Effect of parenterally Acetaminophen on the attenuation of post-operative pain subsequent Colectomy

[1]Eilyad Issabeagloo, [2]Babak Abri Aghdam, [3]Ali Rezaei

1- Department of Pharmacology, Medical Sciences Faculty, Tabriz branch, Islamic Azad University, Tabriz, Iran.
2- Department of special surgery, Medical Sciences Faculty, Tabriz branch, Islamic Azad University, Tabriz, Iran.
3- Department of surgery, Faculty of veterinary medicine, Tabriz branch, Islamic Azad University, Tabriz, Iran.
Dr.e.issabeagloo@gmail.com

Abstract: Introduction: Analgesic efficacy of parenterally acetaminophen is variable in different surgical procedures. Little data is available on its efficacy in Colectomy. Intravenous Acetaminophen is a useful drug in treating postoperative pains and could be used alone or in combination with other drugs. Current study conducted this prospective, randomized, double blind study to evaluate and compare the efficacy acetaminophen with morphine in Colectomy surgery over a 24 hour period. Methods: In a clinical trial, 79 patients candidate for elective lumbar Colectomy were randomly put into groups receiving Acetaminophen (40 patients) or placebo (39 patients). In group one, 1 gr I.V. Acetaminophen infusion started 15 minutes before the end of surgery. Group 2 received 100 ml NaCl 0.9% in the same period. Pain scores were assessed at relaxation with VAS (visual analogue scale) at 0 (after awakening), 5, 10, 15 and 24 hours. Morphine use (according to patient's will due to pain) was recorded in 24 hours. Results: Acetaminophen group had significantly lower mean VAS (less sever pain) than placebo group after recovery (5.73±1.89 versus 6.85±2.11, p=0.004), 5 hours later (5.34±2.03 versus 7.67±1.9, p=0.01), 10 hours later (4.81±1.29 versus 5.71±1.31, p=0.02), 15 hours later (4.11±1.05 versus 4.67±1.61, p=0.02) and 24 hours later (2.61±1.31 versus 3.57±1.41, p=0.01). Morphine requirement in different periods was lower in Acetaminophen group than placebo which had no significant differences. Mean cumulative morphine use in 24 hours in paracetamol group (5.89±2.79 mg) was lower than placebo group (8.48±3.51 mg), however the difference was not significant. Conclusion: Results of current study showed that intravenous Acetaminophen is effective in reducing postoperative pain severity, but do not reduces need for morphine use.
[Eilyad Issabeagloo, Babak Abri Aghdam, Ali Rezaei. **Evaluation of effect of Acetaminophen on the lessen of post operative pain due to Colectomy in parenterally administration**. *Life Sci J* 2013;10(4s):308-313] (ISSN:1097-8135). http://www.lifesciencesite.com. 45

Keywords: Colectomy; Acetaminophen; morphine; Postoperative pain

1. Introduction

Pain relief after the surgeries with a suitable analgesic is an important issue for patients and anesthesiologists. The analgesic method has to be with high efficacy, low side effects, and easy administration. The control of the pain during the surgery (intraoperative) and after it (postoperative) is called preventive analgesia, which results in accelerated recovery and improvement in the Health-Related Quality of Life (HRQL).

Inadequate control of postoperative pain has bad physiological effects including lag returns in respiratory and gastrointestinal functions (1). Not relieved pain increases the stress respond which affects the immune system and leads to delays in healing and recovery (2, 3) and it's a known risk factor for the chronic pain syndrome development (1).

Analgesic Combined diets have been proposed to improve the treatment of postoperative pain. Combination of analgesic medicines causes synergistic effects and can lead to appropriate pain relief. Since lower doses of analgesics are used in combination with pain relief diets, adverse effects are greatly reduced (2). Paracetamol is a central Cycloxygenase inhibitor and its analgesic mechanism has interference with serotonergic system (3). This medicine is anti-fever and pain relieving with slight anti-inflammatory effects. Paracetamol is a pain relieving medicine with effect on the central nervous system which has interaction with Cyclooxygenase system, the endogenous opioid path, serotonergic's descending inhibitory system, NO path and endocannabinoid system. This medicine is widely used to relieve pain (4).

