*First, He founded Azar Mehr Barzin*
*Look at the country to see what practices it established*
*The Mehr Barzin was looking for smoke*
*It was shining without any wood and smoke*

Considering Ferwosi's poems, it can be stated that the fuel of the fire temple has been something different from wood similar to the fire temple of the ancient city of Shiraz, why it did not leave any ash.

### 7.1. The Materials of the Building

The main materials of the building have been the rubble stone, which has been provided from the heights around the Chahar Taqi, and we can see the bigger figures and cutting rocks. The expert of Cultural Heritage and Tourism of Sabzevar talks about the existence of gypsum mortar inside and outside of the building. Moreover, in the furtherance of expert studies of the Organization of Cultural Heritage of Sabzevar, in the entrance of the Hall, and architecture residues, the maintenance of bones in this fire temple on a mountain called Rivand (Rivas), has been identified. By rhubarb that is an herb with thick and fleshy stems, a wine called Haoma, and has been used in the Persian era (the first to the third millennium BC) in religious and ritual ceremonies. In Borhan-e-Ghate, this essence has been named Suma in Sanskrit that has been mixed with the pomegranate twig, and sowed on the fire. The sources of Sassanids' period, and the narratives existed have known the fire temples of Azar Faranabgh, Azar Goshnasb, and Azar Barzin Mehr from the three mythical Zoroastrianism fires, each of which has belonged to one social class, priests' fire, worriers' fire, and farmers' fire, respectively that have been established in Fars, Azerbaijan, and Khorasan by Jamshid, Kai Khsorow, and kai Gashtasb.

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# General Health Variations, in patients with MI, Longitudinal Case-Control Nested Design Study.

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**Abstract:** Studying the status of general heath in patients suffering from heart failure is crucially important taking the increasing prevalence of this disease and its impacts on total lifestyle of the patient and his/her family. This study aims at comparing the general health of patients with acute heart failure with control group during the outbreak of failure and three months after the failure. This study was conducted based on a linear case-study comprising subjects of control and den-like respondents over 83 patients suffering from heart failure and 83 people as the accompanies or neighbors of patient who are consistent with him/her in terms of gender and age were selected as the control group. From the beginning of patient's admission and three months later, they were studied with the GHQ28 Standard questionnaire. The data was analyzed using SPSS software and the core indices, scatter and student $x^2$ and t tests. 78 percent of patients and 22 percent of control group had difficulties with respect to general health. The general health of patients had a significant difference in the beginning and three months later. However, this difference was not significant in the controls. During three months follow up, the patients had a lower general heath in comparison with the control group. This difference increased after three months. The probability of incidence of heart failure in patients having general health problem was 4.85 times more than other individuals. General health problems are considered as the effective risk factors for the incidence of heart failure and exacerbating it. It is necessary to take the trainings about how to control mental pressures and promotion of general health into consideration in order to prevent from MI and also its better recovery.
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**Keywords:** Heart, MI, General Health, Risk factors, Relative Risk.

## 1. Introduction

Cardiovascular diseases are amongst the most common mortality reasons in the majority of the world's countries; more than 30 percent of fatalities happen in the industrial countries of the world caused by these types of diseases. Studying general health conditions of the patients suffering from heart failure has a high significance considering the increasing prevalence of this disease and its impacts on the patient's lifestyle and his/her family. The person affected by this disease may be faced with total changes in his/her family relations, job, values, physical and social ability and also his/her own self care; namely, his/her general health will deteriorate ( 1). The cardiovascular diseases not only have included a high rate of mortality, it has also brought about some constraints in the long-term in people's lives due to having a disabling nature accompanied by developing some disorders in patient's general health and also it will result in patient's shorter lifetime(2). According to report given by World Health Organization in 1996, it has included around 20 percent of the mortality reasons and this amount

reaches 50 percent of the total mortalities rate in developing countries. The American Heart Association also estimates that about half of the people who survive are fired from their works because of having a low level of general health and they impose the maximum possible medical costs to their societies(3). Conducting a study with the objective of determining the clinical results of general health improvement resulting from lifestyle moderation program in patients suffering from arteriosclerosis, Rutledge et al. demonstrated that taking part in the lifestyle change program which includes exercise, pharmacotherapy, consultation and diet and stress reduction techniques play a highly major role in reducing weight, increasing capacity for exercising and reducing risk factor and enhancement of the satisfaction level in the patients(4). In Iran, the total rate of mortality caused by heart failure has exceeded from 24.4 percent in 1979 to 38 percent in 1990. The majority of the deceased have died with the incidence of the first heart failure and/or with the second failures during the first 28 days after the attacks (5). Reducing the age of death caused by

cardiovascular diseases imposes great expenses upon the society, as in 2006, the average age of the patient has amounted to 57 years the majority of which consist of male patients(6). New supporting treatments in order to control heart failure will result in increasing the number of patients survived from heart failure. The study showed that the quality of the life in patients have been decreased from six to thirty month after the first acute heart failure. This reduction in physical scales was more than that of mental ones. In addition, quality of life was reduced by aging and also in female patients it was lower in comparison with male patiants (7).

Thus, in light of the aforesaid discussion, the present study was designed and implemented with the objective of identifying changes of the general health in patients suffering from acute heart failure compared with control group within a three month follow-up period.

## 2. Material and Methods:

This is a longitudinal case- control study. The patients with diagnosis of heart failure who were hospitalized at the cardiac intensive care unit as the case group and individuals consisting of the associates, the relatives and/or his/her neighbors who had not have any cardiac disease records became consistent with the patient in terms of gender and age group and were followed up and studied as the control group within three months in terms of their general health. This study from month of May 2007 began within the framework of a research plan and ended after two years. The general health measuring tools has been a questionnaire containing 28 questions (GHQ-28) standardized and localized for I.R. Iran. This questionnaire is considered as the best and simplest general health measuring tool. Goldberg obtained 84 percent of sensitivity and 84 percent of specificity while assessing the questionnaire (8). This questionnaire has also been translated in form of various samples. In a study conducted by Noorbala et al, this questionnaire has had 84.2 percent of sensitivity, 94.4 percent of specificity and 7.8 percent of error (9).

The scoring of questionnaire including 28 general health questions is in Likert's grading containing 4 options and having values (0, 1, 2, and 3). The questions 1 to 7 which evaluate bodily disorders, questions 8 to 14 evaluate level of anxiety and sleep disorder, questions 15 to 21 ask about the zone of disorder in social function and questions 22 to 28 evaluate zone of depression. The range of scoring of each zone was from zero to 21 and the total score was placed between zeros to 84. Higher scores indicate having general health problems or its areas. The cut-off point of probability of existence of

disorder in each one of four areas score 6 or more was considered, and as per total score for level of general health, being scored higher than 21 for the females and higher than 22 for the males were considered (6, 10-14). General health in total and in separation of the zones was calculated in the beginning and end of study in both subject and control groups and it was compared. The sampling was based on accessible sample, objective-oriented and all patients who were diagnosed as having acute heart failure and hospitalized in cardiac intensive cares ward of Imam Sajjad hospital were questioned until the time of completion of sample size. The size of sample was estimated by considering the main goal of the research and the research type and considering the maximum sampling error of $\alpha$=0.05 and maximum estimation error: d =0.1 and by taking the difference of existence of problems in general health of the patients suffering from heart failure into account and the control group: p=0.70. Considering the similar studies, the value of 5 was estimated equal to 88 persons for every group considering 10 percent of loss during follow-up process of 92 people.

In this study, 92 patients diagnosed heart failure and 92 people as controls were studied. During the follow-up, six people of the patients died and 3 controls were inaccessible during the study and the relative patients were also removed from the study. In addition, six controls whose patients had died were omitted from the study. In total, 83 patients and 83 controls were completely followed up for three months. The data gathered using SPSS software, version 16 was analyzed. In order to describe data, core indices and data scatter and the frequency distribution table and flowcharts were used and for data analysis, student $x2$ and t tests were used; Also, in terms of having health problem at each level, the ratio of the total general health to probability with about 95 percent of confidence interval was evaluated and reported.

## 3. Results:

In this study, 83 patients and 83 controls consistent with the patients were studied and followed up. Among the patients, 32 persons (39%) were female and 51 persons (61%) were male. The average age of the controls was 61.7 years and the cases were 61.1 years without having any significant difference. The patients' ages during the incidence of failure was 66.5±1 in females and 56.2±1 in males which had a significant difference (p = 0.002). In the present study, the epidemiologic factors like age, gender, economic status, education, place of living based on city and village and marital status did not have a significant relationship with general health status. 59 percent (49 persons) of patients had general

health problems, namely, 45 percent (14 persons) were female and 74 percent (38 persons) were male. The level of disorders of general health in the subject group during the first step of the study was 59 percent (49 persons) and three months later, it reached 63 percent (52 persons) which had a significant difference (P=0.012). While, the level of general health problems did not show any significant difference for the controls at the start of the study (23 percent for 19 persons) and three months later (24 percent for 20 persons) (p>0.05). The level of general health disorder at the start of the study showed a significant difference with controls (Fig 1). Probability ratio and 95 percent of confidence interval of incidence of heart failure in those individuals suffering from disorders (8.08 and 1.62) had been 4.85 times more than those individuals with no general health disorders. The probability ratio and related confidence interval within areas of general health have been presented in (table 1).

## 4. Discussion:

The objective of this study is to identify the changes of general health status and its zones in patients diagnosed having acute heart failure and comparing it with status of general health in healthy individuals being consistent with them within three follow-up months. The findings showed that the status of the total general health of patients and also within the first three zones: bodily complaints, symptoms of anxiety and insomnia, social malfunctions have had a significant difference at the start of heart failure's incidence. It can be concluded that those suffering from general health problems or its zones have had a significantly more chance or probability of taking the heart failure. The similar studies have also shown that the status of general health of individual relate to the diseases (7-9, 15), in addition, the incidence of disease and its continuance will result in the severity of disorder in general health status and vice versa (16-19). This chain of severities exacerbates and this leads toward higher patients' sufferings and ultimately ends in their deaths. The normal health status of controls as compared with the normal status of the society achieved by research conducted by Noorbala et al. 6.8 has better conditions; while the status of general health of patients has been worse than in comparison with the normal status of the society. These days, in developed countries, the training courses related to life skills and specific behaviors in order to prevent from incidence of diseases is held prior to incidence of diseases in terms of vulnerability, taking the epidemiological conditions into account, for the society individuals (2,

11, 13, 17 and 20-21). Furthermore, for the patients suffering from various diseases, some consultants have been planned, have active presence and render services in order to render mental, societal and rehabilitation supports (2, 14). While, this matter has not been witnessed or existed in our country yet.

During the study, the general health status of the patients significantly exacerbated after three months. Whereas, the general health status of the controls have not significantly changes in the start and after three months. It may be concluded that after passage of three months, the patients' general health has suffered from disorders and has made them prone to getting other diseases or the second failure. In the present study, epidemiological factors like age, gender, economic status, education and place of living (city and village) did not have a significant relationship with the general health status. It seems that one of the main elements of incidence of any disorder in general health is how the individual thinks about the principle of life and this issue results in some enormous changes being made in his/her behavior and will result in outbreak of many diseases including the heart failure. This behavior did not have a significant relationship with factors like age, gender, marital status, economic conditions and other factors. Whereas, according to study of Tofighian et al, women who had gotten heart failure were more in danger of disorders of general health 7. These results were consistent with the other similar studies (5, 16, 19-23).

The necessity of more attentions paid by the healthcare affaires authorities and trustees in regards with the mental health category and general health of the people of society, planning for training necessary skills to patients and their families in relation with the importance of mental health and introducing elements affecting the incidence of heart failure. Making use of the mass media in line with making the society widely informed about the aforesaid items.

Table 1: Comparison of general health variations in MI patients with their control person's within three months follow up.

| Zone | Time of study | Controls | Cases | Sig , RR *, 95%CI |
|---|---|---|---|---|
| General Health Disorder | Begin of study | 17(21%) | 49(59%) | x2= 40.21　df=1　p<0.001 RR= 4.85, 95%CI=(1.62, 8.08) |
| | 3 months latter | 16(19%) | 52(63%) | x2= 41.91　df=1　p<0.001 |
| First Zone bodily disorders | Begin of study | 17(20%) | 51(61%) | x2= 41.51　df=1　p<0.001 RR=5.76 , 95%CI=(1.87, 9.65) |
| | 3 months latter | 17(20) | 58(70%) | x2= 44.66　df=1　p<0.001 |
| Second Zone anxiety and sleep disorder | Begin of study | 7(7%) | 41(49%) | x2= 32.01　df=1　p<0.001 RR=4.78, 95%CI=(1.92, 7.92) |
| | 3 months latter | 6(7%) | 57(69%) | x2= 41.1　df=1　p<0.001 |
| Third Zone disorder in social function | Begin of study | 17(21%) | 35(42%) | x2= 20.18　df=1　p<0.001 RR= 2.83, 95%CI=(1.16, 4.57) |
| | 3 months latter | 16(19%) | 41(49%) | x2= 22.03　df=1　p<0.05 |
| Forth Zone Depression and Suicide thinking | Begin of study | 17(20%) | 11(13%) | x2= 7.01　df=1　p<0.05 RR=1.66, 95%CI=(0.65, 2.74) |
| | 3 months latter | 17(20) | 13(16%) | x2= 7.99　df=1　p>0.05 |

* RR: Relative Risk
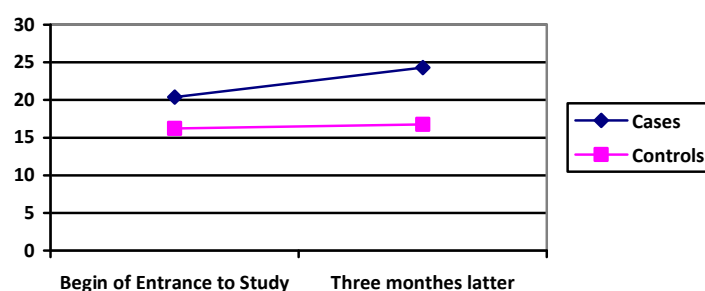


Fig 1: Illustration of general health variations in MI patients with their control person's within three months follow up.

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7/2/2012

# Life expectancy at birth for the rural population of Islamic Republic of Iran,  by sex and age groups, 2007.

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**ABSTRACT:** Life expectancy at birth is one of the most important indices of the social, economical, cultural and health status of a country. The aim of this study was to draw up life tables for the rural population of the Islamic Republic of Iran in 2007 and estimate the life expectancy for males and females. A total of 60 561 deaths among 11 463 702 males and 44 055 deaths among 10 999 627 females were studied. Life expectancy at birth was estimated by the direct and indirect methods. The results were consistent using both methods. Life expectancies at birth for men and women in the rural population in 2007 were 72.2 and 73.9 years respectively and the total was 73.0 years. The percentage of women aged over 65 years was 5.9% and of men was 6.4%. The trend of life expectancy for men and women over the past 30 years showed a 31.0% increase for men and 31.3% for women.
[Ghaffarian Shirazi H.R, Mahmoudi M, Mohamad K, Rahimi Froshani A, Jafari N, Ostevar R, Salesi M, Mirzaee M, Hajivandi A, Mansorian M. **Life expectancy at birth for the rural population of Islamic Republic of Iran by sex and age groups, 2007.** *Life Sci J* 2012;9(3):1180-1183]. (ISSN: 1097-8135). http://www.lifesciencesite.com. 165

**Keywords:** Life Expectancy, Birth, Rural, Iran, 2007.

**Introduction:**

Life expectancy at birth indicates the estimated average years that a newborn will live provided that the possibility of death will be similar to that for present human beings in future years. It is an important index which indicates the cultural, social, economical and health status of any society and is useful for public health policy-making. The World Health Organization (WHO) used this index and other indices, such as *per capita* income, gross national product and the rate of female literacy, to estimate the human development index, which is one of the most important evaluation indices of countries today.

According to a WHO report in 1997, the lowest life expectancy at birth (41 years) was in Guinea Bissau and the highest (80 years) was in Japan. In the same year the Islamic Republic of Iran ranked 80th, among 192 countries [1]. Life expectancy can be calculated for any age; for example, it can be determined how many more years a 45-year-old man will live provided that the possibility pattern of his death in the future will be similar to that for the current population at any age group [2]. In countries with a high infant mortality rate, life expectancy at birth is greatly affected by the rate of deaths in the first year of life. Therefore life expectancy excluding deaths of children under 1 year old may be a better indicator.

Life expectancy has been estimated a number of times in the Islamic Republic of Iran, using different data and calculation methods, for the whole country and its provinces [1–10]. The aim of this study was to draw up life tables for the rural population of the Islamic Republic of Iran in 2007 and estimate the life expectancy at birth for men and women. Comparing life expectancy in a country with that of neighbouring countries can reveal a country's overall health outlook compared with other regions [7,8]. Our data were therefore compared with data for other countries in and around the Eastern Mediterranean region.

**Material and Methods:**

A total of 60 561 deaths among 11 463 702 males and 44 055 deaths among 10 999 627 females from the rural population of Islamic Republic of Iran during the year 2007 were studied. This information was extracted from the life event registration form which is compiled annually in each village and city health centre. The forms are collected and monitored at each stage and then sent to the provincial centres and then to the country development network.

The data were used to calculate the life expectancy by age group and sex. Calculation was done using both the direct [9,10] and indirect methods and data from the 2 methods were compared. Calculating the life table by the direct method was done using the population size and the number of deaths at each age or age group during the year. We also calculated the 1-year-old life expectancy by the indirect method using the population size and number of deaths for male and female children less than 1 year old in a year. This was done using MortPak , the

United Nations software package for mortality measurement [11].

Some limitations of the data were correct as follows. Information belonging to certain cities which had certain and unacceptable errors was excluded with the assumption that deleted information was similar to the rest of the information. Also due to technical and software problems information about men aged over 85 years was not available. Therefore, a significant linear relationship between the male population in 2006 and male population in 2007 with a correlation coefficient of 0.997 and determination coefficient of 0.994 was used for calculations. Based on similar studies, life expectancy at age group of over 85 years of age was considered as 1.1 for women and 1.0 for men [10].

**Results:**

The life tables are shown in Table 1. Life expectancy at birth in the rural population of Islamic Republic of Iran was 72.2 years and 73.9 years respectively for men and women and 72.7 years overall for the whole population. The data also showed that the percentage aged over 65 years of age was 5.9% for women and was 6.4% for men.

Figure 1 shows the trend of life expectancy for men and women in the past 30 years in the rural population of Islamic Republic of Iran. The increasing trend of life expectancy was greater in the first decade, while at the third decade, between the years 1997 and 2007, the trend decelerated. The increase in life expectancy was 31.0% for men and 31.3% for women over the 30-year period. Women had greater life expectancies than men at all decades of data collection and the difference in life expectancy between the sexes was 1.2 years in 1975, 3.0 years in 1987, 2.7 years in 1997 and 1.7 years in 2007 respectively. The results of the 2 methods were consistent.( table 3)

In direct method we use population and death in all groups for calculating life expectancy, but in indirect method we use only: the number of deaths and population of less than 1 year old children, that are more precise than similar data for all age groups of a population, with using Mortpak software.

**Discussion:**

Based on previous studies, the life expectancy at birth in the rural population of Islamic Republic of Iran in 1975 was estimated as 55.1 years for men and 56.3 years for women [3]. In 1987 it was 66 and 69 years respectively [1,4] and in 1997 it was 70.7 and 73.4 years respectively [5]. According to present study results, these values were 73.9 and 72.2 years in 2007for males and females respectively. Considering the similarity of resources and equal calculation method in the 4 recent studies and a 10-

year interval between the studies, the life expectancy at birth had an increasing trend in the past 3 decades (Figure 1).

The high rate of increase in life expectancy in the first decade of data recording, between 1976/77 and 1987/87, decelerated in the third decade, between 1996/97 and 2006/007. This is natural because Life expectancy has increased much faster trend has reached to its normal limit. Then the trend of increasing will reduced, although, some other factors will affect in this trend like war between Iraq and Iran in years 1970 to 1988 and after finishing war. And also because the higher life expectancy which belongs to the more developed countries will be accessible in more times [12,13]. This trend is for a rural population, and the same data for urban areas also needs to be studied. Comparing the results of this study with the past estimates of the region and the latest country estimate showed an increase in life expectancy in Islamic Republic of Iran. Lower life expectancy in rural areas compared with similar studies nationwide and in urban areas in the past 5 to 7 years [2,6–8,14,15] indicates a need for more attention to health in rural areas of our country.

The difference in life expectancy between men and women in advanced countries is about 5 to 8 years, while in less developed countries this difference is close to zero. In rural areas of Islamic Republic of Iran the difference in life expectancy between the sexes was 1.2, 3.0, 2.7 and 1.7 years for the years 1975, 1987, 1997 and 2007 respectively, which it indicates no significant change in life indices related to rural women in recent years. We could not compare the life expectancy of our study directly with that in neighbouring countries due to different calculation methods of life expectancy. Instead we used the WHO reports which compared life expectancy in 2007/2008 and healthy life expectancy at birth in 2003 for males and females [16]. These are shown in Table 2 for the Islamic Republic of Iran and neighbouring countries. Life expectancy at birth in our study was 72.2 and 73.9 years for males and females, and 73.0 in total population versus 70.75 years in the WHO report in total. (Table 2)

Life expectancy and healthy life expectancy in the Islamic Republic of Iran was higher than in Afghanistan, Iraq, Pakistan and Saudi Arabia but lower than in Qatar, Kuwait and Turkey.

Because the number of deaths and population of less than 1 year old children in each year were enough to calculate life tables and life expectancy by the indirect method and using *Mortpak* software, and because these data are more precise than similar data for all age groups of a population, this method is preferably suggested for developing countries.

