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

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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.

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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	25 (71.4%)	23 (65.7%)	0.6
Myomectomy	10(28.6)	12 (34.3%)	
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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