Paracetamol is an effective analgesic and doesn't have the side effects of opioid or NSAIDs medicines (5). Previously suppositories and oral form of Paracetamol were available and recently injectable form is also available.

While all three methods can achieve appropriate plasma concentrations, there are differences in absorption and duration of reaching to the peak plasma levels. In rectal state, absorption can be unpredictable and its viability varies between 24% to 98% which changes by factors such as the formulation of suppositories of paracetamol, the number of used suppositories and particle sizes of

paracetamol (6). Paracetamol in therapeutic dosages rarely causes unfortunate results and side effects and against NSAID it does not cause ulcers or gastrointestinal bleeding (6). Despite Paracetamol Despite efficacy and appropriate tolerability, may cause local pain at the injection site and contact dermatitis.

Paracetamol is in the Non steroidal Anti-Inflammatory medicines categories, the main analgesic mechanism by these medicines is to inhibit the Cyclooxygenase and thus inhibit prostaglandin synthesis, prostaglandins are considered an important environmental factor in pain and sensitivity increases (7). So far at least two forms of Cyclooxygenase have been identified which include the: Cyclooxygenase-1 which is involved in accumulation of platelet, homeostasis and protection of the gastric mucosa, Cyclooxygenase-2 which is effective in pain, inflammation and fever. Recently discovered Cyclooxygenase-3 proposed a central mechanism for the analgesic effect of acetaminophen (8, 9).

Intravenous paracetamol is formulated as it can be used in anesthesia or immediately after that. However, other formulations do not have such a capability. The precise chemical formulation of paracetamol is in the form of Para acetyl aminophenol. Through intravenous prescription, it has started effect about half an hour, a half-life approximately 1-4 hours and 6-8 hours during effect. The maximum recommended dose for adults is 4 grams in twenty-four hours (10, 11). Intravenous Paracetamol is good medicine for postoperative pain treatment and may be used either alone or as part of combination therapy. It is observed that intravenous paracetamol has better analgesic effect, less opioid use, lower need for opioid dose repeated prescription or longer duration for the opioid repeated dose so paracetamol (injecting acetaminophen), is an effective analgesic in a variety of surgery (12).

Using non-steroidal anti-inflammatory medicines are usually effective for mild to moderate pain control. Also, these medicines have been identified as an effective adjuvant to opioids for moderate to severe pains. Recent studies indicated that non steroidal anti inflammatory medicines for pain control, especially paracetamol, alone or in combination with an opioid are more effective than what they ever thought it was (13, 14).

After Colectomy surgery, patients experience severe pain, delayed discharge, and delays in going back to work. Various studies demonstrate the efficacy of paracetamol alone or in combination with other analgesic medicines for pain relief after hard surgeries such as discectomy and increased patient satisfaction rates (15-18). The study is aimed to investigate the role of Intravenous Injection (IV) paracetamol for postoperative pain relief after Colectomy surgery.

2. Materials and Methods

This study is a clinical trial. To perform, 79 patients for whom elective Colectomy surgery was considered were studied after obtaining informed consent.

Exclusion criteria were: hypersensitivity or contraindication because of using paracetamol or opioid, impaired liver function tests, renal dysfunction, mental retardation, illiteracy due to the difficulty in obtaining consent. Patients randomly (double blind) were divided into two groups to receive paracetamol (40 patients) or placebo (39 patients).

Double blind method performed as the researcher who prepared the medicine was totally unaware of the patient who receives the medicine and pain evaluation, also the evaluating person was unaware of analgesic effects of the received medicine. In the first group (*Aeknil-India*) 1 gram paracetamol in 100cc normal saline was injected within 15 minutes of the end of surgery, during the skin closure. In the second group, only 100 ml of sodium chloride %0.9 (no additional medication) was injected in the same way as first group.