Table 1 Population, deaths and life expectancy at birth by age groups and by sex in the rural population of the Islamic Republic of Iran, 2007

| Age (years) | Females Population (no.) | Deaths (no.) | Life expectancy (years) | Males Population (no.) | Deaths (no.) | Life expectancy (years) | Total Population (no.) | Deaths (no.) | Life expectancy (years) |
|---|---|---|---|---|---|---|---|---|---|
| 0 | 197 240 | 3474 | 73.9 | 206 626 | 4 156 | 72.2 | 403 866 | 7630 | 73.0 |
| 1–4 | 714 685 | 690 | 74.3 | 747 197 | 835 | 72.6 | 1 461 882 | 1 525 | 74.0 |
| 5–9 | 916 408 | 325 | 70.5 | 960 774 | 497 | 68.8 | 1 877 182 | 822 | 69.6 |
| 10–14 | 1 237 940 | 343 | 65.6 | 1 301 459 | 628 | 63.9 | 2 539 399 | 971 | 64.6 |
| 15–19 | 1 504 517 | 813 | 60.7 | 1 697 020 | 2 118 | 59.0 | 3 201 537 | 2 931 | 59.8 |
| 20–24 | 1 329 519 | 791 | 55.9 | 1 462 256 | 2 615 | 54.2 | 2 791 775 | 3 406 | 55.2 |
| 25–29 | 1 039 141 | 689 | 51.1 | 1 118 745 | 2 045 | 49.4 | 2 157 886 | 2 734 | 50.6 |
| 30–34 | 810 595 | 552 | 46.3 | 834 823 | 1 441 | 44.6 | 1 645 418 | 1 993 | 45.1 |
| 35–39 | 652 630 | 639 | 41.5 | 633 636 | 1 401 | 39.8 | 1 286 266 | 2 040 | 40.4 |
| 40–44 | 524 122 | 704 | 36.7 | 521 062 | 1 501 | 35.1 | 1 045 184 | 2 205 | 31.8 |
| 45–49 | 472 781 | 1 040 | 32.1 | 448 187 | 1 949 | 30.4 | 920 968 | 2 989 | 31.6 |
| 50–54 | 408 930 | 1 434 | 27.6 | 355 189 | 2 193 | 25.9 | 764 119 | 3 627 | 26.6 |
| 55–59 | 303 832 | 1 820 | 23.3 | 249 923 | 2 348 | 21.7 | 553 755 | 4 168 | 22.6 |
| 60–64 | 242 041 | 2 425 | 19.1 | 215 641 | 2 888 | 17.8 | 457 682 | 5 313 | 18.2 |
| 65–69 | 222 317 | 3 791 | 15.2 | 232 819 | 4 377 | 14.2 | 455 136 | 8 168 | 14.9 |
| 70–74 | 193 044 | 5 950 | 11.8 | 226 542 | 7 513 | 11.0 | 419 586 | 13 463 | 11.4 |
| 75–79 | 129 638 | 7 019 | 8.8 | 156 273 | 8 249 | 8.4 | 285 911 | 15268 | 8.9 |
| 80–84 | 72 489 | 6 761 | 6.4 | 87 265 | 7 969 | 6.3 | 159 754 | 14 730 | 6.3 |
| 85+ | 27 758 | 4 795 | 1.2 | 33 416 | 5 838 | 1.0 | 36023 | 10 633 | 1.1 |

Table 2 Life expectancy, healthy life expectancy at birth and population growth rate in the Islamic Republic of Iran and neighbouring countries

| Variable [reference[ | Islamic Republic of Iran | Qatar | Pakistan | Afghanistan | Iraq | Saudi Arabia | Turkey | Kuwait |
|---|---|---|---|---|---|---|---|---|
| Life expectancy, males/females (years) 2008 [17] | 70/75 | 76/76 | 63/64 | 40/44 | 58/69 | 69/75 | 72/77 | 78/79 |
| Healthy life expectancy at birth, males/females (years) 2003 [18] | 56/59 | 67/64 | 54/52 | 35/36 | 49/51 | 60/63 | 61/63 | 67/67 |
| Population growth rate (%) 2008 [19] | 1.6 | 5.2 | 1.8 | 2.0 | 3.0 | 2.3 | 1.5 | 9.3 |
| Population growth rate (%) 2008 [19] | 0.66 | | 1.83 | 2.36 | 2.62 | 2.06 | 1.04 | 3.56 |

Table 3 life expectancy at birth by sex in the rural population of the Islamic Republic of Iran, 2007

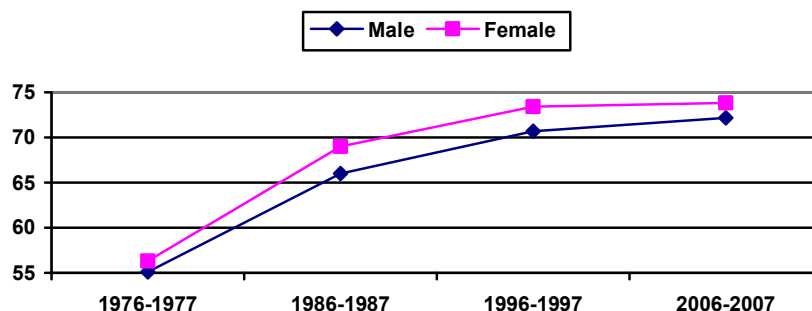| Method | Females | Males | Total |
|---|---|---|---|
| Direct Method | 73.9 | 72.2 | 73 |
| Indirect Method | 73.5 | 71.7 | 72.8 |



Figure 1 Comparison of life expectancy at birth between males and females over a 30-year period in the rural population of the Islamic Republic of Iran

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7/2/2012

# Consider of Micro-Current's effect to variation of Facial Wrinkle trend, Randomized Clinical Trial Study.

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**Abstract:** Beauty is one of the important today's people concerns; the facial wrinkles are including problems of beauty. Today, new non-invasive treatments such as using micro currents in treatment of wrinkles and skin renewal have been used. This study is aimed to determine the effect of Micro-Current in the treatment of facial wrinkles. in this before and after clinical trial, thirty women with three requirements; 1.having less than 45 years of age 2.wrinkles and 3.no skin problems have participated. The cases were treated with micro current for twenty minutes on their face areas, for thirty consecutive sessions. Photos were taken from patients faces at the beginning, end and one month after treatment. Three independent blinded reviewers have rated wrinkles in photos. Also patients have evaluated their treatment. The best results belonged to forehead 18.37% in first step (before and after treatment) and 21.18% in second step ( after treatment and one month later) and the lowest rate in treatment belonged to nose and mouth region; 7.61% in first step and 5.85% in second step . Micro current, recovers facial wrinkles, this recovery was better in the frontal area comparing the nose and mouth. Also comparing the scores of photos, immediately after treatment and one month later shows that not only the effect of treatment has been stable but also the started recovery procedure has been continued after treatment. Treatment satisfaction among patients was over 70%.

**Keywords:** skin, beauty, Facial, Wrinkle, Micro-Current

## 1. Introduction

Beauty is one of most common concerns among human, especially women. Facial wrinkles are one of beauty problems which is produced due to aging or some other factors such as stress, improper diet, smoking, sun damage, fat culmination, and harmful inflammation, and is accelerated due to some other factors including gravity, broking of Collagen and Elastin constitutive materials caused by sunshine, air pollution, smoking, and not to exercise, and signs of aging begin to appear. Passing time, the thin epidermis and connect tissue become weak , facial muscular firmness diminishes, epidermis begin to loose and dropping, natural fold change to cheek , neck , and chin unnatural fat, small vessels tights and blood circulation decreases and lead to decrease of facial brightness (1,2).

There are many therapeutic methods to remove and reduce facial wrinkles and for rejuvenation which can be divided into three group of invasive, semi-invasive, and non – invasive methods.

The invasive methods such as facelift treatment or the cosmetic surgery are intended to remove facial wrinkles. These methods require hospitalization, and besides being expensive and having long recovery period and may cause side effects.

Among semi -invasive methods ,there is use of laser to skin exfoliation , which requires special care after treatment and long recovery period, it also cause respective problems , costs , and side effects(3).

Injection of botulunim toxin also known as Botox is another semi invasive method to remove facial wrinkles. The method may have many dangers associated with misuse, but under supervision of practitioner and use of healthy Botox the side effects reduce. Also the treatment effects are not long standing.

Non-invasive methods include preservative creams, booster creams, and anti wrinkles creams. These are contain of, antioxidant, preservatives, or booster ingredients such as vitamin A, hydroxy acid, α-lipoic acid, Q-10 coenzyme, cu peptides, growth factors, Soy Isoflavones, Tea extract, vitamin C,

vitamin E, or collagen. However the effectiveness of the creams has not been proved yet.

In recent years, the use of micro current has been proposed which enjoys many advantages including: being non –invasive, inexpensive, and having no side effects. It is also argued to be effective in removing facial wrinkles, skin dropping and reducing facial surface spots. It also has been proved that micro currents are very effective in improving of malunion or nonunion bone fractures and curing of resistant ulcers and bed sore .This occurs due to activation of collation system in skin layers. Collagen is a group of naturally occurring proteins found in animals. They are made from fishia strings, making up about 40% of the whole-body protein content. Collagen protects brain nerve system and provides good tensile strength .It also leads to sore recovery through a complex process. During maturation and ulcer recovery, collagen is arranged in line with tensile lines and the unneeded cells are removed by fagositosis, thereby the ulcer recovers (10). Micro current is an electric current delivered at a rate of 1 microampere which equals 1 millionth of an ampere .They are harmless and have recovery effects on damaged tissues and enjoy capacity of toxic trapping. They made blood circulation faster and lead to stimulation of collagen production. Several studies have proven benefits of micro currents for recovery of persistent and chronic ulcers (12).Micro currents are at low level and patient feel comfortable.

Stimulator current above 20 mille ampere, stimulate and contract the muscles leading to strength and firmness of damaged muscles. Common electrodes such as TENS and EMS are reliable and nonallergic. These currents can be used as interferential with sine and square waves , and are more effective because they allow a deeper and softer penetration (13).Currents' effect lead to increase of the amount of ATP in cells (14) , increase of cell protein duplication and DNA transcription (15) , horn cell growth and duplication , increase of blood flow, exchange of oxygen , ions , antioxidants , and nutrients among epidermal , subcutaneous and fat layers , and subcutaneous and lymph capillaries .This lead to release of energy in tissues and stop decreasing elasticity and protein degradation which had been caused by intake of free radicals and to increases collagen I ,II production. (17) By contracting the old and unhealthy collagens, these changes lead to firmness and toning of facial skin.

It seems that the ability of micro currents in resurfacing of thin layer of skin, filling wrinkles and lifting dropping skin is related to stimulation of cells growth and tissues revivals. (18). This study aims to determine the effect of micro current on removing and reducing patient's facial folds and wrinkles.

## 2. Material and Methods

In this before and after clinical trial, every volunteer participated in the research after being informed about the trial and it was conducted in second half of 2010. Sampling was as available goal – oriented sample with volume of 15 subjects .Regarding to a similar study (21-19), limitation of the research, and because of some consideration like possible fail due to time period, and respective problems, 30 women were participate in the research. At the first, at the end and one month after treatment, in the same conditions, photos were taken from areas of right /left eye profiles, forehead front, nasolabial, and eyes feet views. The photos were taken using Canon 5D camera with lens 24105 macro while the participant was sitting in a free mode relying on her head back on chair. The treatment process was as follows: first the person washed her face with soap and water, and then lied on bed and every half of her face was treated for 10 minutes.

Facial areas going under treatment include forehead around eyes, nasolabial area, cheeks and chin. The treatment method is as follow: a positive electrode is fixed and the negative one is sliding. These movements are repeated five times for each point. These electrodes are thin with a tip covered with cotton that are wetted with water to be conductive. For every case, treatment proceeds for 30 consecutive sessions except for vacations, Thursdays and Fridays .The used apparatus A6 is made in China with CE license from England and Europe and United states. The current used in the study are square micro pulse between 70-80 Hertz with amperage range of 0-640 microampere. At the end of the treatment, the consent assessment form about treatment effectiveness, health care center quality staff services and treatment environment was filled by the patients. The questionnaire was prepared using standard form (25) and enjoyed acceptable validity and reliability. At the end of the plan all photos were numbered and each photo was graded between 0-10 by two dermatologists and one plastic surgery specialist by size numbers and depth of folds. The referee was blind on which one is before or after photo and about the related person. The assessment method enjoys acceptable validity and reliability (26).

Inclusion Criteria: being below 45 years old, having facial wrinkles, being free of skin problems diagnosed by dermatologist.

Exclusions Criteria: If any case of complication happens the patient is referred to the practitioner and then leaves out the study. During the study patient should avoid anti-wrinkle cream or any other wrinkle therapy.

Data analysis: To describe data central and dispersion indices and for data analysis the paired student's t- test were used. To assess the improvement rate or treatment effectiveness on each stage and area we used ratio of difference of

before/after wrinkles scores to before score on that stage and area.

Ethics consideration: The aim of the study was explained for the volunteers and they were informed. The micro current is in common use in physiotherapy and their harmlessness has been confirmed. The unanimous photos were coded and evaluated by the referees. The confidentiality of collected information was observed and patients feel comfortable and didn't incur any expenditure.

Table 1: Compare Wricle Scores of Patients faces area In the first stage( Before and after treatment) and second stage( After treatment and one month later) of trteatment.

| Row | Face Area | Stage of Treatment | Number | Before mean±SD | After mean±SD | The recovery rate | P Value |
|-----|-----------|--------------------|--------|----------------|---------------|-------------------|---------|
| 1 | Forehead | Stage 1 | 25 | 1.80± 3.92 | 1.55± 3.20 | 18.37% | 0.0001 |
| 2 | | Stage 2 | 19 | 1.59± 3.21 | 1.68± 2.53 | 21.18% | 0.0001 |
| 3 | Half the right eye | Stage 1 | 25 | 1.56± 3.76 | 1.49± 3.08 | 18.09% | 0.0001 |
| 4 | | Stage 2 | 19 | 1.58± 3.11 | 1.32± 2.79 | 10.29% | 0.0001 |
| 5 | Half the left eye | Stage 1 | 25 | 1.58± 3.56 | 1.54± 3.08 | 13.48% | 0.001 |
| 6 | | Stage 2 | 19 | 1.67± 3.01 | 1.46± 2.79 | 7.31% | 0.028 |
| 7 | Mouth and nose | Stage 1 | 25 | 1.41± 3.68 | 1.38± 3.40 | 7.61% | 0.032 |
| 8 | | Stage 2 | 19 | 1.43± 3.42 | 1.40± 3.22 | 5.85% | 0.104 |
| 9 | The eyes front the face | Stage 1 | 25 | 1.77± 3.96 | 1.69± 3.52 | 11.11% | 0.001 |
| 10 | | Stage 2 | 19 | 1.70± 3.68 | 1.64± 3.37 | 8.42% | 0.055 |
| 11 | Face area (Totally) | Stage 1 | 25 | 1.77± 3.79 | 1.69± 3.52 | 7.12% | 0.0001 |
| 12 | | Stage 2 | 19 | 1.70± 3.58 | 1.64± 3.37 | 5.86% | 0.021 |

Table 2: Patients satisfaction of their treatment results and treatment center factors

| Row | Discution | Mean±SD | Not very satisfaction % | very satisfaction % |
|-----|-----------|---------|-------------------------|---------------------|
| 1 | Your satisfaction about decreasing the depth of wrinkles | 3.95±1.05 | 37 | 63 |
| 2 | Your satisfaction about reduce the length of wrinkles | 3.60±1.04 | 50 | 50 |
| 3 | Your satisfaction about diminish wrinkles away | 3.85±0.74 | 44 | 56 |
| 4 | Your satisfaction  about  loss of skin spot | 3.90±0.91 | 37 | 63 |
| 5 | Your satisfaction about skin tightness | 3.45±1.36 | 52 | 48 |
| 6 | Your satisfaction  about  lighting skin | 3.95±0.83 | 31 | 69 |
| 7 | Your satisfaction,  about  loss of acne and acne scars on the skin | 3.35±0.87 | 57 | 43 |
| 8 | Your satisfaction about the loss of scar | 3.35±0.87 | 60 | 40 |
| 9 | Your satisfaction about closing the pores on your face | 3.95±0.82 | 46 | 54 |
| 10 | Your satisfaction  about soften of your skin | 4.30±0.73 | 11 | 89 |
| 11 | Your satisfaction about Fluoresce of your skin | 4.2±0.76 | 21 | 79 |
| 12 | Your satisfaction about rejuvenating | 3.35±0.74 | 59 | 41 |

After treatment                    Before treatment
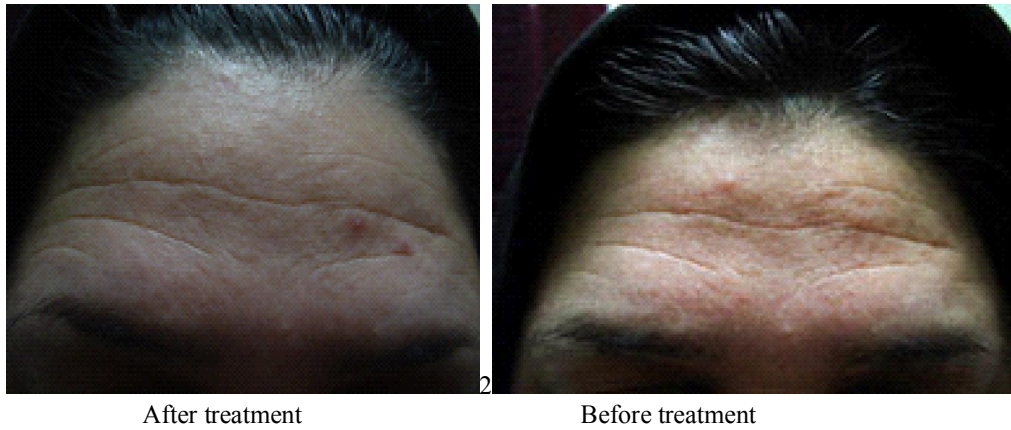


One month later.
Figure 1: Wrinkles, a patient before treatment - after treatment and one month later.



Before treatment                    after treatment
Figure 2: Significant improvement in treatment acne and infectious acne


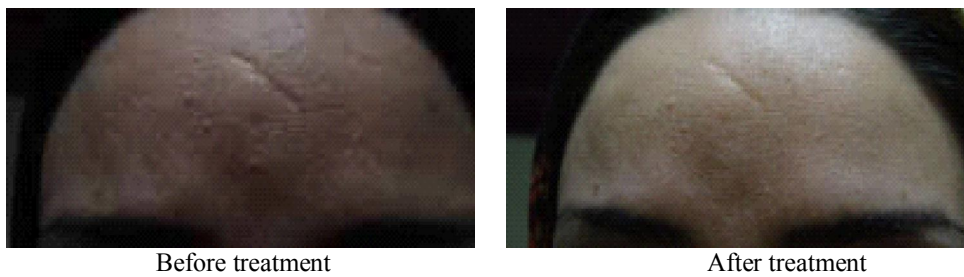
Before treatment                    After treatment
Figure 3: significant improvement in scaring

## 3. Results

This study aims to investigate the effects of micro currents on removing facial wrinkles and was conducted as a before /after trial study. This study consists of 30 women residing in Yasuj and suburbs which last 7 months beginning from 23th Oct 2010.Due to length of the study, 25 women completed the therapy period and despite of our follow up, only 19 women referred for photography, one month after treatment. Age mean and standard deviation of patients were 37/5 _+4/6(25-45). Evaluation of wrinkles of forehead areas, right/left eyes' profiles, eyes front and nasolabial area and face as a whole, indicated the significance of the study. The forehead area show the greatest improvement(%18/37) in the first stage (before treatment and after completion of the study) and %21/18 in the second stage (after treatment one month later).The nasolabial area constituted 7/61 percent of improvement (minimum improvement) in the first stage and 5/85 percent in the second stage(table 1).

Also 70% of patients were satisfied with their treatment results (table 2).

## 4. Discussions

In this study, the effect of micro currents on removing and reduction of facial wrinkles after 30 treatment sessions was significant .The improvement rate was greatest in the forehead area and was the least in nasolabial area .This was perhaps due to possibility of more effective use of the apparatus in the forehead area than the other areas .On the other hand, the tissue texture of forehead has more improvement capability. On the forehead after one month improvement continues significantly. In the right eye and left eye of the profile and eyes of the face both of them t treatment's affect is significant, But, the second stage is less effective. Overall, the treatment effect was significant in both stages.

Also, comparing scores after treatment and one month later shows that not only effect of treatment was sustained but also recovery in the face of the subjects started and has continued.

An important finding in this study was improvement of scars, acnes (especially infectious acnes) and skin rashes in the face of subjects.

Limitation: Regarding problems and limitation of the study and its being novelty in Iran, there was no chance to compare the results with studies of domestic ones. The therapy period (30 sessions) and length of every session (equal 40 minutes with preparation of the patient) caused the slow progress of the research execution.

1-Regarding cultural bound photography of the intended areas by a professional photographer

was not possible, so the photos were taken by the researcher.

Conflict of interest: The authors, certify that there is no actual or potential conflict of interest in relation to this article.