Pain was measured in 1, 5, 10, 15 and 24 hours after surgery with VAS standard (visual analogue scale). Medication side effects such as nausea, vomiting, dizziness, urinary retention and constipation were recorded at each visit. Morphine intake (based on the patient's request) was recorded during 24 hours. Patient satisfaction about postoperative pain control was assessed by VAS scale. Finally, morphine consumption, side effects of medication use and patient satisfaction about pain control and in two groups were compared. In this study, data gathering tools were questionnaire and interviews with patients.

3. Ethical considerations:

Written informed consent was obtained from all patients before entering the study. Patients were free to withdraw from the study at any time they wanted. All patient information is strictly confidential and names and address will not be mentioned anywhere.

4. Statistical Analysis:

All data were analyzed using statistical software SPSS16. For statistical analysis, descriptive statistics methods (frequency, percentage, mean ± SD) were used. The quantitative results between groups were analyzed using the Independent t test and qualitative results between two groups analyzed using chi square

test were. The $p<0.05$ was considered significant in this study.

5. Results

79 patients who underwent Colectomy surgery were studied in 2 groups: Acetaminophen group (n=40) and placebo (n=39).

Demographic Results:

Figure 1 shows the age distribution of the patients. The mean age of patients was 48.2 ± 15.23 years, median and mode age were 46 and 43 years. The youngest and oldest patients were respectively 17 and 68 years old. Of the 79 patients who were studied, 43 (54.4%) were males and 36 (45.6%) were female.

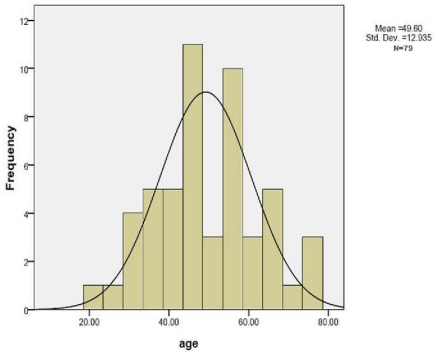

Figure 1. Age distribution of patients

The quantitative results comparison between two groups:

The mean age of patients in the paracetamol group 47.50 ± 11.22 and in the placebo group was 51.2 ± 13.76 years old. No statistically significant difference was found between the two groups in terms of age.

Figure 2 shows the gender distribution of patients between two groups. As it can be seen in the chart, there is no significant difference between two groups in terms of sex.

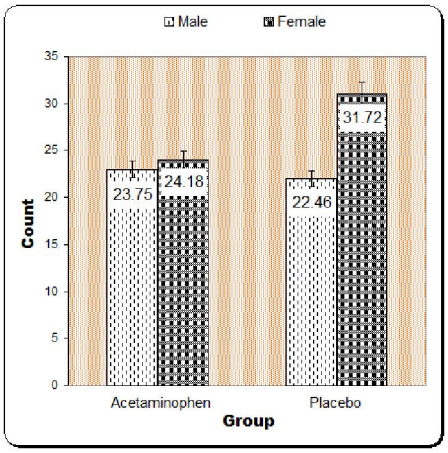

Figure 2. Sex distribution between two groups

Comparison of VAS in different times:

Pain one hour after the recovery:

In evaluating the pain 1 hour after recovery, the mean VAS in the paracetamol group was 5.73 ±1.89 and in the placebo group was 6.85± 2.11. Clearly the pain was lower in the paracetamol group (p=0.004).

Pain 5 hours after recovery:

In evaluating the pain 5 hours after recovery, the mean VAS in the paracetamol group was 5.43 ±2.03 and in the placebo group was 7.76± 1.9. In this case, the pain was significantly lower in paracetamol group than the placebo group (p=0.01).

Pain 10 hours after the recovery:

In evaluating the pain 10 hours after recovery, the mean VAS in the paracetamol group was 4.81 ±1.26 and in the placebo group was 5.71±1.31. It is clearly obvious that pain was less in paracetamol group than placebo group (p=0.02).

Pain 15 hours after the recovery:

In evaluating the pain 15 hours after recovery, the mean VAS in the paracetamol group was 4.11 ±1.05 and in the placebo group was 4.67±1.61. It is clearly obvious that pain was less in paracetamol group than placebo group (p=0.02).

Pain 24 hours after the recovery:

In evaluating the pain 24 hours after recovery, the mean VAS in the paracetamol group was 2.61 ±1.37 and in the placebo group was 3.57±1.45. Statistically significant differences were found between two groups in this case (p=0.01). Pain was less in paracetamol group than placebo group

Consumption of morphine Will in different times after surgery:

Figures 3, 4 and 5 demonstrate the rate of morphine request one hour, 5 hour and 10 hour after recovery. As it can be seen in the figures the Rate of morphine requests in the placebo group was more than paracetamol group. However, the difference is not statistically significant in any case.

Rate of morphine requests after 15 hours in the paracetamol group was 5 cases (16.1%) and in the placebo group was 7 cases(18.9%).Also In this case , the Rate of morphine requests is less in the paracetamol group, However, the difference is not statistically significant (p=0.19).

The Rate of morphine requests 24 hours after recovery in paracetamol and placebo groups, respectively were in zero and two cases (5.11%)

Also In this case, difference in the Rate of morphine requests was not statistically significant.

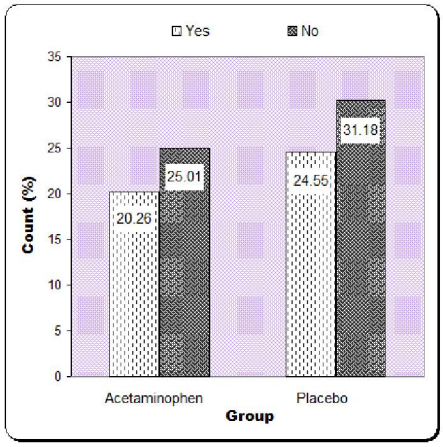

Figure 3. Will rate of morphine one hour after recovery in groups

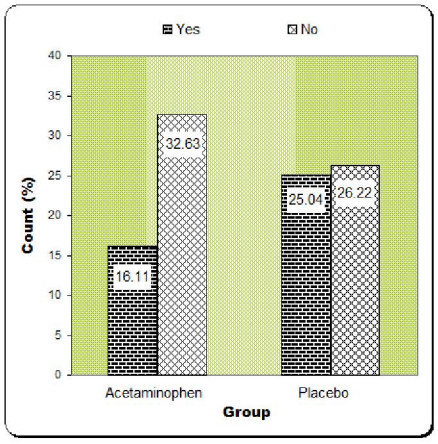

Figure 4. Will rate of morphine 5 hours after recovery

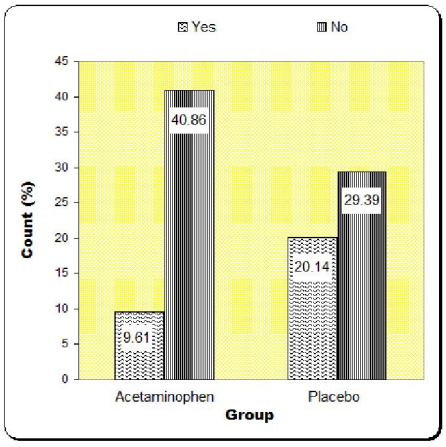

Figure 5. Will Rate of morphine 10 hours after recovery

Cumulative Rate of morphine:

The mean morphine consumption during 24-hour in the paracetamol group was 5.89 ± 2.79 mg and in the placebo group was 8.48 ±3.51 mg, that the difference was not statistically significant. Figure 6 the box plot figures demonstrate the Rate of morphine Consumption in both groups.

No side effect was observed in any case.