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# Comparison of recurrent rate in Nasolacrimal duct obstruction, with and Without Mitomycin C associated with probing

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**Abstract:** Nasolacrimal duct obstruction is the most common cause of tearing in children. Patients with Lacrimal duct obstruction have various symptoms such as tearing, infection, acute or chronic lacrimal sac, conjunctivitis, red eye or eczematous skin reactions to their lower eyelids. This study Compared recurrent rate of Nasolacrimal duct obstruction, with and without Mitomycin C associated with probing, a double blind randomized clinical trial. This study is a double blind randomized clinical trial. 150 patients diagnosed with cramps tearing the tear duct, patients allocated randomly to experimental and control groups. 3 patients from control group and 2 patients from trial group were drop from to follow up. 91 eyes from 72 patients in control group and 98 eyes from 73 patients from trial group were diagnosed with cramps tearing the tear duct. All patients, received general anesthesia, then Patients in control group treated with probing and patients in trial group treated by probing associated with 2 cc solution of Mitomycin 10 mg per cent Mitomycin C injected into the nasolacrimal duct after probing. Each patient followed for one month after treatment at intervals of ten days and one month. After 1 month follow up in 89 from 91 eyes (97/1%) in trial group and 88 from 98 eyes (89.79%) in control group, nasolacrimal duct was symptomatically satisfied and no complication was observed. This study showed that probing and irrigation with Mitomycin c was a method with significantly better success rate and could be an appropriate additive option for treated congenital nasolacrimal duct obstruction.
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Key words: Probing, Mitomycin c, Nasolacrimal duct, obstruction

## 1. Introduction

Tearing is one of common complaints of ophthalmology patients that can be very annoying for patient. Other than those factors that may increase secretion of tears, congenital nasolacrimal duct obstruction is the main cause of tearing in children. Congenital nasolacrimal duct obstruction commonly is the result of nasolacrimal duct distal end non-canalized and obstruction is rare in nasolacrimal duct. Patients with nasolacrimal duct obstruction refer to a doctor with multiple symptoms such as tearing, lacrimal sac acute or chronic infection, conjunctivitis, eye redness or skin reaction eczema of lower eyelids. Tearing occurs in nearly 20 percent of infants, and in more than 90 percent of cases, spontaneous recovery occurs during first 12 months. The incidence of congenital nasolacrimal duct obstruction is 4-7 percent. Treatment of congenital nasolacrimal duct obstruction is hydrostatic pressure on lacrimal sac and using topical antibiotics in early months. In case that obstruction was not healed with supportive treatments, catheterization is a standard method to treat and remove obstruction, and its success rate is high. Mitomycin C application has been started in ophthalmology since about 1993 and it applies in different eye diseases as an adjunct therapy. Mitomycin C is a drug that prevents fibroblasts division and in human and animal studies, it cause to control proliferation of under conjunctiva fibroblasts. Therefore, so far in trabeculectomy operation, preventing recurrence of carcinoma of cornea, reducing recurrence of pterygium, DCR operation (Dacryocystorhinostomy), reducing posterior capsule opacity and vernal conjunctivitis treatment which is resistant against treatment have been used. In study of Kumar, 27 patients have been divided into two groups of subject and control, that mitomycin C (0.4 mg/ml) was used in 15 patients during catheterization and recovery rate of disease symptoms was reported 80% (12 eyes) after one year follow-up in this group and in it was reported 8.3% (1 eye) in control group. No side effects have been observed in using mitomycin.

Tsai study was conducted with the purpose of determination of effective rate and safety of using mitomycin C (0.2 mg/ml) during catheterization on adult patients with nasolacrimal duct obstruction; from 36 under study eyes, 32 eyes (89%) had open nasolacrimal duct and 4 eyes infected recurrent obstruction. This study showed that the use of

mitomycin C has good results in catheterization of nasolacrimal duct in long term. In study of Dolmetsch on children of 16 years or less, 94.4% success was shown in nasolacrimal duct obstruction treatment and safe use of mitomycin C. In a study of Shenasi and colleagues on 80 adult patients with nasolacrimal duct obstruction, a comparison was conducted between the use of mitomycin C during catheterization and using DCR method without use of mitomycin C on recovery rate of nasolacrimal duct obstruction symptoms, and in this study in two weeks follow-up after operation, 95.5% of catheterization group, and 97.5% of subjects of DCR group had recovery symptoms and in six months follow-up, 77.5% subjects of catheterization group and 92.5% subjects of DCR group had recovery symptoms. This research showed that the use of mitomycin during catheterization is beneficial for treatment of nasolacrimal duct obstruction, although its efficacy is reduced over time.

In a study by Angela And colleagues that was done to determine prognosis and safety of using mitomycin C during DCR operation on adult patients with nasolacrimal duct obstruction (congenital, acquired, traumatized), it was shown in eighteen-months follow-up that using mitomycin C (0.5 mg/ml) during DCR operation had 95% success in eliminating secretion and epinephrine immediately.

Study of Tabatabai and colleagues was done on adults with nasolacrimal duct obstruction, it aimed to evaluate the effect of catheterization on nasolacrimal duct in association with mitomycin C 0.2 mg/ml, 58 eyes of 56 patients were studied, after catheterization, nasolacrimal duct was washed with 1 cc mitomycin solution with a concentration of 0.2 mg/ml. After eight months follow-up, 30 eyes (51.7%) had an open nasolacrimal duct, 23 eyes (39.7%) had partial obstruction and 5 eyes (8.9%) had complete obstruction. From Clinical symptoms point of view, it was reported that 35 patients (60.3%) had complete loss of epiphora, 17 patients (29.3%) had reduction of epiphora and 6 patients (10.3%) had no recovery. No complications were reported in the use of mitomycin C. In a study by Razaghie and colleagues on 17 eyes with nasolacrimal duct obstruction that was done to evaluate the effect of using mitomycin C during catheterization on adults; in last patients visit, 4 eyes (23.6%) had no tearing, 2 eyes (11.7%) had little tearing, 3 eyes had moderate tearing and 8 eyes (47%) had severe tearing. In this study it was shown that catheterization with mitomycin C injection can be considered as an alternative for reducing the severity of tearing in patients who are not suitable candidates for surgery, or those who don`t tend to perform DCR operation.

In Bazazie and colleagues study whose aim was to evaluate the effect and complications of mitomycin C during catheterization, 40 patients were studied that 6 patients had bilateral nasolacrimal duct obstruction and 34 patients had unilateral obstruction, after six months follow-up, nasolacrimal duct was wide open in 20 eyes (43.6%), and symptoms recovery were satisfied in 21 eyes (52.5%). In six-month follow-up of patients, no complications were reported in the use of mitomycin. The result of this study showed that this treatment could be a suitable method of partial nasolacrimal duct obstruction on adults. Some advantages of this method are simplicity, no need for general anesthesia, additional and expensive equipment and its low rate of morbidity.

In a study of Michanicie and colleagues that was done to compare the therapeutic effect of catheterization with and without use of mitomycin C in treatment of nasolacrimal duct obstruction, 120 eyes of 106 adults with nasolacrimal duct obstruction were studied. Patients were randomly divided in two groups of 60 eyes. First group was under catheterization operation and in second group in addition to above operation, their nasolacrimal ducts were washed with 1 cc of mitomycin C solution whose concentration was 0.2 mg/ml. One month after operation, treatment success was 55% in catheterization group and 96.6% in catheterization with mitomycin group and after one year follow-up, treatment success was reported 40% in catheterization group and 95% in catheterization with mitomycin C group. The result of this study showed that using mitomycin C during catheterization is an effective method for opening nasolacrimal duct obstruction. Despite the fact that several studies were done about effectiveness of using Mitomycin during catheterization on adults with acquired nasolacrimal duct obstruction and they had acceptable results, but no study has been done on children with congenital nasolacrimal duct obstruction treatment by catheterization in association with mitomycin C injection. This study aims to determine the effect of 0.1 mg/ml dose of mitomycin C injection with nasolacrimal duct catheterization to prevent nasolacrimal duct recurrent in children under eighteen months.

## 2. Material and Methods

In this study which was done during 2010-2011, children less than eighteen months who refer to Department of Ophthalmology in Yasuj city and had a complaint of tearing were entered into the plan with their parents' informed written consent. Entry requirements: complaint of tearing, less than 18 months old, and no secondary symptoms include: eye

dryness, entropion, ectropion, glaucoma, eyelids tumors and lacrimal system and no history of nasolacrimal duct surgery. Those patients, who did not regularly refer for follow ups, were excluded from plan. Sampling procedure: Available sample was based on target, and given the limitations and type of study and according to similar studies; sample size was considered 80 people for each group that finally 70 children from experimental group and 75 children from control group were participated in the plan until the end.

Treatment method: All patients were examined by a doctor and after general anesthesia they underwent catheterization operation with similar method. In children from experimental group, after catheterization, 2cc mitomycin solution of 0.1 mg per cent was injected into nasolacrimal duct and only catheterization was done in control group. Each patient had follow-up for two months after treatment and they were visited at intervals of ten days, one month and two months after catheterization, and the results were recorded.

Catheterization procedure: At first, patients were anesthetized generally by anesthesiologist in operating room. After washing around eyes with Betadine and preparation, because upper punctum is dilated under general anesthesia, using zero probe bowman, it was vertically inserted into upper punctum then probe is rotating in horizontal direction parallel to upper canaliculus, at the same time upper eyelid was pulled out to ensure that canaliculus is unruffled, simultaneously probe is driven inside too slowly until it is stopped and then it slowly pulled out and then it is vertically rotated until slip on inside nasolacrimal duct. Because obstructions often occur in lower level of nasolacrimal duct, probe needs to have a bend so that it could go directly into lower and back of duct, when it arrives to lacrimal sac.

After probing lacrimal duct and assurance of duct openness, using a 2 cc syringe with dull tip that has been passed from punctum and canaliculus, 2 cc mitomycin 0.1% which had already been prepared was injected into duct of patient slowly and over several seconds. During injection, the patient's nose and pharynx were suctioned to prevent leakage of mitomycin into throat. After one minute of injection time, nasolacrimal duct was washed with normal saline and finally the eye was dried and two drops of gentamicin were dripped into each eye. Patients were evaluated at intervals of ten days, one month and two months after catheterization and in each follow-up; child tearing and any eye secretion were asked from parents and eye was examined for cornea and conjunctiva complications. Data collection tool was a questionnaire in which a check list was recorded by therapist physician for situation and symptoms including: age, sex, symptoms, involvement of left or right eyes or both of them, age at diagnosis time, catheterization history, drug history, age at the time of catheterization, date of catheterization, interval follow-up of ten days, one month and two months after catheterization. Collected data was analyzed by SPSS-17 software and Fisher's exact test. Central and dispersion indices and frequency distribution tables were used to report data.

## 3. Results

The average age of diagnosis of nasolacrimal ducts obstruction was $6.5 \pm 2.1$, average age at surgery, with a minimum 9 and maximum 18 months was equal to $12 \pm 1.5$ months and the interval between diagnosis and surgery was equal to $5.6 \pm 1.2$ months. Patients were under examination and evaluation for 10 days, one month and two months after catheterization. Profile Details of patients are presented in Table 1.In first follow-up of experimental group, 89 eyes of 91 eyes with 97.1% success and in control group, 88 eyes of 98 eyes with 89.79% success, had no re-obstruction of nasolacrimal duct and this situation did not change until the end of study. Using mitomycin C significantly prevented nasolacrimal duct re-obstruction in patients. Success rate in one month follow-up after operation of 97.1% with 95% confidence was 95.35-98.96. Also no special effect was observed for mitomycin C injection in experimental patients group. Details of patients' treatment are presented in Table 2.

## 4. Discussions

Nasolacrimal duct catheterization has been accepted as a standard method with high achievement in children with congenital nasolacrimal duct obstruction. The success rate of catheterization is 85-95% in children less than one year, and its prognosis is reduced with increasing patient's age and increasing number of catheterization. In Honavar and colleagues study on 2 years children and older, catheterization success rate was reported 80% and it is significantly different with results in children under one year. Factors that had caused failure: older than 36 months, failure of supportive therapy, and failure in early catheterization, dilated lacrimal sac, and bilateral obstruction. This study was done on children under eighteen months with nasolacrimal duct obstruction in order to have no effect of age for success rate. In Sturrock and colleagues study that was conducted to examine long-term results of catheterization operation in children with nasolacrimal duct obstruction, after 4-13 years follow-up, 30% of patients still had symptoms of obstruction. Mitomycin C is an antibiotic with anti-

proliferation cell property that it has been used in various reports. There has been a significant difference (P=0.0014) between success rate 97.1% that was obtained in this study and Sturrock and colleagues study` success rate 86% that was obtained by catheterization without using mitomycin C. In michanicie and colleagues study on adult patients with nasolacrimal duct obstruction, after catheterization, duct was washed with 0.2 mg/ml dose of mitomycin and after a month, the success rate in catheterization with mitomycin group was reported 96.6% in comparison with no mitomycin group that its success rate was 55%, and in one-year follow-up, success rate was reported 95% in mitomycin group while this rate was 40% in without mitomycin group. This study showed that the use of mitomycin, during catheterization, increase considerably success rate in long-term, results of our study on one-month follow-up of patients (97.1%) is near to results of this study in one-month follow-up of their patients. Tabatabai and colleagues studied adult patients with nasolacrimal duct obstruction, after catheterization, they washed nasolacrimal duct with 1 cc mitomycin solution with a concentration of 2 mg/ml. After eight months follow-up, 51.7% of subjects had an open nasolacrimal duct, 39.7% of subjects had partial obstruction and 8.9% of subjects had complete obstruction. No complications were reported in the use of mitomycin C in study. Its success rate is less than present study. Dolmetsch and colleagues in a study conducted on children aged 16 years and under, showed success rate of 94.4% in nasolacrimal duct obstruction treatment with the use of mitomycin C, therefore they indicate mitomycin as an effective drug for increased likelihood of successfulness of operation. Our study success rate has been more than this study. In a study by Bazzazi and colleagues that was conducted on patients with nasolacrimal duct obstruction, after catheterization, nasolacrimal duct

was washed with mitomycin C that after a six-month follow-up nasolacrimal duct was completely open in 20 eyes (43.6%) and 21 patients (52.5%) were satisfied with improvement in symptoms. In six-month follow-up of patients, no complications were reported in using mitomycin. Result of this study showed that this treatment could be an appropriate method for treatment of nasolacrimal duct obstruction in adults. Some advantages of this method are simplicity, no need for general anesthesia, additional and expensive equipment and its low rate of morbidity. Its result is lower than the results of present study.Kumar and colleagues in a study on patients with nasolacrimal duct obstruction, after catheterization, washed duct with dose of 0.4 mg/ml, and they obtained 80% for rate of improvement in symptoms after one year follow-up (compared to 8.3% in control group). In this study, no side effects caused by mitomycin were observed.

In a study by Tsai and colleagues that was conducted with the purpose of determination of effective rate and safety of using mitomycin C (0.2 mg/ml) during catheterization on adult patients with nasolacrimal duct obstruction; after 9 months follow-up, 89% of subjects had widely open nasolacrimal duct. It was concluded in this study that the use of mitomycin C has good results in long term in nasolacrimal duct catheterization and it is suggested as a simple, effective and yet least invasive technique. Final result is that the use of mitomycin C during nasolacrimal duct catheterization leads to increase the success rate of catheterization and prevention of duct re-obstruction in children with congenital nasolacrimal duct obstruction.

Limitations of study: it was better to follow study in 3,4,5,6 months and it was not possible due to dispersion of patients and specific problems of province.

Table 1: General conditions of children under 18 months participants in the project.

| Discussion | Sex | | | Eye | | | History | |
|---|---|---|---|---|---|---|---|---|
| | Female | Male | Total | Right | Left | Both eyes | Drug use History | Family History |
| Control | 41(55) | 34 (45) | 75(100) | 28(37) | 24(32) | 23(32) | 70(93) | 2(3) |
| Cases | 40(57) | 30(43) | 70(100) | 25(36) | 24(32) | 21(30) | 68(97) | 1(1) |
| Total | 81(56) | 64(44) | 145(100) | 53(65) | 48(59) | 44(54) | 138(95) | 3(1) |

Table 2: Distributions of Eye surgery in terms of re-occlusion or obstruction of lacrimal canal in two groups

| Discussion | Without Recurrent | With Recurrent | Eyes | Successful Rate (%) |
|---|---|---|---|---|
| Controls | 88 | 10 | 98 | 89.79(87.86, 92.24) |
| Cases | 89 | 2 | 91 | 97.80(94.86, 99.64) |
| Total | 180 | 9 | 189 | ---- |

$\chi^2 = 5.09$     df= 1     P< 0.05

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7/2/2012

# Opiate and Alcohol abuse and related factors in Yasouj University of Medical Sciences (south of Iran)

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**Abstract: Introduction:** Substance abuse is a major concern all over the word and among medical students and physicians should be taken more seriously. **Materials and methods:** samples were selected by randomized systematic sampling of all students of Yasouj University of medical sciences. Sample size was estimated 215 students. Data were collected using questionnaire prepared by researchers. **Result:** 30 (13.95%) of 215 students had usage of alcohol, 14 (6.5%) had usage of opium with inhalation method, 3 (1.39%) had usage of morphine and 2 (0.93%) had usage of heroin with inhalation method, with significant male and single predominance. **Conclusion:** There is substance abuse in medical students with high usage rate and most intuition factor is seeking pleasure. Hashemi Mohammad Abad Nazir , Zadeh-Bagheri Ghader and Ghafarian Shirazi Hamid Reza.. *Life Sci J* 2012;9(3):1195-1198]. (ISSN: 1097-8135). http://www.lifesciencesite.com. 168

**Key word:** opiate, alcohol, medical student, Yasouj

## Introduction:

Substance abuse is a major concern all over the word and potentially holds a number of negative implications for the health. Different factors affect epidemiology of substance abuse (1).

Substance abuse among medical students and physicians should be taken more seriously because their own attitudes towards substances may influence their professional behavior (2).

Two of substance abuse that publicly despised and prohibited by law and religion in Iran are opiate and alcohol. There is anecdotal report of substance abuse with very wide range in Iran. Mohammad Poorasl et al., from Tabriz, a province of Iran, reported 12.7% 0f students have ever used alcohol and 2% have used illicit drugs. The reasons for substance abuse were older age, having self injury and high socioeconomic class for use of alcohol (3). Ahmadi et al., from Shiraz, a province of Iran, reported 30% of high school students had usage of substance: alcohol 9.6%, opium3.5%, heroin 2% and morphine 0.8%. The most common reasons for substance abuse were seeking pleasure and release of tension (4). Ahmadi et al., in another report of nursing students reported 27.3% had usage of substances: opium 8.5% and alcohol 5.8%. The major reasons for usage of substance were pleasure purposes, habit and decrease tension (5). Ziaaddini H et al., from Kerman, a province of Iran, reported opium abuse was the most frequent substance abuse (17.1%), any one consumed alcohol and there was no injection. Drug abuse in male is more than female (6). In another report from Kerman by Nakhaee et al., the

most common substance abuse among male was alcohol 11.4%, the most common substance abuse among female was sedative tablets 12.2% (7). Alizade et al., from Kurdistan, a province of Iran, reported: substance abuse among medical students was: alcohol 17.1, opium 4.8% and heroin 0.7%. The most common motivation for opium use was Curiosity and the most common reason for alcohol and heroin use was pleasure. Drug abuse in male is more frequent than female (8). Momtazi et al., From Zanjan, reportd: alcohol and opium are one of the most frequently used illicit drugs between Zanjan University. Alcohol use with a lifetime rate of at least 9.9%, opiate use - mostly opium - was between 1.2% and 8.6%. Substance abuse could be due to role modeling by parents mainly fathers, also cultural tolerance of some substances and Early onset of tobacco smoking. It is necessary to design and implement drug prevention programs to protect them (9).

Epidemiology of opiate and alcohol  and related factor are vary in other part of the word for example in USA opioids are commonly administrated for the treatment of moderate to severe pain and are among the most widely prescribed drugs, while these drugs have an essential role in pain management. Opioids regularly used in us population were 2% and at previous week were 5%. Pain dominated the reasons reported for opioid use (10). In the United States: among university students, the prevalence rates of lifetime alcohol use 84.7% (1). Drinking and smoking among 15- and 16- year- old in the UK, 94% had at some time consumed alcohol. Living in single-

parent family, lack of constructive hobbies, presence of psychiatric symptoms, and an aggressive outgoing delinquent lifestyle bore the strongest association with use of alcohol and illicit drugs (11 and 12). The prevalence of current drinkers of alcohol has risen over the period, to 82.5% among western students of Irish University in 2002. Findings show a marked increase in alcohol and drug consumption between 1973 and 2002. Missing study, more sexually involved and getting into a physical fight or argument, stress and high anxiety, personality traits were implicated in alcohol consumption (13). 86% of the students of Leeds University drank alcohol and among those who drank, a high proportion (52.6% of the men and 50.6% of the women), exceeded the recommended weekly limit of alcohol consumption of 21 units for men and 14 units for women per week (14). Nearly half of the Turkish medical students (46%) were alcohol-drinkers, risky alcohol use was 7.4%. Alcohol was the most frequently used substance in both groups (male and female). Senior students are more likely to use alcohol than junior students. Only 4% of students reported using illicit drugs at least once in their lifetime. 25.5% of the students had anxiety and 36.8% had depression (2). There was an increase use of illicit drugs between students of Brazil University, especially among male's students in the early undergraduate years. Lifetime prevalence of alcohol use was 94.8% and previous 12 months was 85.7% and lifetime prevalence of opiates use was 1.9% and previous 12 months was 1.4%. There was no significant gender difference between them (1).

Therefore, due to publicly despised and prohibited by law and religion of opium and alcohol in Iran, and there is no any report of substance abuse drug in Yasuj province, this is the purpose of this research.

**Materials and methods:**

**Subject**: samples were selected by randomized systematic sampling of all students of Yasouj University of medical sciences (214 medical students, 167 under graduate students, 274 Resourceful students).

**Sample size**: based on purpose and type of study with considering sampling error ($\alpha$=0.05), conservative rate value of drug abuse (p=0.50),

maximum error estimation (d=0.1) and taking 2 level for categorical sampling, sample size was estimated 215 students.