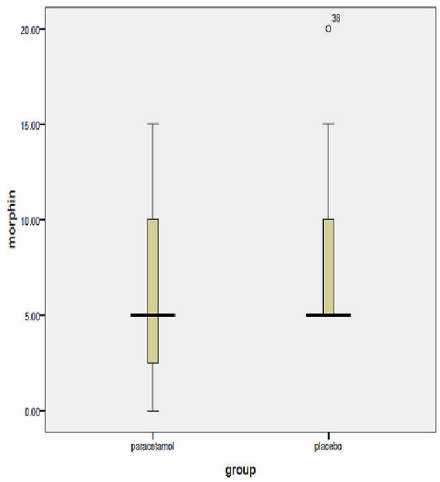

Figure 6. box plot figures Rate of morphine Consumption in groups

6. Discussion:

Intravenous paracetamol is an appropriate medicine in postoperative pain treatment and may be used alone or as part of combination therapy. It is observed that intravenous paracetamol has better analgesic effects , less opioid Consumption, less need to receive the re-dose or longer time to receive opioid again; Thus, paracetamol (acetaminophen injecting), is an effective analgesic in variety of surgical procedures (12). In the present study it was observed that paracetamol reduces postoperative pain and morphine requests. In this study, paracetamol group significantly had less VAS mean and pain in comparison to placebo group after 1, 5, 10, 15 and 24 hours after recovery.

Toygar and colleagues also observed that the VAS scores in the two groups which paracetamol was injected to them 15 minutes before anesthesia and 15 minutes after the end of surgery was significantly lower than the control group (17).

In Cakan and his colleagues study the pain score in different hours after surgery in paracetamol group was significantly less and more patients reported pain control at excellent levels (15). Dilmen and colleagues also observed that the pain significantly was reduced in a group who received paracetamol compared with control group, during 24 hours (16).

Also in Fletcher and colleagues study the pain score in the group who received Ketoprofen, paracetamol and the combination of these two medicines was less than the control group during rest

and movement (18). However, Grundmann and colleagues achieved results which contrast with these findings; they reported that there is no difference between paracetamol and placebo in this case (19).

In this study, the rate of morphine requests in the paracetamol group was less than the placebo group in examined hours, That 10 hours after surgery, this difference was significant. The mean 24-hour morphine consumption in the paracetamol group was non-significantly less than placebo group. Although in Dilmen et al study morphine consumption in the paracetamol group was decreased during the time and during 24 hours consumption was significantly lower. However, the cumulative amount of morphine consumption during 24 hours was not significantly different between groups (16).

However Toygar and colleagues in their study observed that the time to need the first analgesic, total consumption Rate of morphine and Consumption rate of morphine during 24 hours in two groups which paracetamol was started for them 15 minutes before anesthesia and 15 minutes before surgery was completed was significantly lower than the control group (17).

In Cakan and colleagues study no attenuation effect on opioid requirements in patients who received paracetamol was observed (15). Also in Grundmann and colleagues study no different in terms of the needs and demands for morphine between paracetamol and placebo group was observed (19). Also Fletcher and colleagues in a study observed that Cumulative dose of morphine during 48 hours in the group who received the combination of Ketoprofen and paracetamol was lower than other groups (18). According to the results of this study can be stated that paracetamol has no role in the rate of patients receiving morphine. In Fletcher and colleagues study side effects were equal in studied groups (18).

Grundmann and colleagues according to side effects observed one case shivering in the paracetamol group and in the placebo group; there were 6 cases (19). Cakan and colleagues also reported that the Rate of vomiting in patients who received paracetamol is reduced (15). Dilmen and colleagues did not report any side effects associated with morphine consumption in examined cases (16). In the present study no side effect related to morphine Consumption was observed in two groups. The findings are consistent with previous studies.

The results of present study demonstrated that injecting paracetamol is very effective in reducing postoperative pain; however, it has no effect on the total morphine requirement.

Corresponding Author:
Dr. Eilyad Issabeagloo Department of Pharmacology, Medical Sciences Faculty, Tabriz branch, Islamic Azad University, Tabriz, Iran.
E-mail: Dr.e.issabeagloo@gmail.com