**Collecting data instruments:** data were collected using questionnaire prepared by researchers for purposes of this study; the questionnaire contains 50 questions in two parts. Parts one include demographic data and part two include related questions to drug abuse. Its validity confirmed by specialist. Its reliability calculated by $\alpha$-Kranbakh method ($\alpha$=0.74).

Students were free to answer in any way or no answer to some questions. A "ballot box" placed in front of the salon entrance ensured anonymity.

**Data analysis:** Collected data were analyzed by SPSS version 17, percents, central, Dispersion indices and tables were used for descriptive study and appropriate test use for analytics.

**Results:**

Among 215 participants, 126 (58.6%) students were male and 89 (41.4%) were female. 161(74.9%) were single and 54 (25.1%) were married. 39 (18.0%) were medical students, 90 (42.0%) were undergraduate students and 86 (40.0%) were resourceful students. their age were between 19-35 years with mean SD (21±2.8). Among 215 students, 49 (22.8%) had substance use: 30 (13.95%) had usage of alcohol, 14 (6.5%) had usage of opium with inhalation method, 3 (1.39%) had usage of morphine and 2 (0.93%) had usage of heroin with inhalation method. Among 49 students with substance usage, 31(63.2%) were male and 18(36.7%) were female. Among 215 students, the most opiate and alcohol abuse were between medical students and the lowest between undergraduate students. Using per year was the most patterns and daily use was the lowest [Table 1 and 2].

The most intuition toward substance abuse by their self were seeking pleasure (more than 50%), socializing with unsavory friends (25%), educational problem (8.3%), psychiatry disorder (5.7%), social problem (6%), economical problem (5%).

The most source of taking information about substance were radio and TV (45.1%), study of journal (27%), conversation with friends (22.4%), study of newspaper (4.6%).

**Table 1: Demographic characteristics of Participant students**

|  | No. | single | married | medical student | under graduate student | resourceful student |
|---|---|---|---|---|---|---|

| male | 126(58.6%) | 96(44.6%) | 30(14.0%) | 18(8.0%) | 56(26.0%) | 52(24.0%) |
| female | 89(41.4%) | 65(30.2%) | 24(11.1%) | 21(10.0%) | 34(16.0%) | 34(16.0%) |
| total | 215 (100%) | 161(74.9%) | 54(25.1%) | 39(18.0%) | 90(42.0%) | 86(40.0%) |

**Table 2: distribution of studied students with abused and their related factors**

| | alcohol | opium | morphine | heroin | total |
| --- | --- | --- | --- | --- | --- |
| male | 17(54.0%) | 9(29.0%) | 3(9.6%) | 2(6.4%) | 31(100%) |
| female | 13(72.2%) | 5(27.7%) | - | - | 18(100%) |
| single | 22(59.4%) | 10(27.0%) | 3(8.1%) | 2(5.4%) | 37(100%) |
| married | 8(66.6%) | 4(33.3) | - | - | 12(100%) |
| daily | 5(50%) | 2(20%) | 2(20%) | 1(10%) | 10(100%) |
| sometimes per month | 10(58.8%) | 5(29.4%) | 1(5.8%) | 1(5.8%) | 17(100%) |
| sometimes per year | 15(68.1%) | 7(31.8%) | - | - | 22(100%) |
| medical student | 7(58.3%) | 3(25%) | 1(8.3%) | 1(8.3%) | 12(100%) |
| undergraduate student | 10(62.5%) | 5(31.2%) | 1(6.2%) | - | 16(100%) |
| resourceful student | 13(61.9%) | 6(28.5%) | 1(4.7%) | 1(4.7%) | 21(100%) |

**Discussion:**

This study shows 22.8% of Yasouj University of Medical students had substance use. 13.95% had usage of alcohol and 8.8% had usage of opiate, with significant male and single predominance. This ranges of alcohol usage approximately the same as Kurdestan University, as but more than Kerman, Zanjan, Shiraz andTabriz Universities (some Universities of Iran). This rate of alcohol usage is very lower than USA, UK, Turkish, Brazil, Irish and Leeds Universities. Therefore usage of alcohol in Iranian Universities is very lower than European and American countries, may be due to prohibition by religious and law.

The opium usage in this study by students of Yasouj University of Medical sciences lower than Kerman University but approximately the same as Zanjan and Shiraz Universities and more than Kurdestan and Tabriz Universities( some universities of Iran). This rate of opiate usage is more than USA, UK and Brazil. Therefore usage of opiate in Iranian Universities is more than European and American countries may be due to prohibition by religious and law.

Male predominance usage of alcohol and opiate is the result of this study, approximately the same as other Iranian Universities and opposite to European American countries. This result may be due to social and cultural idea of male predominance, because male is responsible for all thing of family e.g. income, having house, having car, welfare, safe, security and etc in Iran.

Some related factor to alcohol and opiate usage in this study is the same as other study in Iran, Turkish, UK, Irish Universities e.g. seeking pleasure, educational problem and psychiatry disorder, but in USA the most related factor is treatment of pain.

These results shows radio, television, journal and newspaper had the most effect on the Iranian students lives, so planning preventive and therapeutic program is considered in their program.

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7/19/2012

# Analysis and Nursing of Cerebrovascular Disease Patients with Insomnia

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**Abstract**: Objective: Investigate and analyze the insomnia type and insomnia causes of 152 patients with cerebrovascular disease, and explore effective measures for treating cerebrovascular disease patients with insomnia. Methods: PSQI, SAS, SDS, SCL-90 scale was used for evaluation. Results: Symptoms of insomnia include prolonged sleep latency, short sleep duration and sleep disorders; causes of insomnia include anxiety, depression, somatization factor, the environment and drug factors. Conclusion: Prevention of insomnia could not rely solely on the drug, the targeted measures based on the cause of the insomnia should be taken to improve the quality of patients' sleep.

**Key words**: acute cerebrovascular disease; insomnia; nurse

## 1. Introduction

Insomnia is a very common problem (Sateia, 2004), especially in patients with acute cerebrovascular disease. Dysfunction of language and body movement which affects quality of life is easy to produce physical and psychological discomfort and lead to insomnia. Insomnia would result in mental disorders, increased physical symptoms and affect the rehabilitation process (McCarberg, 2003). Therefore, improving the sleep quality of patients with cerebrovascular disease is particularly important for the promotion of rehabilitation. Nursing also plays an important role in improving the patient's sleep (Maher, 2004; Nadolski, 2005). A series of effective measures were taken to help patients with insomnia as follows through investigation and analysis of 152 cases with cerebrovascular disease and insomnia admitted from February 2011 to February 2012.

## 2. Materials and methods

2.1 Subject:

The group of 152 cases, 86 cases of male and 66 cases of female, age ranging from 42 to 92 years old; 124 cases of cerebral infarction, 13 cases of cerebral hemorrhage, 15 cases of subarachnoid hemorrhage (SAH). No conscious obstacles, Diagnosis was confirmed by the head CT/MRI scan.

## 2.2 Methods:

2.2.1 Pittsburgh Sleep Quality Index (PSQI): The PSQI (Buysse et al., 1989) is a 9-question, 19 item self-report instrument designed to measure sleep quality and disturbance over a 1-month period (Carpenter & Andrykowski, 1998). PSQI questions 1-4 request specific respondent information that is filled in by hand, such as customary bed time and length of time to fall asleep. PSQI questions 5-8 are answered on a 0-3 scale with 0 indicating no symptom presence and 3 representing symptom presence 3 or more times the

past week. Question 9 is answered on a 0-3 scale with 0 meaning "very good" and 3 representing "very bad" (Carpenter & Andrykowski, 1998). All scores are combined according to the scoring criteria included with the form to produce a Global PSQI Score. Scores above 5 indicate clinically meaningfully disturbed or poor sleep (Holcomb,2006) .

2.2.2 SAS, SDS, SCL-90 scale assessment: Self-Rating Anxiety Scale (SAS), the standard score> 50 for clinical significance; Self-Rating Depression Scale (SDS), the standard score> 53 for meaningful; Symptom check list-90 (SCL-90) scale, standard score> 2 is meaningful. Two would be choosed according to the patient among the above three types of methods, 1 week after hospitalization.

## 3. Results

3.1 Types of insomnia and incidence: prolonged sleep latency, shortened sleep duration and sleep disorders. The PSQI Investigation results showed that: 94 cases,of prolonged sleep latency ,the incidence rate is 61.8%; 58 cases of short sleep duration, the rate is 38.2%; 36 cases of sleep disorders, , the rate is 23.7%.

3.2 Causes of insomnia: evaluation results according to SAS, SDS, SCL-90 scale, causing the causes of insomnia are: 106 cases of anxiety and depression, accounting for 69.7%; 69 cases of somatization factor, accounting for 45.4%; 32 cases of environmental factors, accounting for 21.1%; 22 cases of the influence of drugs, accounting for 14.5%.

## 4. Discussion

4.1 Anxiety and (or) depression: With the constant awareness of depression and anxiety disorders, patient population was expanding, insomnia is one of the important symptoms (Voyer, 2005). The data showed that most common causes of insomnia of patients with cerebrovascular disease is anxiety and depression, 106 cases of 152 cases in this group, the incidence rate of

69.7%. Due to fear of disease causing disabilities and burdening families, self-image changes by upper limb paralysis, aphasia, and other dysfunction would produce negative emotions such as anxiety, depression, pessimism, worry about their future, which can easily cause to sleep difficulties and sleep disorders.

4.2 Somatization factors: somatization disease can be accompanied by insomnia symptoms, such as heart disease, cancer, hypertension, tuberculosis, liver disease, frequent urination, and a variety of pain. There is insomnia at some stage of physical illness. or severe disease would affect sleep. With the improvement of disease, insomnia symptoms can be reduced. Cerebral infarction is a common brain disease, mostly on the basis of hypertention and atherosclerosis. Movement and sensory disturbances, headache, dizziness due to local tissue ischemia and hypoxia would   affect normal sleep, ultimately lead to insomnia. In this group sleep of 69 patients were affected by somatization factors, and paraplegic patients who can not own changing position and need others to assist in the regular turning, often lead to sleep disruption. Sometimes the limbs pain, joint pain, will also produce an adverse impact on sleep. Some patients with cerebral hemorrhage and subarachnoid hemorrhage, were often difficult to sleep due to headache. Other incontinence, diabetes mellitus, prostatic hypertrophy, stimulation of nasal feeding tube and catheter, constipation and abdominal distension could cause sleep disruption。

4.3 Environmental factors: fail to adapt to the new environment , the sick room temperature and humidity, noise in ward can affect sleep quality.

4.4 The influence of drugs: 22 patients of the group relied on estazolam for a long time have produced varying degrees of drug resistance. After admitted to the hospital the doctor's orders to stop or reduce the dose would leave the patients to produce insomnia.

**5. Nursing**
Henderson, the U.S. nursing experts, pointed out that to meet the patient rest and sleep is a basic duty of care, In clinical work, nurses should take the overall care and an integrated approach to improve patients' quality of sleep based on the bio-psycho-social medical model (Krishnan，2008；Wang，2010；Gilsenan，2012；Hedges，2012).

5.1 Psychological care: insomnia in patients with cerebrovascular associated with depression and anxiety are closely related with the family, social, psychological, physiological and other factors. Nurses should take the initiative to give patients psychological support and help patients to rational treatment of diseases, and lift the ideological concerns of patients, to avoid irritation in spirit to give comfort to eliminate the patient's anxiety and pessimistic mood. Strengthen social support, to make patients understand that his friends

and family who are concerned about them is their strong backing. Nurses and family members should be caring patient, so that patients feel the warmth of the family. Family members could participate in the activities of the rehabilitation of patients so that self-confidence of patients will be enhanced and better treatment and care will be achieved in a relaxed and harmonious environment. If encountered psychological problem cannot be solved, care nurses should guide them to focus thinking half an hour after dinner, and then learn to short-term forgetting, temporarily remove the interference in the mind, to reduce the affect of insomnia by excessive ideological concerns.

5.2 Create a good sleep environment and conditions: the sick room should be quiet, suitable temperature and humidity, the bed is not too soft, so as not to turn over with difficulties. At the same time, providing the individual environment closed to the family, for the purpose of convenience and comfort of the patient's is very important （ Test ， 2011 ）  . Avoid the implementation of treatment and care operations in a limited sleep time, the operation of the care must be performed in the natural awakening of the patients, so as not to reduce the number of passive awakening.

5.3 Reduce the impact of paralytic disease on the body: turn over every 2 h,and pat the back side ,put the involved limb in good limb position, the bed should be raised 15 ° ~30 ° for cerebral hemorrhage patients, help patients to remove or alleviate the discomfort caused by various diseases before going to bed.

5.4 Sleep hygiene education: guide patients to develop good sleep habits and establish more regular activities and rest periods. Urge patients formulate time activities every morning regardless of sleep state, increase physical activity during the daytime and   minimize daytime sleep time.in order to sleep good at night. Avoid exercise with excitability, smoking, the use of greasy food and alcoholic or caffeinated beverages and drugs before sleep. Recommend patients with a number of measures to promote sleep, such as drain urine 1h before going to bed, wash with warm water before going to sleep, and drink hot milk （Valtonen，2005）.

5.5 Light treatment: place light box than can be issued 2 500 lux (equivalent to 200 times the indoor light) 1 m in front of patients, 2 to 3 h, continuous lightening in the early morning or evening, to change the sleep-wake rhythm , forward or delay the the human biological clock. The mechanism of light therapy is to suppress melatonin secretion,it is mainly applied to the sleep rhythm disorders and elderly patients.

5.6 Cognitive behavioral therapy: cognitive behavioral therapy is for intractable insomnia patients able to get out of bed (Vance, 2011), which includes: ① go to bed when feeling sleepy; ② bed and bedroom only for sleep, can not read, watching TV or working in bed; ③ If can

not sleep in 15 to 20 minutes, you should get up and go to another room, only go back to bed when sleepy again( Li,2011); ④get up on time early in the morning regardless of how long night sleep is；⑤do not doze off during the day in order to improve sleep efficiency. In addition, there are several effective methods,such as relaxation training, the ambitendency training (Espie, 2007).

5.7 Nursing efficacy and safety of drug :nurses need to be familiar with the treatment of cerebrovascular disease and the effect and adverse reactions of the sedative and hypnotic drugs.

5.8 The guidance of drug knowledge: nurses should introduce patients with details, the name of the medication, the therapeutic effect, time of reasonable daily medication, adverse reactions of drugs. Strengthen the publicity of the importance of prescribed medication, caution patients to not be secretly altered the medication time or change the dosage without medical advice, such as Meclofenoxate and citicoline drug.

5.9 The proper application of sedative hypnotic drugs: sedative and hypnotic drugs should be used for intractable insomnia or sleep interrupted, nurses should take the initiative to inform patients and their families to the principle of the use of sedative-hypnotics, such as the minimum dose, intermittent, short-term medication and pay attention to withdrawal rebound (Holmquist, 2005). Nurses should contact with the doctor in charge for sleep disorders of patients, so that the doctor choose the targeted sedative and hypnotic drugs based on the different types of sleep disorders and drug half-life.

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# Calculation of Inviscid Compressible Flow past a Symmetric Aerofoil Using Direct Boundary Element Method with Linear Element Approach

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**Abstract:** In this paper, a steady, irrotational, inviscid compressible flow past a symmetric aerofoil has been calculated using direct boundary element method (DBEM) with linear element approach. The velocity distribution for the flow over the surface of the symmetric aerofoil has been compared with the analytical results.
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**Keywords:** Direct boundary element method, Inviscid Compressible flow, Symmetric aerofoil.

## 1. Introduction

In the present period of science and technology, the popularity of boundary element methods (BEMs) rises for solving fluid flow problems. These methods exist under different names such as panel methods, surface singularity method, boundary integral equation method, and boundary integral equation. Previously, finite difference method, finite element method, etc. were being used to solve numerically the problems in computational fluid dynamics. Later on, boundary element method has received much attention from the researchers due to its various advantages over the domain type methods. One of the advantages is that with boundary elements one has to discretize only the surface of the body, whereas with domain methods it is essential to discretize the entire region of the flow field. Moreover, this method is well–suited to problems with an infinite domain. The boundary element method can be classified into two categories i.e. direct and indirect. The direct method takes the form of a statement which provides the values of the unknown variables at any field point in terms of the complete set of all the boundary data. On the other hand, the indirect method utilizes a distribution of singularities over the boundary of the body and computes this distribution as the solution of integral equation (Brebbia, 1978 & 1980). The direct and indirect methods have been used in the past for flow field calculations around bodies (Morino 1975, Hess & Smith, 1967, Kohr, 2000, Luminita, 2008, Muhammad, 2008; Mushtaq, 2008, 2009, 2010, 2011& 2012). Most of the work on fluid flow calculations using boundary element methods has been done in the field of incompressible flow. Very few attempts have been made on flow field calculations using boundary element methods in the field of compressible flow. In this paper, the DBEM has been used for the solution of inviscid compressible flows around a symmetric aerofoil.

## 2. Mathematical Formulation

We know that equation of motion for two – dimensional, steady, irrotational, and isentropic flow (Mushtaq, 2010, 2011 & 2012, Shah 2011) is

$$( 1 - \mathrm{Ma}^2 ) \frac{\partial^2 \Phi}{\partial X^2} + \frac{\partial^2 \Phi}{\partial Y^2} = 0 \qquad (1)$$

where Ma is the Mach number and $\Phi$ is the total velocity potential of the flow. Here X and Y are the space coordinates.

Using the dimensionless variables, $x = X$, $y = \beta Y$, where $\beta = \sqrt{1 - Ma^2}$, equation (1) becomes

$$\frac{\partial^2 \Phi}{\partial x^2} + \frac{\partial^2 \Phi}{\partial y^2} = 0$$

or $\quad \nabla^2 \Phi = 0 \qquad\qquad (2)$

which is Laplace's equation.

## 3. Inviscid Compressible Flow Past a Symmetric Aerofoil

Consider the flow past a sy. aerofoil and let the onset flow be the uniform stream with velocity U in the positive direction of the x – axis as shown in figure (1).
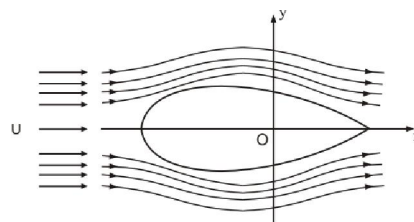


Figure 1: Flow past a symmetric aerofoil.

**Exact Velocity**

The magnitude of the exact velocity distribution over the surface of a sy. aerofoil is given by Chow [3] & Mushtaq [12, 16, 17,19]

as $\quad V = U \left| \dfrac{1 - \left(\dfrac{r}{z-b}\right)^2}{1 - \left(\dfrac{a}{z}\right)^2} \right|$

where r = radius of the circular cylinder,

a = Joukowski transformation constant

and b = a − r = x-coordinates of the centre of the circular cylinder

In Cartesian coordinates, we have

V = U

**Error!**

$x \dfrac{\sqrt{\left[ (x^2+y^2)^2 - a^2(x^2-y^2)\right]^2 + 4a^4 x^2 y^2}}{(x^2+y^2)^2 - 2a^2(x^2-y^2) + a^4}$

**Boundary Conditions**

Now the condition to be satisfied on the boundary of a symmetric aerofoil is (Mushtaq, 2011)

$\dfrac{\partial \phi_{s.a}}{\partial n} = U \dfrac{(x+b)}{\sqrt{(x+b)^2 + y^2}}$ (3)

Where the subscript s . a stands for symmetric aerofoil

Equation (3) is the boundary condition which must be satisfied over the boundary of a symmetric aerofoil.

**Equation of Direct Boundary Element Method**

The equation of DBEM for two–dimensional flow [Mushtaq, 2008, 2009, 2010 & 2011] is :

$-c_i \phi_i + \dfrac{1}{2\pi} \int\limits_{\Gamma - i} \phi \dfrac{\partial}{\partial n}\left[ \log\left(\dfrac{1}{r}\right)\right] d\Gamma + \phi_\infty$

$\quad = \dfrac{1}{2\pi} \int\limits_{\Gamma} \log\left(\dfrac{1}{r}\right) \dfrac{\partial \phi}{\partial n} d\Gamma$ (4)

where $c_i$ = 0 when i is exterior to Γ

$\quad\quad$ = 1 when i is interior to Γ

$\quad\quad$ = $\dfrac{1}{2}$ when i lies on Γ and Γ is

$\quad\quad\quad\quad$ smooth.

**Matrix Formulation with Linear Element Approach**

The equation DBEM (4) can be written for this case as

$-c_i \phi_i + \sum\limits_{j=1}^{m} \int\limits_{\Gamma_j - i} \phi \dfrac{\partial}{\partial n}\left(\dfrac{1}{2\pi} \log \dfrac{1}{r}\right) d\Gamma + \phi_\infty$

$\quad = \sum\limits_{j=1}^{m} \int\limits_{\Gamma_j} \dfrac{\partial \phi}{\partial n}\left(\dfrac{1}{2\pi} \log \dfrac{1}{r}\right) d\Gamma$ (5)

Since $\phi$ and $\dfrac{\partial \phi}{\partial n}$ vary linearly over the element, their values at any point on the element can be defined in terms of their nodal values and the shape functions $N_1$ and $N_2$ as

$\phi = [N_1\ N_2]\left\{\begin{matrix}\phi_1\\\phi_2\end{matrix}\right\}$

$\dfrac{\partial \phi}{\partial n} = [N_1\ N_2]\left\{\begin{matrix}\dfrac{\partial \phi_1}{\partial n}\\\dfrac{\partial \phi_2}{\partial n}\end{matrix}\right\}$ (6)

The integrals along an element 'j' on the L.H.S. of equation (5) can now be written as

$\int\limits_{\Gamma_j - i} \phi \dfrac{\partial}{\partial n}\left(\dfrac{1}{2\pi} \log \dfrac{1}{r}\right) d\Gamma$

$= \int\limits_{\Gamma_j - i} [N_1\ N_2] \dfrac{\partial}{\partial n}\left(\dfrac{1}{2\pi} \log \dfrac{1}{r}\right) d\Gamma \left\{\begin{matrix}\phi_1\\\phi_2\end{matrix}\right\}$

$= \left[ h_{ij}^1 \quad h_{ij}^2 \right] \left\{\begin{matrix}\phi_1\\\phi_2\end{matrix}\right\}$

where $h_{ij}^k = \int\limits_{\Gamma_j - i} N_k \dfrac{\partial}{\partial n}\left(\dfrac{1}{2\pi} \log \dfrac{1}{r}\right) d\Gamma$,

$\quad\quad\quad\quad\quad$ k = 1, 2. (7)

The integrals on the R.H.S. of equation (5) can be written as

$\int\limits_{\Gamma_j} \dfrac{\partial \phi}{\partial n}\left(\dfrac{1}{2\pi} \log \dfrac{1}{r}\right) d\Gamma$

$= \int\limits_{\Gamma_j} [N_1\ N_2]\left(\dfrac{1}{2\pi} \log \dfrac{1}{r}\right) d\Gamma \left\{\begin{matrix}\dfrac{\partial \phi_1}{\partial n}\\\dfrac{\partial \phi_2}{\partial n}\end{matrix}\right\}$

$= \left[ g_{ij}^1 \quad g_{ij}^2 \right] \left\{\begin{matrix}\dfrac{\partial \phi_1}{\partial n}\\\dfrac{\partial \phi_2}{\partial n}\end{matrix}\right\}$

where $g_{ij}^k = \int\limits_{\Gamma_j} N_k \left(\dfrac{1}{2\pi} \log \dfrac{1}{r}\right) d\Gamma$,

$\quad\quad\quad$ k = 1, 2. (8)

Again the integrals in equations (7) and (8) are calculated numerically as before except for the element on which the fixed point 'i' is lying. For this element the integrals are calculated analytically. The integrals $h_{ii}^1$ and $h_{ii}^2$ are zero because $r$ and $\hat{n}$ are orthogonal to each other over the element. The value of the integrals $g_{ii}^1$ and $g_{ii}^2$ are given by

$$g_{ii}^{(1)} = \frac{\ell}{8\pi}\,[\,3 - 2\log\ell\,]$$

and $g_{ii}^{(2)} = \frac{\ell}{8\pi}\,[\,1 - 2\log\ell\,]$

Also the velocity midway between two nodes on the boundary can then be approximated by using the formula

$$\text{Velocity } \overset{\otimes}{V} = \frac{\Phi_{k+1} - \Phi_k}{\text{Length from node } k \text{ to } k+1}$$

(9)

Where the total velocity potential $\Phi$ is the sum of the perturbation velocity potential $\phi_{s.a}$ and the velocity potential of the uniform stream $\phi_{u.s}$.

**Process of Discretization**

Now for the discretization of the boundary of the symmetric aerofoil, the coordinates of the extreme points of the boundary elements can be generated within computer programme using Fortran language as follows:

Divide the boundary of the circular cylinder into $m$ elements in the clockwise direction by using the formula (Mushtaq 2009, 2010, 2011 & 2012).

$$\theta_k = [\,(m+2) - 2k\,]\frac{\pi}{m},$$

$$k = 1, 2, \ldots, m \qquad (10)$$

Then the extreme points of these $m$ elements of circular cylinder are found by

$$\xi_k = -b + r\cos\theta_k$$

$$\eta_k = r\sin\theta_k$$

Now by using Joukowski transformation

$$z = \zeta + \frac{a^2}{\zeta}$$

the extreme points of the sy. aerofoil are

$$x_k = \xi_k\left(1 + \frac{a^2}{\xi_k^2 + \eta_k^2}\right)$$

$$y_k = \eta_k\left(1 - \frac{a^2}{\xi_k^2 + \eta_k^2}\right)$$

where $k = 1, 2, \ldots, m$.

Therefore the boundary condition (3) in this case takes the form

$$\frac{\partial\phi_{s.a}}{\partial n} = U\frac{(x_k + b)}{\sqrt{(x_k + b)^2 + y_k^2}}$$

$$= \frac{(x_k + b)}{\sqrt{(x_k + b)^2 + y_k^2}}$$

taking $U = 1$ (11)

The following tables show the comparison of computed and analytical velocity distribution over the boundary of a sy. aerofoil for 8, 16, 32, and 64 direct linear boundary elements.

**Table (1)**

| ELEMENT | X | Y | $R = \sqrt{X^2 + Y^2}$ | VELOCITY | EXACT VELOCITY |
|---|---|---|---|---|---|
| 1 | -1.94 | .39 | 1.98 | .72178E+00 | .83769E+00 |
| 2 | -1.39 | .94 | 1.68 | .17456E+01 | .20086E+01 |
| 3 | -.62 | .93 | 1.12 | .17562E+01 | .20216E+01 |
| 4 | -.01 | .38 | .38 | .80442E+00 | .70748E+00 |
| 5 | -.01 | -.38 | .38 | .80442E+00 | .70748E+00 |
| 6 | -.62 | -.93 | 1.12 | .17562E+01 | .20216E+01 |
| 7 | -1.39 | -.94 | 1.68 | .17456E+01 | .20086E+01 |
| 8 | -1.94 | -.39 | 1.98 | .72178E+00 | .83768E+00 |

**Table (2)**

| ELEMENT | X | Y | $R = \sqrt{X^2 + Y^2}$ | VELOCITY | EXACT VELOCITY |
|---------|-------|-------|------|-----------|-----------|
| 1 | -2.06 | .21 | 2.07 | .38552E+00 | .39565E+00 |
| 2 | -1.90 | .60 | 1.99 | .10980E+01 | .11264E+01 |
| 3 | -1.60 | .89 | 1.84 | .16440E+01 | .16923E+01 |
| 4 | -1.22 | 1.05 | 1.61 | .19407E+01 | .20055E+01 |
| 5 | -.79 | 1.05 | 1.32 | .19438E+01 | .20115E+01 |
| 6 | -.40 | .89 | .98 | .16542E+01 | .16985E+01 |
| 7 | -.10 | .58 | .59 | .11197E+01 | .10938E+01 |
| 8 | .11 | .20 | .23 | .48102E+00 | .30764E+00 |
| 9 | .11 | -.20 | .23 | .48102E+00 | .30764E+00 |
| 10 | -.10 | -.58 | .59 | .11197E+01 | .10938E+01 |
| 11 | -.40 | -.89 | .98 | .16542E+01 | .16985E+01 |
| 12 | -.79 | -1.05 | 1.32 | .19438E+01 | .20115E+01 |
| 13 | -1.22 | -1.05 | 1.61 | .19407E+01 | .20055E+01 |
| 14 | -1.60 | -.89 | 1.84 | .16440E+01 | .16923E+01 |
| 15 | -1.90 | -.60 | 1.99 | .10980E+01 | .11264E+01 |
| 16 | -2.06 | -.21 | 2.07 | .38551E+00 | .39565E+00 |

**Table (3)**

| ELEMENT | X | Y | $R = \sqrt{X^2 + Y^2}$ | VELOCITY | EXACT VELOCITY |
|---------|-------|-------|------|-----------|-----------|
| 1 | -2.09 | .11 | 2.10 | .19601E+00 | .19530E+00 |
| 2 | -2.05 | .32 | 2.08 | .58051E+00 | .57871E+00 |
| 3 | -1.97 | .51 | 2.04 | .94275E+00 | .94085E+00 |
| 4 | -1.85 | .69 | 1.98 | .12688E+01 | .12682E+01 |
| 5 | -1.70 | .84 | 1.90 | .15463E+01 | .15485E+01 |
| 6 | -1.52 | .96 | 1.80 | .17645E+01 | .17706E+01 |
| 7 | -1.32 | 1.04 | 1.68 | .19151E+01 | .19256E+01 |
| 8 | -1.11 | 1.08 | 1.55 | .19925E+01 | .20067E+01 |
| 9 | -.90 | 1.08 | 1.41 | .19936E+01 | .20097E+01 |
| 10 | -.69 | 1.04 | 1.25 | .19187E+01 | .19331E+01 |
| 11 | -.49 | .96 | 1.07 | .17707E+01 | .17783E+01 |
| 12 | -.31 | .84 | .89 | .15559E+01 | .15493E+01 |
| 13 | -.16 | .68 | .70 | .12832E+01 | .12519E+01 |
| 14 | -.04 | .50 | .50 | .96547E+00 | .89212E+00 |
| 15 | .06 | .29 | .29 | .63407E+00 | .47258E+00 |
| 16 | .15 | .09 | .17 | .27901E+00 | .17793E+00 |
| 17 | .15 | -.09 | .17 | .27902E+00 | .17793E+00 |
| 18 | .06 | -.29 | .29 | .63407E+00 | .47258E+00 |
| 19 | -.04 | -.50 | .50 | .96547E+00 | .89212E+00 |
| 20 | -.16 | -.68 | .70 | .12832E+01 | .12519E+01 |
| 21 | -.31 | -.84 | .89 | .15559E+01 | .15493E+01 |
| 22 | -.49 | -.96 | 1.07 | .17707E+01 | .17783E+01 |
| 23 | -.69 | -1.04 | 1.25 | .19187E+01 | .19331E+01 |
| 24 | -.90 | -1.08 | 1.41 | .19936E+01 | .20097E+01 |
| 25 | -1.11 | -1.08 | 1.55 | .19925E+01 | .20067E+01 |
| 26 | -1.32 | -1.04 | 1.68 | .19151E+01 | .19256E+01 |
| 27 | -1.52 | -.96 | 1.80 | .17645E+01 | .17706E+01 |
| 28 | -1.70 | -.84 | 1.90 | .15463E+01 | .15485E+01 |
| 29 | -1.85 | -.69 | 1.98 | .12688E+01 | .12682E+01 |
| 30 | -1.97 | -.51 | 2.04 | .94275E+00 | .94085E+00 |
| 31 | -2.05 | -.32 | 2.08 | .58050E+00 | .57871E+00 |
| 32 | -2.09 | -.11 | 2.10 | .19601E+00 | .19529E+00 |

**Table (4)**

| ELEMENT | X | Y | $R = \sqrt{X^2 + Y^2}$ | VELOCITY | EXACT VELOCITY |
|---|---|---|---|---|---|
| 1 | -2.10 | .05 | 2.10 | .98434E-01 | .97607E-01 |
| 2 | -2.09 | .16 | 2.10 | .29438E+00 | .29139E+00 |
| 3 | -2.07 | .27 | 2.09 | .48748E+00 | .48261E+00 |
| 4 | -2.04 | .37 | 2.07 | .67590E+00 | .66939E+00 |
| 5 | -2.00 | .47 | 2.05 | .85784E+00 | .85001E+00 |
| 6 | -1.95 | .56 | 2.03 | .10315E+01 | .10228E+01 |
| 7 | -1.89 | .65 | 2.00 | .11953E+01 | .11861E+01 |
| 8 | -1.82 | .74 | 1.96 | .13476E+01 | .13383E+01 |
| 9 | -1.74 | .81 | 1.92 | .14870E+01 | .14781E+01 |
| 10 | -1.66 | .88 | 1.88 | .16120E+01 | .16040E+01 |
| 11 | -1.57 | .94 | 1.83 | .17217E+01 | .17148E+01 |
| 12 | -1.47 | .99 | 1.78 | .18147E+01 | .18093E+01 |
| 13 | -1.37 | 1.03 | 1.72 | .18904E+01 | .18867E+01 |
| 14 | -1.27 | 1.06 | 1.66 | .19480E+01 | .19459E+01 |
| 15 | -1.17 | 1.08 | 1.59 | .19868E+01 | .19864E+01 |
| 16 | -1.06 | 1.09 | 1.52 | .20067E+01 | .20075E+01 |
| 17 | -.95 | 1.09 | 1.45 | .20073E+01 | .20090E+01 |
| 18 | -.84 | 1.08 | 1.37 | .19888E+01 | .19906E+01 |
| 19 | -.74 | 1.06 | 1.29 | .19512E+01 | .19524E+01 |
| 20 | -.63 | 1.03 | 1.21 | .18950E+01 | .18946E+01 |
| 21 | -.53 | .99 | 1.12 | .18208E+01 | .18174E+01 |
| 22 | -.44 | .93 | 1.03 | .17294E+01 | .17213E+01 |
| 23 | -.35 | .87 | .94 | .16217E+01 | .16072E+01 |
| 24 | -.27 | .80 | .85 | .14988E+01 | .14756E+01 |
| 25 | -.19 | .73 | .75 | .13620E+01 | .13275E+01 |
| 26 | -.12 | .64 | .65 | .12131E+01 | .11637E+01 |
| 27 | -.06 | .55 | .55 | .10538E+01 | .98490E+00 |
| 28 | -.00 | .45 | .45 | .88675E+00 | .79156E+00 |
| 29 | .04 | .34 | .35 | .71606E+00 | .58415E+00 |
| 30 | .08 | .23 | .24 | .55181E+00 | .36688E+00 |
| 31 | .12 | .11 | .16 | .43243E+00 | .18028E+00 |
| 32 | .17 | .03 | .17 | .12239E+00 | .17941E+00 |
| 33 | .17 | -.03 | .17 | .12238E+00 | .17941E+00 |
| 34 | .12 | -.11 | .16 | .43243E+00 | .18028E+00 |
| 35 | .08 | -.23 | .24 | .55181E+00 | .36688E+00 |
| 36 | .04 | -.34 | .35 | .71605E+00 | .58415E+00 |
| 37 | -.00 | -.45 | .45 | .88676E+00 | .79156E+00 |
| 38 | -.06 | -.55 | .55 | .10538E+01 | .98490E+00 |
| 39 | -.12 | -.64 | .65 | .12131E+01 | .11637E+01 |
| 40 | -.19 | -.73 | .75 | .13620E+01 | .13275E+01 |
| 41 | -.27 | -.80 | .85 | .14988E+01 | .14756E+01 |
| 42 | -.35 | -.87 | .94 | .16217E+01 | .16072E+01 |
| 43 | -.44 | -.93 | 1.03 | .17294E+01 | .17213E+01 |
| 44 | -.53 | -.99 | 1.12 | .18208E+01 | .18174E+01 |
| 45 | -.63 | -1.03 | 1.21 | .18950E+01 | .18946E+01 |
| 46 | -.74 | -1.06 | 1.29 | .19512E+01 | .19524E+01 |
| 47 | -.84 | -1.08 | 1.37 | .19888E+01 | .19906E+01 |
| 48 | -.95 | -1.09 | 1.45 | .20073E+01 | .20090E+01 |
| 49 | -1.06 | -1.09 | 1.52 | .20067E+01 | .20075E+01 |
| 50 | -1.17 | -1.08 | 1.59 | .19868E+01 | .19864E+01 |
| 51 | -1.27 | -1.06 | 1.66 | .19480E+01 | .19459E+01 |
| 52 | -1.37 | -1.03 | 1.72 | .18904E+01 | .18867E+01 |
| 53 | -1.47 | -.99 | 1.78 | .18147E+01 | .18093E+01 |
| 54 | -1.57 | -.94 | 1.83 | .17217E+01 | .17148E+01 |
| 55 | -1.66 | -.88 | 1.88 | .16120E+01 | .16040E+01 |
| 56 | -1.74 | -.81 | 1.92 | .14870E+01 | .14781E+01 |

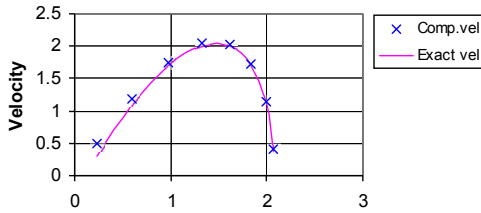| 57 | -1.82 | -.74 | 1.96 | .13476E+01 | .13383E+01 |
| 58 | -1.89 | -.65 | 2.00 | .11953E+01 | .11861E+01 |
| 59 | -1.95 | -.56 | 2.03 | .10315E+01 | .10228E+01 |
| 60 | -2.00 | -.47 | 2.05 | .85783E+00 | .85001E+00 |
| 61 | -2.04 | -.37 | 2.07 | .67590E+00 | .66939E+00 |
| 62 | -2.07 | -.27 | 2.09 | .48747E+00 | .48261E+00 |
| 63 | -2.09 | -.16 | 2.10 | .29438E+00 | .29139E+00 |
| 64 | -2.10 | -.05 | 2.10 | .98439E-01 | .97606E-01 |
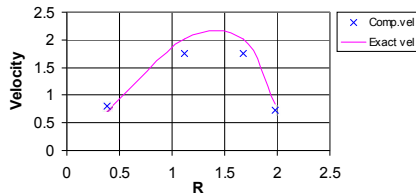


Graph 1: Comparison of computed and analytical velocity distributions over the boundary of a symmetric aerofoil using 8 boundary elements with direct constant element approach for r = 1.1, a = 0.1 and Ma = 0.7.



Graph 2: Comparison of computed and analytical velocity distributions over the boundary of a symmetric aerofoil using 16 boundary elements with direct constant element approach for r = 1.1, a = 0.1 and Ma = 0.7.



Graph 3: Comparison of computed and analytical velocity distributions over the boundary of a symmetric aerofoil using 32 boundary elements with direct constant element approach for r = 1.1, a = 0.1 and Ma = 0.7.



Graph 4: Comparison of computed and analytical velocity distributions over the boundary of a symmetric aerofoil using 64 boundary elements with direct constant element approach for r = 1.1, a = 0.1 and Ma = 0.7.
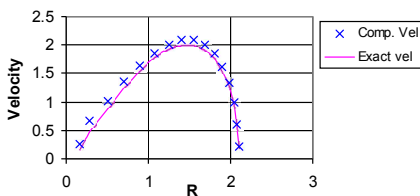
## 4. Conclusion

A direct boundary element method has been applied for the calculation of inviscid compressible flow past a symmetric aerofoil with linear element approach. The calculated flow velocities obtained using this method is compared with the analytical solutions for flow over the boundary of a symmetric aerofoil. The tables and graphs, indicate that the computed results obtained by this method are good in agreement with the analytical ones for the body under consideration and the accuracy of the result increases due to increase of number of boundary elements.

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# Satisfaction of Selective Farmers of theFarmer's House from Extension-Education Courses Held

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**Abstract:**The purpose of this descriptive-correlation study was to investigate satisfaction of selective farmers of the Farmer's House from extension-education courses held. The research instrumentation was structural questionnaire with close-ended questions, which its validity and reliability were confirmed. The statistical population of this study consisted of all selective farmers of the Farmer's House in 2010 (N=550) out of which, according to Israel table, a number of 225 people were selected, using simple random sampling method. Finally, 212 questionnaires were gathered and analyzed (n=212). Descriptive results of research indicated that 178 (84%) farmers have been attended extension-education courses during the three last years. Approximately 55% of them stated that dissatisfied from last courses attended, however, 70% of them stated that they had motivation to attend the next course. There was a statistically significant positive relationship between farmers' motivation level for attending these courses with their satisfaction level of these courses.

## Introduction

Agricultural extension system is one and the most important tools for distributing modern technology in agriculture, and that has significant role in development process especially the rural development. Rivera and Sulaiman[12] stated that is as a means of knowledge's transfer, innovation and development.

The purpose of agriculture extension system is informal education to the farmers for improving agriculture methods, so that they can utilize efficient and useful technologies in their own farming activities (TecerAtsan*et al*) [14]. Rivera and Qamar[11] believe that agriculture extension system via extension, technical and attitudinal trainings results in removing farmers' technical, skilling and informational needs and provides them with empowering and increasing quality of life and the efficient management of product resources. Karbasioun*et al* [7] believe that to help the farmers for making-decision is the most important role in agriculture extension, and that causes that they understand their goals and have their own learning based on their experience. Bahn&McAleer [3] divided extension-education courses into three categories; developmental, informational and institutional, and stated the goals as solving-problem, information' transfer, knowledge and ability in turn.

Fealy*et al* [4] believe that in order to have such successful findings from extension-education courses, many factors should be taken into consideration. Education satisfaction is one of the factors, by asking and having the learner' ideas about satisfaction level of educational courses; it is a way towards the adaption and acceptance level of educational material and its modification. Appraisal of acceptability of education materials and qualified level and satisfaction of the learners provide some pieces of useful information for designing, organizing, developing and implementing education programs. Pezeshki Rad *et al* [10] believe that agriculture instructors should understand the satisfaction level of the adult learners from their previous educational experiences in order to have better learning expectations for them. Gathering information about the adult learner' satisfaction makes the extension agents determine the best time and place for giving better education services. YazdanPanah*et al*[15] believe that organizations such as extension organization will recognize its client's expectations and needs by the results of the surveys;

then by removing the needs, that organization will provide the client's satisfaction and stability, and making interest because the client' dissatisfaction has bad and high costing outcomes for that organization. So information about the client's satisfaction for all organizations is acceptable, and no organizations would like to be closed because of dissatisfaction and client's absence. On the other hand, the farmers' satisfaction of governmental extension services is a necessary condition for moving towards extension privatization. Oladosu[9] stated that investigating the farmers' view about the satisfaction of extension services is one of important approaches for determining the qualified extension services.