References

1. DeLeo, J.A., Tanga, F.Y., and Tawfik, V.L., 2004, *Neuroimmune activation and neuroinflammation in chronic pain and opioid tolerance/hyperalgesia*. *Neuroscientist*; 10:40–52.
2. Kehlet, H., and Dahl, J.B., 1993, *The value of ''multimodal'' or ''balanced analgesia'' in postoperative pain treatment*. *Anesth Analg*.77: 1048–1056.
3. Pickering, G., Loriot, M.A., and Libort, F., 2006, *Analgesic effect of acetaminophen in humans: first evidence of a central serotonergic mechanism. Clin Pharmacol Ther*. 79:371–378.
4. Malaise, O., Bruyere, O., Reginster, J.Y., 2007, *Intravenous paracetamol: a review of efficacy and safety in therapeutic use. Future Neurol*. 2:673–88.
5. Bannwarth, B., and Pehourcq, F., 2003, *Pharmacologic basis for using paracetamol: pharmacokinetic and pharmacodynamic issues*. *Drugs*; 63:5–13.
6. Oscier, C., Bosley, N., and Milner, Q., 2007, *Paracetamol: a review of three routes of administration. Update Anaesth*. 23:112–14.
7. Miller, R.D., 2005, *Anesthesia*. 6 th ed. Philadelphia: Churchill Livingstone; P. 2734-2736.
8. Chandrasekharan, N.V., Dai, H., Roos, K.L., 2002, *Cox-3 a cyclo oxygenase-1 varient inhibited by acetaminophen and other analgesic antipyretic* drugs. Proc Natl Acad Sci. 99: 1326-9.
9. Beck, D., and Schenk, M., 2000, *Rectal paracetamol has a significant morphine spring effect after hysterectomy*. BJA; 85(4): 658-671.
10. Stephan, A., and Schung, D.A., *1999, Effect of general anesthesia and surgery on the kinetics of intravenous proparacetamol*. BJA , 82(Suppl 1): 121-125.
11. Keays, R., Harrison, P., and Alexander, J., 1991, *Interavenous acetyl cysteine in paracetamol induced fulminant hepatic failure*. BMJ; 303: 1026-29.
12. Macario, A., Royal, M.A., 2010, *A Literature Review of Randomized Clinical Trials of Intravenous Acetaminophen (Paracetamol) for Acute Postoperative Pain*. *Pain Practice*, no. doi: 10.1111/j.1533-2500. 00426.x
13. Mackanes, S., and Spendlove, J.L., 1998, *Acetaminophen as an adjuant to morphine by*

patient-controlled analgesia in the management of acute post operative pain. Anesthe Analg; 87(2): 368-371.

14. Warner, T.G., and Mitchell, J.A., 2002 *Cyclooxygenase-3 filling in the gaps toward a cox continuum*. Proc Natl Acad Sci. 99: 1336-9.
15. Cakan, T., Inan, N., Culhaoglu, S., Bakkal, K., and Basar, H., 2008, *Intravenous Paracetamol Improves the Quality of Postoperative Analgesia but Does not Decrease Narcotic Requirements*. *J Neurosurg Anesthesiol* , 20:169–173.
16. Dilmen, O.K., Tunali, Y., Cakmakkaya, O.S., Yentur, E., Tutuncu, A.C., and Tureci, E., 2010, *Efficacy of intravenous paracetamol, metamizol and lornoxicam on postoperative pain and morphine consumption after lumbar disc surgery*. *Eur J Anaesthesiol*. 27:428–432.
17. Toygar, P., Akkaya, T., Ozkan, D., Ozel, O., Uslu, E., and Gümüş, H., 2008, *Does iv paracetamol have preemptive analgesic effect on lumber disc surgeries?* .[Article in Turkish]. *Agri.* 2008 Apr;20(2):14-9.
18. Fletcher, D., Negre, I., Barbin, C., Francois, A., Carreres, C., and Falgueirettes, C., 1997, *Postoperative analgesia with i.v. propacetamol and ketoprofen combination after disc surgery. Can J Anaesth*. 44(5 Pt 1):479-85.
19. Memis, D., Inal, M.T., Kavalci, G., Sezer, A., and Sut, N., 2010, *Intravenous paracetamol reduced the use of opioids, extubation time, and opioid-related adverse effects after major surgery in intensive care unit*. J Crit Care.25 (3):458-62. Epub 2010 Mar 1.

2/20/2013