Researchers have done many projects, using continuously studies in case of the farmers' satisfaction appraisal from agriculture extension services. For instance, Fealy*etal*'s[4] studies can be mentioned. The result of their study show the level of satisfaction of the majority of Qom gardeners from extension-education courses which held in the average. Yet the results show that the level of respondents satisfaction from principle of educational courses, in turn, in domain of educational goals, education of faculty, course content, educational methods, environment and educational facilities. In an investigation of qualified educational methods, it shows that the majority of respondents would tend to have practical education, a visit to of gardens and extension movie show. In their study Abdolmaleki*et al*[1] showed that the level of satisfaction majority of gardeners (45.70%) from extension-education courses held is on average. Beside, the results show that there is a positive and significant relationship (level of 1 percent) between characteristics of educational courses (the learner participation in educational subjects, the ability and the power of speech of instructor, well-fare facilities, having friendly relations, educational content's being clear, the time for holding classes and content's being new) with the respondents satisfaction. In their study, Karbasioun*et al* [8] showed that to attain new skill, experience, and information; and personal interests are the most important farmers' motivation in participation of extension-education courses. Moreover, the course time permanence, the course content utility in real environment, and contact with the members of the program are the most important characteristics of extension-education courses in which the farmers took part. SadighiandDarvishinia[13] gained a significant relationship between the farm size and the area under cultivated; and there isn't a significant relationship

between age and the level of the farmers' education with the level of satisfaction. Pezeshki Rad *et al* [10], in a study, indicated that the level of the satisfaction of the majority of the farmers (41.30%) from extension-education courses is on average. In addition, in the farmer' opinion the most important characteristics of the courses which held are time, place of courses and respect to the learners. On the other hand the findings showed that there is a significant relationship between yield rate, yearly income, and the number of participation in courses and there isn't a significant relationship between job experience, level of education and the area under cultivated of the respondents with their satisfaction level from education courses which held. In their studyAsaduzzamanSarkerandItohara[2] showed that the majority of farmers had (62%) a positive view toward efficiency of extension courses. Oladosu[9] the majority of the farmers (67%) were "satisfied and strongly satisfied" regarding the agriculture extension services. The present study has been held based on previously study with this goal; the satisfaction analysis of selective farmers as members of the Farmer's House from extension-education courses.

It is worth noting that the selective farmer as member of the Farmer's House is referred to as members'representativesof the Farmer's House in each village, were selected from the formal members of the House in that village. These groups of farmers, the majority of which contact farmer, local leader, sample farmers and so on are as the proper patterns by which other farmers can take them as a pattern, and the farmers can turn to them for solving different technical problems; accepting their recommendations better; and finally they become as instructor in informal educational environment to make distribution of innovations with social qualified value. On the other hand, applying the selective farmers in the process of extension activity can be paid attention to in terms of local management and the participatory they have in the process of local making decision. These types of farmers can be considered by having impact on the people of the society the society, and treated in a using that others are trying to be like them.

## Goal and Objectives

The purpose of the present study is to investigate the satisfaction of the selective farmers as members of the Farmer's House from extension-education courses. To attain the goal the following objectives should be regarded:

1- Investigating the state of the selective farmers' participation in extension-education courses over the three last years,
2- Describing professional and individual characteristics of the selective farmers,
3- Identifying the selective farmers' motivations for participating in extension-education courses,
4- Describing the satisfaction of the selective farmers from the last courses they took part in, and
5- Investigating the relationship between the professional and individual characteristics of the selective farmers with their level of satisfaction in extension-education courses.

**Materials and Method**

This study is of descriptive-correlation type, and it uses survey method with questionnaire. The statistical population of the present study consists the whole selective farmers as members of the Farmer's House (N=550), among which 225 selected by simple random sampling by using the Israel table (1992), and finally 212 questionnaires were analyzed (n=212).

The instrumentation for gathering data and information was questionnaire whose questions were designed into 2parts based on the review of literature [4, 1, 8 and 10]. The first part was devoted to the assessment of the farmers' participatory motivation in extension-education courses. The second part was devoted to information gathering about the individual characteristics of the farmers. To determine the validity of questionnaire, several copies of that questionnaire were in front of a group of experts like the professors of agriculture extension and education, and some necessary modifications based on, the expert suggestions were done. To determine the reliability coefficient, 30 questions were distributed out of statistical population. After gathering the questionnaire mentioned, the data were to be analyzed by a computer. The variables reliability of the motivation for participation and satisfaction level gained by Alpha Cronbach as 0.82 and 0.85 in turn. The statistical method in the present study was descriptive statistics (mean, standard deviation, frequency, frequency percentage, minimum and maximum) and analytical statistics (Pearson coefficient correlation). To analyze data the statistical software SPSS version 16 used.

**Findings and Discussions**

*The state of the selective farmers' participation in extension-education courses over the three last years*

Approximately 85% responded "Yes" to the question "Have you participated in extension-education courses in the three last years or not?" And 34 of participants (16%) responded "No" (Table 1). Therefore, in this study, the opinion of the respondents who participated in extension-education courses was used and the rest who not participated were taken out of the analytical statistic.

Table 1- The state of the selective farmers' participation in extension-education courses over the three last years (n=212)

| Participation | Frequency | Frequency Percentage |
|---|---|---|
| Yes | 178 | 84 |
| No | 34 | 16 |

*Professional and individual characteristics of the selective farmers*

The average age of the people who participated in extension-education courses is 46 (46.14) years with standard deviation 7 (7.10), majority of which are in the age group of 42-53 years. They are in the range of 7 to 50 years in case of agriculture experience, which (98 people or 55.1%) have agriculture experience of 23 to 38 years. The findings show that the education level of the farmers varies from 5 to 16 years, majority of them (65 people or 36.50%) have secondary degree, as well (Table 2).

Table 2- Professional and individual characteristics of the selective farmers who participated in extension-education courses (n=178)

| Variable | Variable levels | Frequency | Frequency Percentage | Mean | SD | Min. | Max. |
|---|---|---|---|---|---|---|---|
| Age | 30-41 | 37 | 20.80 | | | | |
| | 42-53 | 105 | 59 | 46.14 | 7.10 | 31 | 66 |
| | 54-66 | 36 | 20.20 | | | | |
| Agriculture Experience | 7-22 | 51 | 28.70 | | | | |
| | 23-38 | 98 | 55.10 | 25.58 | 9.04 | 7 | 50 |
| | 39-50 | 29 | 16.30 | | | | |
| Level of Education | Primary School | 63 | 35.40 | | | | |
| | Guidance School | 19 | 10.70 | 9.024 | 3.86 | 5 | 16 |
| | Secondary and Diploma | 65 | 36.50 | | | | |
| | University Education | 31 | 17.40 | | | | |

### The selective farmers' motivations for participating in extension-education courses

In the study, to assess the respondents' motivation for participating in extension-education courses a five-partLikertscale; very little (1), little (2), average (3), very (4) and very much (5) was used. Then the respondents were asked to state their opinion on 11 items. The mean, standard deviation, and item ranking have been mentioned in Table 3. The results of Table 3 show that 7 items out of 11 have an average higher than 3 and are on average. The item "expansion of social relationship with other farmers and extension stuff" (SD=1.16 and M=3.70) has got the highest mean. HoweverKarbasioun*et al* [8] in their study showed that to attain new skill, experience, and information; and personal interest is the most important farmers' motivation in participation of extension-education courses.

The results of Table 3 show that 4 items out of 11 items have the mean lower than average and less than that. The results of Table 4 show that the majority of the participants (125% people or 70.20%) for participating in the next extension-education courses

have some sort of motivation, and 143 people (29.80%) have no motivation.

Table 3- Ranking respondents' motivations for participating in extension-education courses (n=178)

| Items | Mean [*] | SD | Rank |
|---|---|---|---|
| -Expansion of social relationship with other farmers and extension staff | 3.70 | 1.16 | 1 |
| - Curiosity | 3.70 | 1.22 | 2 |
| - Personal interest | 3.70 | 1.35 | 3 |
| - Attaining new skill, experiences | 3.69 | 0.94 | 4 |
| - Attaining new information | 3.66 | 1.05 | 5 |
| - Having good feeling by participating in the extension-education courses | 3.35 | 1.18 | 6 |
| - Getting certificate | 3.70 | 1.17 | 7 |
| - Having access to more facilities and services by extension centers after passing the course | 2.91 | 1.28 | 8 |
| - Applying for extension staff | 2.82 | 1.45 | 9 |
| - Friends' insisting in participating in extension-education courses | 2.76 | 1.47 | 10 |
| - Having free time and entertainment | 2.65 | 1.48 | 11 |
| Total | 3.27 | 0.87 | - |

[*] **Very little= 1, little= 2, average= 3, very= 4, very much= 5**

Table 4- Classifying respondents' motivations for participating in extension-education courses (n=178)

| Classification | Motivation Levels | Frequency | Frequency percentage |
|---|---|---|---|
| 1-1.99 | No motivation | 14 | 7.90 |
| 2-2.99 | No motivation — Approximately Without motivation | 39 | 21.90 |
| 3-3.99 | With motivation — Approximately With motivation | 96 | 53.90 |
| 4-5 | With motivation — With motivation | 29 | 16.30 |

### The satisfaction of the selective farmers from the last courses they took part in

In the study, to assess the respondents' motivation for participating in extension-education courses a fives-part Likertscale; very little (1), little (2), average (3), very (4) and very much (5) was used. Then the respondents were asked to state their opinion on 17 items. The mean, standard deviation, and item ranking have been mentioned in Table 5. The results of Table 5 show that 8 items out of 17 have an average higher than 3 and are on average. The item "proper time for holding the course" (SD=1.08 and M=3.38) has got the highest mean. The items relevant to educational content had the lowest rank; this result is in contradictory with Fealy*et al*[4] and Karbasioun*et a*l's[7] findings.

The results of Table 5 show that 9 items out of 17 items have the mean lower than average and less than that. The results of Table 6 show that the majority of the participants (100% people or 55.10%) participated in the rest (78 people or 44.90%) were satisfied. This result is in contradictory with Pezeshki Rad *et al*[10] and Oladosu's[9] findings.

Table 5- The satisfaction of respondents from the last courses they took part in (n=178)

| Items | Mean* | SD | Rank |
|---|---|---|---|
| - The proper time for holding the course | 3.38 | 1.08 | 1 |
| - The proper place for the course (chair, light, air conditioner, …) | 3.37 | 1.03 | 2 |
| - The proper transportations for participants to attend the classes | 3.28 | 1.15 | 3 |
| - The instructor ability in clarifying the contents | 3.27 | 0.90 | 4 |
| - The quality of serving (food, entertainment, …) during the course | 3.14 | 1.11 | 5 |
| - The educational content's being clear in courses in real situation | 3.12 | 0.98 | 6 |
| - The educational content's being practical of the course in the farmers real situation | 3.04 | 1.32 | 7 |
| - Having easy access to the class | 3.02 | 1.21 | 8 |
| - Evaluation quality which used in the beginning, during, at the end of course | 2.99 | 0.61 | 9 |
| - The balance between the participatory groups (sex, age, job, and work background) | 2.95 | 1.06 | 10 |
| - Making a good and friendly relationship between instructors and farmers | 2.93 | 0.94 | 11 |
| - Making use of various educational methods in presenting contents by the instructors (lecture, discussion, …) | 2.90 | 0.96 | 12 |
| - Making the farmers participate in discussing the course content by the instructors | 2.85 | 1.05 | 13 |
| - The educational content's being new presented in the course | 2.74 | 1.10 | 14 |
| - The proper period of the course (for instance; a one- day period, a two- days period, etc.) | 2.49 | 1.16 | 15 |
| - The use of teaching aid equipment like audio-visual tools, poster, projector, overhead, etc. | 2.40 | 1.10 | 16 |
| - Combining the course content with practical activities | 2.20 | 0.97 | 17 |
| Total | 2.95 | 0.60 | - |

*Very little= 1, little= 2, average= 3, very= 4, very much= 5

Table 6- Classifying respondents' satisfaction from the last courses they took part in (n=178)

| Classify | Satisfaction Levels | | Frequency | Frequency percentage |
|---|---|---|---|---|
| 1-1.99 | | Dissatisfied | 6 | 3.40 |
| 2-2.99 | Dissatisfied | Approximately Dissatisfied | 94 | 51.70 |
| 3-3.99 | Satisfied | Approximately Satisfied | 73 | 41 |
| 4-5 | | Satisfied | 7 | 3.90 |

### Relationship between the professional and individual characteristics of the selective farmers with their level of satisfaction in extension-education courses

The investigation of correlation coefficients shows that there isn't any significant relationship among the

age (r=0.227, P>0.05), job background (r=0.221, P>0.05) and the education level of the farmers (r=0.123, P>0.05) with their satisfaction level of extension-education courses (Table 7). These hypotheses have been investigated in Sadighi and Darvishinia[13] and Pezeshki Rad *et al*'s[10] study, they claim that there isn't any significant relationship. It is worth noting that a Hinkle *et al*'s[5] model for describing the level of correlation has been used.

The calculated Pearson correlation coefficient for the variable of motivation level of the farmers in participating the extension-education courses (r=0.67, P<0.01) with the satisfaction level from the last extension-education course show that there is a positive and significant relationship between the mentioned variables and satisfaction level of the farmers, and this relationship is reported on average regarding the Hinkle *et al*'s[5] model. It means that the more the farmers' satisfaction increases in extension-education courses, the more their motivation increases in participating the courses, and the vice versa is true.

Table 7- Relationship between the professional and individual characteristics of the selective farmers with their level of satisfaction in extension-education courses (n=178)

| Variable | Significant Level and Correlation Coefficient | | Correlation Description Frequency percentage |
|---|---|---|---|
| | r | P | |
| Age | 0.227 | 0.052 | Detailed |
| Farmers' experience | 0.221 | 0.072 | Detailed |
| Education level | 0.132 | 0.081 | Detailed |
| The motivation level for participating in the course | 0.670[**] | 0.000 | Average |

[**]P<0.01

## Conclusion

The agriculture extension services, attention to the selective farmers, the qualitative and quantities increase the ability of farmers, and finally their promoting technical knowledge are highly important, because these groups are as influential factors in educating other farmers. Regarding that these farmers possess the familiarity with the culture, educational-social state, the presence and close contact with people, and reciprocal interaction with local communities and play important role as a facilitator

in the processes of the economical, social, and management collaborative activities. Therefore the present study has an attempt to investigate the farmers' satisfaction of extension-education courses.

The study findings show that more than $\frac{3}{4}$ (84%) of the farmers participated in extension-education courses in the three last years, and 70% of them stated that they would have motivation to participate in the future courses. However, half of them (100 people or 55.10%) who participated were dissatisfied. Yet the findings show that there is positive and significant relationship between the farmers'satisfaction from extension-education courses with their motivation level participating in the courses**.**

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# Propranolol decreases the post-operative pain and analgesic administration following abdominal hysterectomy

Running Head:
## Propranolol decreases the post-hysterectomy pain

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**Abstract:** Post-operative pain results in many complications. Studies suggest beta blockers to be effective in decreasing postoperative pain and analgesic requirements. This study evaluated the influence of perioperative administration of 40mg orally propranolol on patients' post-operative pain score and analgesic consumption following abdominal hysterectomy. In this double-blind randomized clinical trial, 73 women who had referred for elective abdominal hysterectomy surgery during years 2010-2011 were reviewed. Patients were randomly divided into case (receiving 40 mg orally propranolol tablet 30 min before surgery) and control (receiving orally placebo 30 min before surgery). General anesthesia was done the same for both groups. Postoperative time of first need to morphine, total morphine consumption dose and pain severity during the first 24 hours after surgery was measured among both groups. age and hysterectomy indication was not statistically different between two groups (p>0.05). Total morphine consumption in the propranolol group (2.85±2.5 mg) was lower than control group (10.35±2.2 mg) (p<0.001). The Initial morphine administration time (min) in the propranolol group was significantly longer than the control group (998.7 ± 49 vs. 261.7 ± 139.1) (p<0.001). The Pain Score (VAS scoring) (Mean±SD) in propranolol group was lower than the control group (1.03±0.58 vs. 2.76 ±0.8) (p< 0.001). administration of 40mg orally propranolol 30 minutes before abdominal hysterectomy is effective in decreasing patients' post-operative pain and morphine administration dosage. It also elongates the Initial morphine administration time in the first 24 hours following abdominal hysterectomy

**Introduction:**

Hysterectomy is one of the most common gynecological operations with annual rates of 5.0/1000 in USA (1). Post-hysterectomy acute pain may lead to wound healing delay, increase oxygen consumption and hypercoagulability state. It also suppresses the immune system and by changing the breathing pattern can cause retention of pulmonary secretions and atelectasis (2). So, high-quality pain management after hysterectomy is a major challenge. Although opioids such as morphine sulfate have been the corner stone of postoperative pain management, they have some side effects. So, a multimodal approach such as combining local anesthesia and non-opioid analgesics or using other drugs in order to minimize the need for  opioid and their  side effects, has recently become more  popular (3, 4).

In an experimental study, the b-antagonist propranolol significantly prolonged sciatic nerve blockade (5) some Clinical studies demonstrated that patients receiving pre-operative metoprolol had significantly more rapid recovery, reduced post-operative analgesic administration and more stable of intraoperative hemodynamics (6). On the other hand, some studies suggested that b-antagonists could be beneficial in reducing post-traumatic stress disorder (PTSD). It has been suggested that these symptoms are the psychiatric sequel of intraoperative awareness (7-9). Also, another study has recently demonstrated that administration of intravenous esmolol during elective abdominal hysterectomy may reduce morphine consumption for the first 3 postoperative days (10).

Therefore, we hypothesize that preoperative beta-blocker administration may be beneficial in reducing patient's post-operative pain and analgesic administration dose. So, due to Low cost and easy administration of propranolol, we designed this study to investigate the efficacy of 40 mg orally administration of propranolol, 30 minutes before operation, on decreasing patient's pain and morphine consumption dose after elective abdominal hysterectomy.

**Material & Methods:**
This double-blinded clinical trial is done in Ali-Ebn-e-Abitaleb hospital, Zahedan, IRAN during 2010-2011. Approval by the Human Investigation Committee and written, informed consent from each patient were obtained. A total of 73 patients were initially selected from the patients undergoing elective abdominal total hysterectomy. Patients were randomly selected, using a table of random digits, and divided into two groups: 1.Propranolol (n=37) and 2.Control (n=36). Three patients were excluded from the study: Two patients in Propranolol group due to prolonged surgical time and massive bleeding and one of the patients in control group due to non-cooperating to complete the entire study. The patients who consumed analgesics during the last three days before surgery (including NSAIDs, acetaminophen and opioid drugs), also whom with past medical history of ischemic heart disease, heart block, renal, Hepatic or pulmonary disease or were addicted to opioid drugs were not included to our study. Although, we excluded the patients who had massive bleeding during surgery, allergic to anesthetic drugs, failed to complete the study due to personal causes, prolonged surgical time and canceled surgical procedure due to medical problems in operation room.

All of the patients were trained regarding the use of the visual analogue scale (VAS; 0=no pain, 10=worst possible pain) before the surgery.

Thirty minutes before the surgery, 40 mg propranolol was administered orally by the patients of propranolol group while control group patients received placebo at the same time. Multivitamin capsules (Toliddaru, Iran) were evacuated for using as placebo or container of propranolol tablets. General anesthesia was the same for both groups and induced by injection of midazolam (0.02 mg/kg), phentanyl (2 µg/kg), sodium thiopental (3-5 mg/kg), lidocaine (1mg/kg) and atracurium (0.5 mg/kg). After tracheal intubation, anesthesia maintained by injection of propofol (6-8 mg/kg) and remifentanil (0.1 mg/kg/hr) and inhalation of N2O (60%) and O2 (40%). After hemodynamic stability (systolic blood pressure ≥100mmHg), a bullous dose of morphine (0.1 mg/kg) was injected intravenously.

During operation, an anesthetist, who was not involved with postoperative patient evaluation with no prior contact to the patients, monitored the entire course of anesthesia. Hypotension during operation was defined as Mean Arterial Pressure less than 50 mm Hg which was treated with intermittent ephedrine (5 mg) or atropine (0.5 mg).

After the patient's recovery and transmission to the ward, the visual analogue scale (VAS) score of pain was measured at the first request of the patients for analgesics. Patients of both groups were visited by a nurse. In case of recurrent pain, based on the VAS score of pain, a proportionate intravenous dose of morphine was administered for the patients of both groups (Table.1). Patients of both groups were monitored for a period of 24 hours in this study. Initial analgesic request and total dose of morphine administration were recorded.

All data are analyzed using SPSS software, ver.20, IBM Co, USA and presented as mean±SD. Patient's characteristics, initial morphine administration time (min) and total morphine consumption dose were analyzed using one-way analysis of variance (ANOVA) with Post-hoc Bonferroni's adjustment. Pain scores were analyzed using the Mann–Whitney U-test. Data were considered statistically significant at the level of $P<0.05$.

**Results:**
From 73 patients, 3 were failed to continue the study. Finally 70 patients were studied in two groups (propranolol and control). During the study, none of the patients were encountered drug side effects. Patient's characteristics, surgical indication and morphine administration time and dosage of both propranolol and control groups are shown in table-2.

Pain Score (based on VAS scoring system) was significantly higher in control group in comparison to propranolol group ($p<0.001$).

There was no statistically significant difference between both groups from the aspect of age ($p=0.48$). Abnormal uterine bleeding and myomectomy were two indications for elective hysterectomy of the patients

involved in this study. Although AUB was more prevalent among both groups, but there was no significant difference (p=0.6)

We found that total morphine administration dose (mg) among the patients of propranolol group was significantly lower than those of control group ( P<0.001 ). Also, Initial morphine administration time (min) in control group was significantly lower than propranolol group which means that pain control group patients (P<0.001).

In both propranolol and control groups, there was a significant correlation between VAS pain score and Total morphine administration in first 24 h (mg) (p<0.001). VAS pain score and initial morphine administration time were not significantly correlated in propranolol group (p>0.05) while they were significantly correlated in control group (p<0.001). Also, in both propranolol and control groups, we found no significant correlation between the hysterectomy indication and VAS pain score, Initial morphine administration time (min) or total morphine administration in first 24 h (mg) (P>0.05).

**Discussion:**

In this study, we found that 40 mg orally administered propranolol, 30 minutes before onset of elective abdominal hysterectomy can significantly decrease the Pain Score ,Initial morphine administration time and Total morphine administration dose in first 24 hours after operation in propranolol group in comparison to control group (p<0.001).

Although in many previous studies, it has been shown that β-adrenergic receptor blockers significantly play an important antinociception role following experimentally induced hyperalgesia (11-15), there are few studies on the effect of β-adrenergic receptor blockade on acute post-operative pain management following hysterectomy.

 In a study in 2004, Y. Y. Chia and colleagues found that b-blocker (Esmolol) administration before and during abdominal hysterectomy reduced the intraoperative use of inhalation anaesthetic and morphine consumption during  the first 3 postoperative days(10). Results of this recent study confirms our findings about propranolol in decreasing the post-operative pain, however their patients received the drug intravenously and also during the operation which was different from our study protocol.

It has previously shown that Preoperative cutaneous and vaginal mechanosensitivity is related to acute post-hysterectomy pain (16). In 1990, Jakobsen and colleagues found that consumption of metoprolol in combination with diazepam 1-3 hours before elective hysterectomy significantly decreased anxiety evaluated by visual analogue scoring. The patients also were significantly better sedated and more calm compared with placebo plus diazepam group(17). Similarly, Dyck J. B and colleagues in 1991 found the anxiolytic effects of oral consumption of 80 mg propranolol in patients undergoing outpatient dilatation and curettage (D&C) for therapeutic abortion(18).These findings support previous studies that preoperative pain is related to immediate postoperative pain among operations done on uterus (including caesarean section and hysterectomy)(19-21) and also support that preoperative administration of b-blockers are useful in pain management after these operations.

One of the major findings of our study is the effect of propranolol on reduction of total morphine consumption for first 24-hours post-operation analgesia. Few studies demonstrated that β-adrenergic receptor blockers can significantly potentiate and lengthen the action of morphine(22) or reduce the requirements of morphine as an anaesthetic (23, 24). In our study, we found that the initial morphine administration time was significantly decreased which was not evaluated before in previous studies. It has been shown that propranolol administration can reduce hepatic blood flow (25) which could affect and prolong the metabolism of fentanyl. So, this leads to prolongation of the analgesic effect of fentanyl and consequently a reduction in post-operative consumption of analgesics such as morphine (10, 23, 24).

In our study, treatment of abnormal uterine bleeding (AUB) and myomectomy were the major indications for hysterectomy which are in agreement to other studies (26). Besides, we found that hysterectomy indication type is not correlated to VAS pain score, in the first 24 hours of post-operation period (p>0.05) which is supported by the findings of previous studies (27, 28).

**Conclusion:**

We found that preoperative use of propranolol attenuated post-operative nociceptive stimulation responses and reduced postoperative morphine consumption. This will help the patients to experience less pain, less analgesic side effects and faster recovery from anesthesia. These findings also help to consider b-adrenergic receptor blockers as a part of multi-modal approaches to pain management after hysterectomy. However, we recommend further studies with intra-venous form of propranolol or other b-adrenergic receptor blockers to evaluate the exact mechanism of anti-nociceptive these drugs.

**Table.1:** Intravenous morphine administration dose (mg) based on VAS score of pain. VAS: Visual analogue scale

| Pain intensity (VAS score) | 1-2 | 3-5 | 6-8 | 9-10 |
|---|---|---|---|---|
| Morphine dose administration (mg) (IV) | No morphine-Just indomethacin suppository as needed | 2.5 | 5 | 7.5 |

**Table.2:** Patients characteristics, surgical indication and morphine administration time and dosage of both propranolol and control groups. Values are Mean±SD or number. *P<0.05, significant inter-group differences. There was no significant difference among groups for age and surgical indication. But pain score, initial morphine administration time and Total morphine administration were significant between groups. [a,b,c], significant intra-group differences.

|  | Propranolol group (n=35) | Control group (n=35) | *p*-value |
|---|---|---|---|
| Age (year) (Mean±SD) | 45.89±9.03 | 44.6±5.1 | 0.48 |
| Hysterectomy indication: AUB  Myomectomy | 25 (71.4%) 10(28.6) | 23 (65.7%) 12 (34.3%) | 0.6 |
| Pain Score (VAS scoring) (Mean±SD) | 1.03±0.58 [a] | 2.76±0.8 [b,c] | < 0.001* |
| Initial morphine administration time (min) (Mean±SD) | 998.7±49 | 261±139.1 [c] | < 0.001* |
| Total morphine administration in first 24 h (mg) (Mean±SD) | 2.85±2.5[a] | 10.35±2.2 [b] | < 0.001* |

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9/20/2012

# A comparison between Curie temperature of nano and bulk Al doped nickel ferrite (NiAlFeO₄)

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**Abstract**: Nanocrystalline Al-doped nickel ferrite NiAlFeO₄ has been synthesized by sol-gel method. The X-ray diffraction (XRD) revealed that the powder obtained is single phase with spinel structure. Average crystallize size has been calculated by Scherrer's formula. The morphology of the sample was investigated by TEM and the mean particle size of the sample was obtained, which was 65 nm. Magnetic hysteresis loop was measured at room temperature with a maximum applied field of 3000 Oe. The Curie temperature (Tc) obtained by Faraday balance. The results show that magnetization decreases whit decreasing of particle size and Curie temperature increases. The magnetization of the sample is lower than the bulk one. The reduction of magnetization compared to bulk one is a consequence of surface spin disorder. The Curie temperature of the powder was determined using a Faraday balance and the result shows that the Curie temperature of the sample is higher than the bulk counterpart.

## 1. Introduction

There are many methods for preparation of fineparticle ferrites [1]. The preparation technique plays an important role in surface properties and the Curie temperature (Tc) can also be varied by substitution of non-magnetic cations[2]. In the present investigation, we have employed sol-gel method to synthesize Al-doped nickel ferrite nanoparticles. This method offers a significant saving in time and energy consumption over the traditional methods, and requires less sintering temperature. This method is employed to obtain improved powder characteristics, more homogeneity and narrow particle size distribution, thereby influencing structural, electrical and magnetic properties of spinel ferrites. Ni ferrite and substituted ones are technologically important materials, which have been studied in many experimental and theoretical works. $NiFe_2O_4$ spinel ferrite combines a wide range of useful magnetic properties with relatively low electrical conductivity. Thus, unlike the metallic magnetic materials, they display low eddy current loss in alternating current applications and they are particularly useful in the radio frequency range. Therefore, this ferrite has numerous applications in recording heads, core materials for various transformers, inductors and TV deflection units.

In this work, NiAlFeO₄ fine powder was prepared by sol-gel method. It has been shown that single-phase Ni-Al ferrite fine particles can be prepared by this method, at a temperature much lower than is associated with the conventional ceramic method. In the inverse spinel

Structure of $NiFe_2O_4$ the tetrahedral sites are occupied by ferric ions and octahedral, by ferric and nickel ions. Substitution of Al ions in above structure is for Fe ions.

## 2. Experimental procedure

Nanocrystalline powder of NiAlFeO₄ was prepared by sol-gel method. The citric acid ($C_6H_8O_7.H_2O$), nickel nitrate (Ni ($NO_3)_2.6H_2O$), ferric nitrate (Fe $(NO_3)_3.9H_2O$), and aluminum chloride ($AlCl_3.6H_2O$) were used as starting materials. The metal nitrates were dissolved together in a minimum amount of de-ionized water to get a clear solution. A clear solution of citric acid was mixed with metal nitrates solution, then ammonia solution was slowly added to adjust the pH at 7. The mixed solution was heated on a hot plate with continuous stirring at 90-100°C. During heating the solution became viscous and finally formed a very viscous green gel and began to bubble, after 1h a hard black mass was remained. The as-prepared powder was heat treated at 1100°C for 2h to get the final product.

The structural characterization of the as prepared ferrite powder was carried out, using Bruker D8 XRD system with CuKα radiation (wavelength, λ=1.5406Å). The average particle size D was calculated using XRD data, employing the Scherrer's formula:

$$D=0.9\lambda/\beta Cos\theta$$

Where β is the angular line width at half maximum intensity and θ is the Bragg angle of the peaks.

Magnetic measurements were performed using the AGFM. Magnetic hysteresis loop was measured at room temperature with maximal applied magnetic fields up to 3000 Oe.

The Curie temperature of the sample was measured by Faraday balance.

The morphology of the nanopowders was studied by a transmission electron microscope; Philips CM-12.

### 3. Results and discussions

Fig. 1 shows XRD pattern of $NiAlFeO_4$ sample. The XRD pattern clearly indicates that the prepared sample contains cubic spinel structure only. Average crystallite size has been calculated by Scherrer's formula. The results are as showed in table 1.

superexchange interactions, which tends to align the neighboring dipoles antiparallelly. This substitution decreases the magnetization of the sample, compared to $NiFe_2O_4$ as was reported in other works [4].

In the inverse spinel structure of $NiFe_2O_4$, the tetrahedral sites are occupied by ferric ions with a magnetic moment of 5 $\mu_B$ and octahedral sites are occupied by both ferric and nickel ions together with a magnetic moment of $7\mu_B$ in opposite direction to that of tetrahedral sites.

This leads to a net magnetic moment of $2\mu_B$. The substitution of diamagnetic $Al^{3+}$, which has strong preference for occupying the octahedral sites for $Fe^{+3}$, decreases the magnetic moment of octahedral site. This leads to a decrease in the net magnetization of the sample.
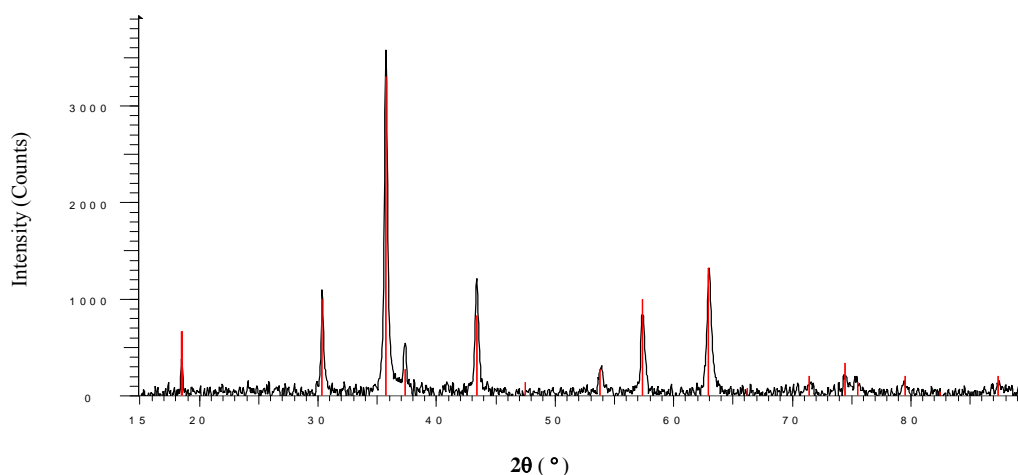


**Fig1.** X-ray diffraction pattern of $NiAlFeO_4$ nanoparticles .

**Table 1**: Structural and Magnetic properties of $NiAlFeO_4$ nanoparticles .

|  | NiAlFeO₄ |  |  |
| --- | --- | --- | --- |
| D(nm) | a(Å) | M(3000 Oe)(emu/gr) | Tc(∘c) |
| 21.42 | 8.23 | 0.7 | 670 |

TEM image of the sample is illustrated in Figs. 2, indicating the nanoscale nature of ferrite particles. The image also shows that mean particle sizes of the powders are about 65 nm.
 $Al^{3+}$ ion has strong preference to occupy octahedral sites [3]. The removal of magnetic $Fe^{3+}$ ion from magnetic sublattice in $NiFe_2O_4$ and substitution of the nonmagnetic $Al^{3+}$ ion in its place weakens the
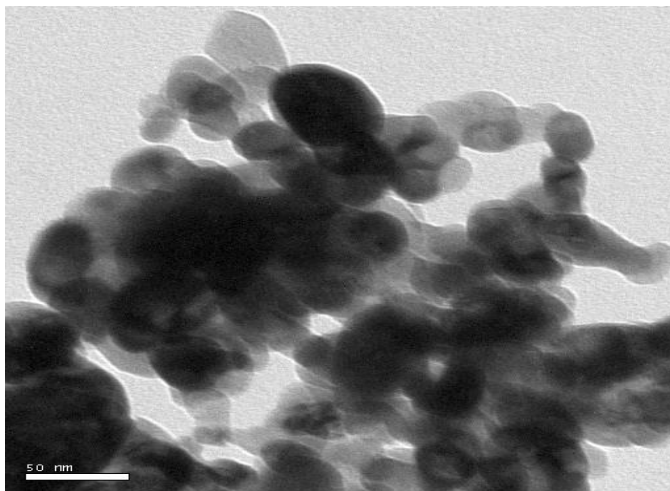
**Fig. 2.** TEM photograph of the NiAlFeO$_4$ nanopowders.

Magnetic hysteresis loop of Al-doped nickel ferrite NiAlFeO$_4$ nanoparticles measured at room temperature using AGFM are shown in Fig. 3. At maximal applied field of 3000 Oe, the saturation was not achieved.

The value of magnetization at applied magnetic field of 3000 Oe for NiAlFeO$_4$ nanoparticles was measured to be 0.7emu/gr. This is approximately lower than the value of the bulk sample at room temperature[5].
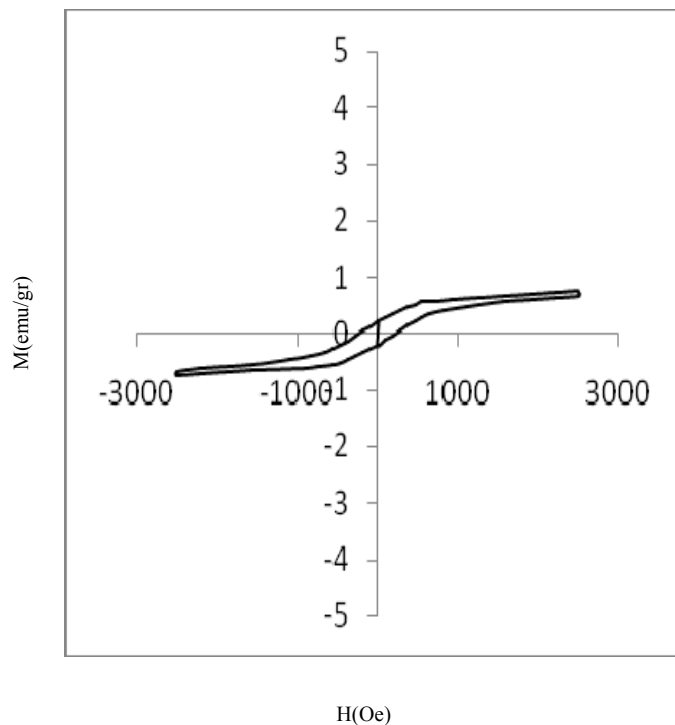


H(Oe)

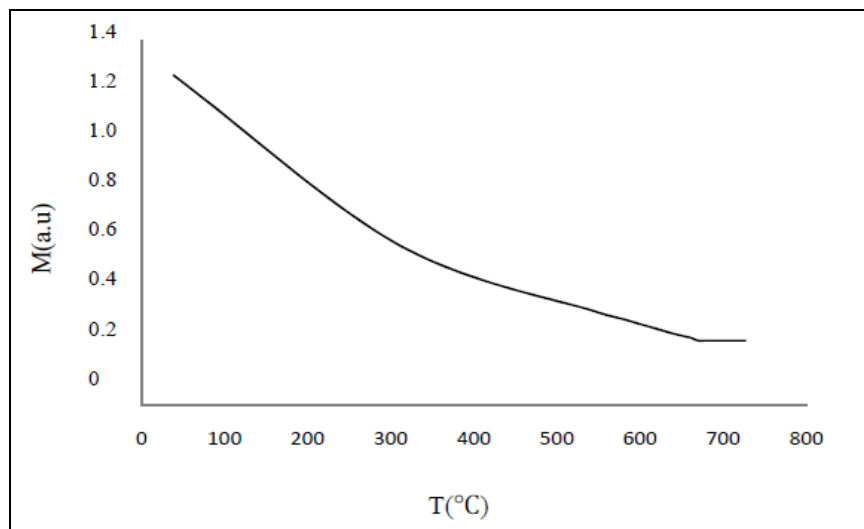**Fig.3.** Magnetic hysteresis loop of NiAlFeO$_4$ sample.

**Fig.4.** M-T curve of $NiAlFeO_4$ nanopowders.

This is due to particle size reduction of this sample in which the surface to volume ratio has been increased.

In this case surface spin disorder will be increased as particle size are reduced and leads to a decrease in magnetization [6-7]. Beside the canting of the surface spin caused by broken exchange bonds, the core spins could also have canted spin structure due to the large magnetocrystalline anisotropy resulting from the occupation of the tetrahedral sites by $Ni^{2+}$ ions [8].

Fig. 4 shows the result of measuring Curie temperature by Faraday balance.

Perhaps most noteworthy of our results is that the Curie temperature measured for $NiAlFeO_4$ nanoparticles, approximately $670°C$, is higher than the measured bulk value of $510°C$ [9].

This result can be very valuable for industry purposes. The finite size scaling [10] can be used to explain the behavior of Tc. In order to explain the increase of Tc transition temperature of the bulk, it should depend on the dimension of the system in the following manner: $[T_C(D)-T_C(\infty)]T_C^{-1}(\infty) = \pm(D/D_0)^{-\lambda}$ where the exponent is predicted to be related to the correlation length exponent by $\lambda=1/\nu$, the system dependent sign may be either positive or negative, and $D_0$ should be of the order of the characteristic microscopic dimension of the system [10].

**4. Conclusion**

In this work we have prepared single phase Ni–Al ferrite nanopowders by the sol-gel method. Measured magnetic parameters of the sample show that

magnetization of Al substituted Ni ferrite nanopowders are lower than those related to bulk ones. This is because of the surface spin disorder an increase in surface to volume ratio in nanoparticles. The Curie temperature of the sample is higher than the one related to bulk counterpart, which is a result of a reduction in superexchange interaction.

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# Public Sector Innovation through e-Governance in Pakistan

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**Abstract:** This study examines the process of innovation in the Federal Government Agencies (FGA[1]) of Pakistan to enhance the efficiency and effectiveness of the public sector. This paper looks at the rationales for e-Governance implementation in Pakistan. The policy analysis here will look at how ICT policy is decided, who participates in the decision-making processes, who initiates radical change, and how information was shared. This research paper focuses on Government of Pakistan's experience with innovation in public service delivery. Innovation through implementation of e-Governance initiatives in the public sector is still an under-researched area in developing countries. It deals with governance, cultural and human issues which are very difficult to resolve. Research objective of this study is to provide a systematic understanding and e-Governance Implementation Model of how innovation in the public sector, particularly in ICT is carried out. The study concludes that the public sector needs to overcome its traditional characteristics of poor agenda setting and bureaucratic layers of decision-making processes.
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**Keywords:** citizens; e-Governance; ICT Policy; innovation; public sector.

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[1]FGA is defined as a Ministry, Division, Commission, Statutory Body, Corporation, Institution established or controlled by the Federal Government of Pakistan.

## 1. Introduction

e-Governance offers a new way forward, helping improve government processes, connect citizens, and build interactions with and within civil society. e-Governance is the latest trend in the governance process all over the world. The aim, ultimately, is to simplify and improve governance and enable people's participation in governance through email and internet.

According to the United Nations e-Government Survey, measured for 192 countries, Pakistan's ranking of 137 in 2003, improved in 2005 and 2008 (with rankings of 136 and 131 respectively (Figure 1). However, in 2010 its ranking dropped dramatically by 15 ranks to 146. The majority of the high scorers in the 2010 e-Government development index are South Korea, United States and Canada, all high-income countries, who have the financial resources to expand and rollout advanced e-Governance initiatives, as well as to create a favorable environment for citizen engagement and empowerment. Meanwhile emerging economies such as China and India rank 72 and 119 respectively while even Bangladesh has a 12 point lead over Pakistan.
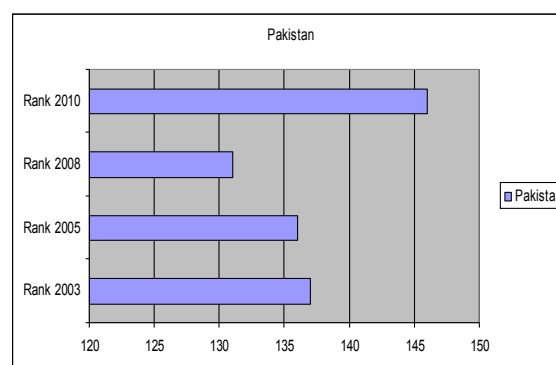


Figure 1. United Nations e-Government Development Index for Pakistan
Source: UN e-Government Survey from 2003 – 2010

After almost twelve years of various e-Governance initiatives, Pakistan seems to have failed to improve on the e-readiness criteria set by the United Nations indicators[2]. There are many factors

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[2] Among the criteria of e-readiness ranking set by United Nations (2010) are:

a.    Internet Users/100 persons

that contributed to this poor ranking. The road-map of e-Governance has revealed the truth of what really is happening. The road map shows the poor realization of added value of public administration. The preliminary analysis has highlighted a common misconception of e-Governance: it is all about bringing in new technology to replace paper-based work routines and the belief that the IT community has to have a major role in it. Not surprisingly, the e-Governance is so far is all about adding electronic devices to government and has little actual added value to the public administration. Path dependency (in which one of the examples is that the Ministry of IT always determined the policies and strategic direction of IT diffusion in Pakistan), makes the situation even more difficult to change. To change this entire picture, an external shock in the form of policy change of the system or institution is thus fundamental.

Therefore, it is imperative to analyze the key actors and institutions that are involved in the introduction of e-Governance and the strategies that have been adopted in stimulating the e-Governance initiatives. The aim of this research paper is, therefore, to demonstrate how the rationales of e-Governance and group of actors that is responsible in formulating it, are key in the success or failure of e-Governance. In other words, the policy making process and the role of policy in e-Governance will be analyzed. e-Governance in Pakistan is going at a very slow rate and concentrated mainly at the infrastructure building and implementation of a few e-Governance initiatives.

**2. Road Map of the ICT Policy Analysis**

Federal Government Agencies do not have their own ICT policies and they follow the ICT policy of the Federal Ministry of Information and Technology. In this regard, three level of policy analysis framework are now explored as applied to this present research paper.

**2.1. Macro-level analysis**

Macro-level analysis will show that the e-Governance started mainly due to global trends. Many countries around the world have embarked on

b.    PCs/100 persons

c.    Main Telephones Lines/100 persons

d.    Cellular telephones/100 persons

e.    Broad banding/100 persons

f.    Their institutional capacity, leadership role and willingness to engage their citizens by supporting and marketing participatory decision making for public policy; and

g.    The structures that are in place which facilitate citizens' access to public policy dialogue.

e-Governance in order to meet the pressure to modernize the government and also in meeting the demand from the increasingly ICT-literate society and enterprises. Pakistan is no exception, and predictable that there was a decision to embark on e-Governance in Pakistan. Since other governments were doing it, together with hearing the success stories in neighbouring countries such as India, China, UAE and Singapore, Pakistan could not afford to do nothing and be left behind.

To stop the analysis of policy making at the macro-level provokes the criticism. It is common knowledge that almost every country is moving in the same direction of utilizing ICT in its public sector to provide services to its citizens.

**2.2. Meso-level analysis**

This is considered as the main focus of the policy analysis of this study. It is here the *when, how* and *why* the idea of e-Governance started, by whom and what is wrong with the policy. This study is an analysis of the policy process. Gordon et al. (1997) stated that there lies a continuum of activities namely: *analysis of policy determination* and *analysis of policy content*. In the analysis of policy determination, the emphasis is upon the inputs and transformational processes upon the construction of public policy. It is investigating the forces that drive the policy formulation such as internal objectives, environmental forces or perhaps by internal perceptions of the external environment. Analysis of the policy content will look at the mission and objectives of the policy; is it being practiced and does the content meet the intended targets?

A statement appears in paragraph 3.21.1.2 of the IT Policy (2000) that says *'The e-Government model for Pakistan is a gigantic task. It may take 5-7 years because of financial constraints as well as inadequate professional know-how to undertake system re-engineering of different government departments and use of I.T. so that use of paper is minimized. Therefore, a modular approach will be adopted to achieve the goal of e-Government'.* Some of the reactions from the interviewees were: *go send the civil servant for training and employ various IT consultants to develop e-Government model. What happens next? Are they going to use the skills back in the office? Is the technology or system already available? Is there any application for develop model, this will be a complete waste of budget. An identification of training modules related to their working routine and the existence of the technology to be utilised combined together will produce a more positive return on the investment.* Although the general problem is identified, the specific problems are not, and neither is there an evaluation of how to solve the problem.

To make the situation even more complicated, the actions under IT Policy strategies infrastructure development # 3.7.2 appear very ambitious. For example, IT parks and incubators were to be established. There was no evidence that a study has been conducted on the capability of Pakistan to embark on these strategies. It is important how realistic the projects were and how Pakistan can compete with other established software parks such as Multimedia Super Corridor (MSC) in Malaysia. Were these actions simply put to make the content of the IT Policy trendy and in line with the global trends?

The government reports, however, identified critical gaps such as the need to have more IT manpower, skills, knowledge and competency for the success of e-Governance. If these have been identified as the constraints, why did the content of the IT Policy not reflect the reality of ICT innovation capability in Pakistan? In last eleven years to achieve all the goals was almost impossible when the infrastructure and human resources were not yet in place. The policy style here seems to be making grand plans at a political level; but not following through with planning and implementation.

Batini et al. (2009) emphasize the integration of back office processes for improving the quality of services, and say that a one stop shop should be available for the citizens in case of residency change, updating of new address on a driving license and in health services. e-Governance can help build trust by enabling citizen engagement in the policy processes, promoting open and accountable government and helping to prevent corruption. Policy makers cannot stand aloof from these trends, as they are forced to implement innovations as well as to explore new opportunities. New possibilities offered by ICT give government chances to rethink ways of working and providing services for citizens and businesses (Verdegem & Verleye, 2009; Bekkers & Homburg, 2007; Heeks, 2003; and Prins, 2001).

### 2.3. Micro-level Analysis

This analysis looks at the individuals involved in the implementation of e-Governance. This analysis principally asks what happens to policy at the point in time when it is finally delivered – e-Governance policy implementation. The role of the individuals and their influence in shaping the destiny of the policy are analysed here.

When the policy has been delivered to the 'junior-level bureaucrats' or to the administrators, it is assumed that they will just simply do whatever they were told by the policy makers. Nevertheless this is not the case, and the policy even failed to be delivered as intended. According to Pressman and Wildavsky (1973) many policies fail to meet their goals because of factors such as lack of coordination between government agencies, lack of clear direction, underestimation of ability to implement and weak control over resources.

Pressman and Wildavsky (1973) further stressed that implementation should not be divorced from policy. It must not be perceived as a process that takes place after, and independent of the design of policy. The great problem, they added, is to make the difficulties of implementation a part of the initial formulation of policy. In other words, the anticipation and solutions to the challenges implementation must be included during the initial policy making process.

Another alarming issue at this micro-level is the lack of IT resources. Mostly, government agencies are depending on the seconded IT staff from EGD to assist them in developing their e-Governance projects. No policy has been formulated on how to overcome the lack of IT resources in Pakistan. When there was a huge shortage of IT manpower in each federal agency and hence lack of qualified IT person, how could they design, monitor and review the e-Governance projects?

### 3. Critical Appraisal of e-Governance in Pakistan

The e-Governance in Pakistan was mostly driven by technology. There was no evidence of organizational restructuring and e-Governance policy to meet the demands and consequences of engaging innovation in the government agencies. This study now expresses its concern as to what the future of e-Governance in Pakistan might hold.

The situation in Pakistan implies that not everything can be done online. Only a few governments in the world have actually managed to achieve the fourth stage of e-Governance i.e. 'transformation stage' whereby the government is able to provide a one-stop service with the capability to interact with the citizens on decision making matters. Most governments are yet unable to achieve this final stage as it requires organizational changes that challenge the current bureaucratic culture of most government organisations. Various implementation issues arise in many e-Governance initiatives. As a result, many governments failed to reach the final stage of e-Governance. This study believes that this statement is only partially true. To conclude it this way indicates that all government organisations have one similar mission of transforming the governance style away from the traditional one.

Does Pakistan really want to achieve a new governance style that challenges its current institutional setup and its way of interacting with the citizens? However, there has been no evidence so far to indicate that different government organisations are contemplating to reengineer themselves to

transform the traditional set up of the bureaucracy. Organisational change has been very minimal in the government agencies during adoption of e-Governance. Evidence of innovation in policy was limited and policy making process has followed the same old style. Is Pakistan really serious in migrating its government organisations towards the new e-Governance by applying 'shock' to the current system? Perhaps, the answer is no and this can explain the slow nature of the e-Governance progress which so far has only concentrated on automation of the government agencies. It can be assumed that there is no priority for the Pakistani government to reform its governance, to empower the people and to have democratic interaction processes with the society.

## 4. e-Governance Implementation Model for Pakistan

How should the government agencies adopt e-Governance in order to achieve better success? This study now develops an e-Governance implementation model which is based on the empirical findings. e-Governance in the government organisations deals with governance issues. The most neglected aspects of the modernisation of government organisations' literature and policy aspects which are in fact the backbone for a meaningful adoption of e-Governance (Arfeen, 2011). The e-Governance implementation model is hereby proposed (see Figure 1.2):

### 4.1. Leadership for e-Governance Initiatives

Once a concrete and feasible aim to implement e-Governance has been identified, a leader must be appointed as a driving force for whole process. The leader must themselves understand the purpose of e-Governance initiatives, have a strong interest in it, have power to access resources and most importantly, believe that e-Governance is under their executive ownership. The presence of a strong leader can overcome the resistance and inertia in the government agencies to embark on e-Governance.

### 4.2. Change Management Strategy

The process of identifying the e-Governance initiatives to be implemented is actually a change management process. It is about brining in change to the government agencies for many reasons. The right change management strategies at the initiation stage and also along the process enable the identification of bottlenecks or barriers of e-Governance. Lack of human resources, poor ICT infrastructure, and resistance to change can be anticipated which influence the strategy on how the adoption of e-Governance is to be carried out.

### 4.3. Visionary and Charismatic Leadership

The leader must understand the costs and benefits of technology in order to better explain to the stakeholders before, during and after the implementation period. A leader must be able to persuade, motivate, and gain support from various levels of government. Top leadership involvement and clear lines of accountability for making management improvements are critical to overcoming organizations' natural resistance to change, marshalling the resources needed in many cases to improve management, and building and maintaining the organization wide commitment to new ways to doing government (McClure, 2001). The leader can have direct support from the Prime Minister. A dedicated full-time authority is also effective in ensuring any reform efforts in the government agencies take off[3].

### 4.4. Raise Awareness about e-Governance Initiatives

Awareness programmes are vital at the start and during the e-Governance implementation. Workshops, seminars and conferences should be conducted to the top-level management (including leaders), government officials, academia and the public to raise awareness about the real objectives, benefits and opportunities of the e-Governance initiatives. As shown by this study, there was a period of inertia in the early stage of e-Governance, as the government agencies were clueless about what to do.

When e-Governance began, it was followed by a period of transition, confusion and resistance to change. The government should have prepared its change management strategy here. Similarly, in Pakistan 66% of the population has still not used the internet. Without awareness and e-readiness of the users, e-Governance initiatives may fail. In other words, the government must ensure that e-Governance becomes a national priority.

### 4.5. Approaches to e-Governance

Centralised, decentralised and hybrid are three possible approaches to the management of e-Governance initiatives (Heeks, 2006). In the centralized approach decisions are taken at the top level. In the decentralised approach decisions are taken some level lower than the most senior. However, in the hybrid approach decision are taken at both top and lower levels, either separately or integrated manner. Hybrid approach is also known as federal or federated in some governments.

Large scale e-Governance initiatives in the government organisations must be policy driven i.e. coming from the insight of the policy makers (top-down). In other words, the primary source for policy advice must not come from the operational level.

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[3] e-Governance in Pakistan, due to lack of champion, the ministries relied too much on the style of implementation of the MoIT which became a source of innovation for government agencies. The truth is that over-reliance on MoIT is a barrier to innovative culture of the government organisations, because other groups wait to follow a MoIT rather than developing their own ideas.

Giving the middle and front line workers the opportunity to shape the e-Governance initiatives (bottom-up) may bring a conflict of interest and ideas with the policy makers. Delays and even termination of an e-Governance initiative can occurs leading to wastage of resources. The absence of top-level political commitment to adopt e-Governance would also cause the various committees to degenerate to a forum for recording events rather than taking decisions (Polidano, 2001). This is evidence in the case of EGD in Pakistan which has little power in influencing the e-Governance initiatives because of working as attached department under the federal Ministry of IT. Furthermore, allowing the IT people to lead e-Governance in Pakistan resulted in purely automation of processes and the purchase of irrelevant technologies. In a country like Pakistan where there is federal government, centralised e-Governance with hybrid approach is favourable as implementation should be easier to manage and align.

### 4.6. Start Small

Most of the time attention is given to technology as well as the governments' tendency to start all too often from existing ways of working (Van Deursen et al., 2006; Ebbers et al., 2008). eGovernment portals that are not available in the national and local languages (speaking by significant majority groups) are not going to be used by a critical mass of citizens: one can only assume that much, or even the vast majority of the population may be unable to comprehend the information and services provided (Davison et al., 2005). Indeed there is also evidence that eGovernment is for the educated minority in developing countries like Pakistan. This would be truly unfortunate situation, since it is often the less educated that have most to gain from online initiatives that empower them to make decision based on what is in their best interest, and would stand in stark contrast to the presumably universal principle of government: serving all citizens. e-Governance initiatives must start small and must not be too ambitious. It is better to follow the e-Governance development curve rather than to leapfrog the curve by doing everything at the same time. Chaos tend to occur especially when a country not ready in its technology, infrastructure and human resources.

### 4.7. Citizen Centric Approach

There must be citizen centric approach for improving the e-services otherwise desire results are impossible. Today, governments recognize that e-Governance is a key tool to support and enhance government functions and processes as a lever for new approaches to service delivery. Governments are turning their attention to this broader view rather than focusing on the tools themselves. They are shifting from a *government-centric* paradigm to a *citizen-*

*centric* paradigm, putting more attention on the context (*e.g.* social, organisational, and institutional factors) in which e-Governance is developing and on the outcomes for users (OECD, 2009).

### 4.8. Learn from Experiences of other Government Organisations

Some of the mistakes that happened in e-Governance initiatives are not unique such as the issue of duplication and lack of leadership. The government agencies should look around the best practices in formulating its strategies. Mistakes and bad practices ought not to be repeated. Gadot et al (2005) similarly mentioned that the link between information management and organisational performance is not country specific and should be studied in models that look at policy learning in globalizing government agencies, beyond cultures and region.
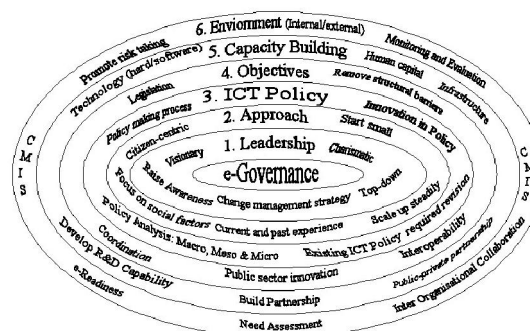


Figure 1.2: e-Governance Implementation Model

### 4.9. Policy and Guidelines

e-Governance initiatives failed due to poor goal definition and poor alignment of actions to goals. There is no connection between goals and means in the policy design (as in the case of 'ICT Policy and Action Plan' as well as 'e-Government Strategy and 5-year plan'). Sometimes even symbolic policies are adopted to (appear to) address a problem without actually offering the means that could achieve the stated objectives (Winter, 2003). As a result of this, policy setting and formulation must be conducted through a meticulous process of consultation with various stakeholders in the government agencies, educational institutions, private organisations, citizens and other stakeholders. Policy, organizational, operational, technological, economical and social issues must be identified and prioritised together with future requirements or anticipations on the political, social and economical environment of the country. The objectives of e-Governance must be stated explicitly and be understandable to everyone involved. Simultaneously, the goals must be linked to explicit actions such as projects and ideas to specific

goals. There should be detailed implementation guidelines, and strategies to overcome the identified challenges for change and barriers of e-Governance in the government agencies of Pakistan.

### 4.10. Required revision of ICT Policy

Policy making process must take into account the consequences of adopting old policy. A policy may have been present in the government organisations for quite some time without proven benefits. It is then vital to ensure that poor practices are identified and not repeated again in the new e-Governance journey. Path dependency, which can be mitigated by strong leadership, must be dealt with to prevent failures.

### 4.11. Innovation in Policy

In relation to the above point, there is a strong urgency for a government to exercise innovation in policy, policy making process and also policy monitoring and evaluation. Bad policies can be terminated, for example by using evidence-based policy making process and path dependency analysis which is supported by a solid policy evaluation strategy.

### 4.12. Objectives

Unclear objectives of e-Governance implementation lead to an eventual failure. e-Governance initiatives especially on a large scale must be initiated when there is a problem or anticipated problem that needs a solution. It should not be based on outside influence that pushes a government to blindly imitate. e-Governance initiatives to solve the internal problem tends to have small scale impact. Questions must be asked such as *does (Pakistan) really need e-Governance initiatives and why?*

### 4.13. Eliminate Structural Barriers

Red-tape and bureaucratic procedures must be eliminated in order for adoption of e-Governance to diffuse quickly into the government agencies. Rigid recruitment processes should be replaced with flexible recruitment practices with promotion to be based on skills and competence. Too many layers in the e-Governance initiatives and its budget approval have been shown by this study to create huge setbacks.

### 4.14. Technological and Human Capacity Building

e-Governance initiatives requires strong human and technological base. It is somewhat sensible not to embark on e-Governance before these two important capabilities are strengthened. In the case of Pakistan, this study proposes that the e-Governance has a 'cooling-off period' where infrastructure (computerisation of government agencies and building database) and human capacity building (IT skills and software engineers) are

expanded before the implementation of application systems can re-start.

### 4.15. Partnership with Private Organisations

A government must create synergy with different stakeholders involved in the e-Governance initiatives. Partnerships with the private organisations benefit the government in terms of getting the expertise and technology not available in the government agencies. Models of partnership (outsourcing) must be carefully scrutinized with strict regulations in order to protect the interest of the government and also the private organisations in long-run.

### 4.16. Develop R&D Capability

Strong R&D capability is crucial in e-Governance initiatives. This can be achieved by building strategic linkages with universities, and software industry. Miles (2001) stated that historically the public sector has often been the vanguard innovator for major new technologies and the driver for enabling research in academia. In other words, collaboration and coordination between various government agencies and stakeholders must be stimulated for a better cross fertilisation of ideas, solutions and knowledge (Ndou, 2004). Investment in national R&D resources must be done to strengthen the higher education and research system to improve human capital in strategic areas of importance. Furthermore, R&D funding schemes must be formulated to promote strong interest from academia and industry.

### 4.17. Scanning of the Environment

It should be considered as most important step in any e-Governance process for government organisations. Analysis of the political, economical and social environment significantly contributes to the objectives, the policy to be formulated and the change management strategy to be undertaken. The outcomes of the analysis support the formulation of strategic and regulatory frameworks, human capacity building, technology and infrastructures.

### 4.18. Risk-taking Environment

Support from the top-level management must be given to encourage the government agencies and individuals to be more creative and take more risks. 'Smart failures' should be tolerated in the government agencies. e-Governance awards and recognition or incentives must be established for the innovators in the government agencies. Innovators must be protected and provided with resources such as funds and given ample time for them to work on their e-Governance initiatives and perhaps a reduction in other responsibilities.

### 4.19. Need Assessment

Need assessment of the e-Governance is essential to enable the government to assess the

current level of human capacity and technological infrastructure. Similarly, stakeholder analysis would enable the investment in e-Governance to be more justifiable and relevant to the demand of the citizens.

### 4.20. Monitoring and Evaluation

e-Governance initiatives can not be evaluated only at the end of the process. This is a wrong approach as constant monitoring and evaluation can identify whether or not to proceed. Duplication of data centres could have been prevented if earlier evaluation was conducted. Earlier evaluation also ensures that the scares human resources can be re-deployed. Concrete performance indicators or measurement of productivity gains must be established, although this can be very tricky in the government agencies.

### 4.21. Inter Organisational Collaboration

Information and policy in the e-Governance implementation must be made transparent and available to government agencies involved. The government must foster partnerships and strong collaboration among the government agencies to promote information sharing, build cohesion and minimize the silo mentality. Although inter organisational collaboration is probably a new practice in the government agencies, this must be encouraged.

The overall proposed e-Governance implementation model above has been summarised in Figure 1.2. It is normative and tries to include the essential elements missing in the Pakistani experiences. The e-Governance implementation model is derived from the combination of the evidence from Pakistan and the literature of e-Governance initiatives. Important features such as problem identification, capability assessment, identification of policy options, consistent evaluation process, and CMIS have been included in the e-Governance implementation model. Most importantly, the model also goes beyond the rational policy making process model. Other features such as leadership, building partnership, scanning the environment, human capacity building, incorporation of good practices, the promotion of risk taking environment and complaint handling systems have been included to certify the e-Governance implementation model as an ideal conceptual model that can act as a useful reference before embarking on an e-Governance journey.

### 5. Validation of e-Governance Implementation Model

The e-Governance implementation model was derived from the extensive research, fieldwork and literature review. Validation process is crucial to confirm validation of the model. During the development phase, the model critical elements were

considered like; simplicity of the model, applicability, doable, flexible, renewable and expandable. The newly developed e-Governance implementation model was passed through this process in the form of a validation. Selected ICT experts, e-Governance practitioners (peer review) and officials of government agencies were involved for the validation process. The overall outcome of validation indicates that the model is highly satisfactory from all perspectives (factors) mentioned earlier.

The completed validation process shows high acceptability from the ICT experts of the federal government agencies in Pakistan. The model was found applicable for to the current needs at federal and provincial level government agencies in Pakistan.

### 6. Conclusion

The above situations resulted in confusion in understanding what the government really wants in e-Governance. Due to this, conflicts of interest occur when the junior-level bureaucrats finally implement the ambiguous policy. Poor priority in e-Governance by the policy-makers resulted in no leadership, poor coordination, sharing of knowledge and policy at every level in the public sector. The lack of key performance indicators and evaluation strategy add further mess to the e-Governance process.

This paper developed the e-Governance implementation model which highlighted the priority areas for a government to consider the aspect of policy – the decision making process, the content of the policy and its enforcement – meticulously before embarking on e-Governance journey. e-Governance initiatives in the federal government agencies of Pakistan is not merely about technology but has to be about governance. The validation of model foresees that model will be implemented in the near future at federal and provincial level in the government agencies of Pakistan. It is sincere hope, the Government of Pakistan will be able to improve allocation of resources and responsibilities to promote delivery of services to public sector organizations.

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