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Prophylactic Effect of Ondansetron for Intrathecal Fentanyl-Induced Pruritus

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Abstract

***Background*:** Using opioids along with local analgesic increase anesthesia duration and provide appropriate postoperative analgesia. However, intrathecal injection of opioids is associated with upsetting side effects including pruritus. Ondansetron (5-HT3 receptor agonist) has anti-pruritus effects. Therefore, we conducted a double blind randomized case-control study to evaluate prophylactic effects of ondansetron for preventing intrathecal fentanyl-induced pruritus.

***Materials and Methods*:** Two hundred seven patients with ASA status I, II or III, who were candidate for pelvic or lower extremity surgery with spinal anesthesia (SA) using bupivacaine hyperbaric (10-15 mg) and fentanyl (25 µg) were included in the study. Patients were randomly assigned to two groups of case (ondansetron 8 mg IV) and control (4 ml normal saline IV). Patients' hemodynamic indexes and side effects were evaluated at 5, 10, 30, 60 minutes and then hourly up to 6 hours after SA. Pruritus presence, degree, and site were evaluated after two and six hours. Data were analyzed using Kolmogorov-Smirnov test, student *t*-test, Mann–Whitney *U*, χ^2, Fisher exact test, and Spearman linear correlation coefficient.

***Results*:** The pruritus incidence was 60% in control and 34% in case group. Severe pruritus was observed in 18% of control group and 6% of case group. Ninety four percent of patients with pruritus in control group expressed it in above T_6 dermatomes and 74% of patients with pruritus in case group had pruritus in T_6-L_1 dermatomes. The incidence of pruritus in L_1-lower dermatomes was similar in two groups. Headache and nausea after anesthesia were more common in control group (p=0.035).

***Conclusion*:** Ondansetron decrease incidence and degree of intrathecal fentanyl-induced pruritus. This reduction was more significant around injection area T_6-L_1 dermatomes. Ondansetron injection does not influence systolic blood pressure, duration of anesthesia and analgesia, and does not induced urinary retention and back pain.

Introduction

Addition opioids to local anesthetics increase anesthesia duration and provide appropriate analgesia after surgery. However opioids have various side effects. The most common side effect of intrathecal injection of fentanyl is pruritus, with a reported incidence of 60 to 100% [1, 2], which cause patient dissatisfaction. Many drugs have been used for treating fentanyl-induced pruritus, one of them is ondansetron, a 5-HT_3 receptor agonist, which was successful in preventing pruritus [3, 4]. However, researches showed dissimilar results about its prophylactic effect [5-7]. Ondansetron was essentially used to prevent nausea and vomiting, and some studies confirmed its benefit for it [4, 6], while some other studies did not [8]. Ondansetron effect on back pain, blood pressure changes, palpitation, urinary retention, post-operative pain, and headache was also evaluated and no significant relation was observed [3, 5-8]. This study aimed to investigate efficacy of prophylactic ondansetron in the prevention of fentanyl-induced pruritus during spinal anesthesia, in a randomized, double-blinded, case-controlled trial.

Materials and Methods

This was a clinical trial on 207 patients (ASA status I-III) who were candidate for pelvic or lower extremity surgery and received spinal anesthesia (SA). The study was conducted in vascular surgery division of surgery department, Imam Reza hospital, Mashhad Medical Sciences University in 2009-2010. Considering study goals and limited number of patients, for selecting study units census methods was used and all the patients with inclusion criteria, who arrived in the study period, were included in the study. Patients reluctance to participation, spinal anesthesia contraindication, opium dependency, known allergy to 5-HT_3 receptor agonist or other drugs in the study, electrolytes disorder, prolonged QT, skin disease with pruritus, age more than 75 years old, history of psychosis, history of systemic disease with pruritus, and complain from pruritus before operation, were exclusion criteria.

Ethic committee of Mashhad Medical Sciences University approved the study and written informed consent was obtained from patients. Patients were

assigned into two groups based on simple randomization, which was their arrival.

The study group received 8 mg ondansetron (made by Aboraihan company, Iran) after having an IV line and usual monitoring, then SA was induced with bupivacaine hyperbaric (made by Milan company, France), and fentanyl 25 µg (made by Aboraihan company, Iran). Ondansetron dose was chosen based on previous studies that reported its effectiveness in preventing fentanyl-induced pruritus [5, 9].

Bupivacaine dosage was adjusted based on required level of sensory block, and patients' characteristics like height and weight. Control group had the same method of anesthesia and received 4 ml normal saline instead of ondansetron. A questionnaire was used to document patient demographics and medical history, and patients information during and after operation including:

1- Medical history specially focused on liver disease, renal failure, diabetes mellitus, polycythemia, psychosis, and pruritus

2- History of used drugs specially anti-pruritics

3- Blood pressure and heart rate were measured after administrating ondansetron or placebo at 5, 10, 30, 60 minutes and then every hour until sixth hour post-operation.

4- If pruritus occurred, its degree and site was documented at 2, and 6 hours.

5- Nausea, vomiting, headache, and back pain, were recorded with their severity until 6 hours. In the case of urinary retention, it was also recorded up to 6 hours.

To protect study blindness, medical staff that administrated drugs did not participate in filling questionnaire. Twenty seven gauge needles were used for all the patients and entrance space was between L_{4-5} or L_{4-5}. Data were analyzed with SPSS-11.

Kolmogorov-Smirnov test was used to assess normal distribution of quantities variables. To compare side effects like pruritus, nausea, vomiting, headache, and back pain, blood pressure, and heart beat between two groups student test for independent variable and its equal nonparametric tests like Mann–Whitney *U*, χ^2, and Fisher exact test was used. To evaluate the association between side effects Spearman linear correlation coefficient was used. All test considered significant at 0.05 level.

Results

This study was preformed as a randomized double blind clinical trial on 207 patients who were under spinal anesthesia with fentanyl 25 µg and bupivacaine hyperbaric 10-15 mg. 207 patients were randomly assigned to case group (N=107, received Ondansetron 8 mg IV) and and control group (N=100, received 4 ml normal saline). Participants in two groups were similar from demographic aspects and ASA status (Table 1). Analgesic duration (until patient complains from pain), and blockade duration (lost of block in two dermatome) was similar in two groups. Incidence of pruritus was 60% in control group and 34% in study group (Fig. 1). Pruritus degree was also significantly lower in study rather control group. In patients who had pruritus, distribution of pruritus under L_1 dermatome was the same in two groups, while the most common site of pruritus in control group was in T_6-L_1 and in study group was in T_6-upper dermatomes of (Table 2).

Blood pressure, heart beat, urinary retention and back pain was similar in two groups during 6 hours after operation. The incidence and intensity of nausea was less in study group compared with control group (p=0.001) (Table 3).

In total 36 patients complained from headache that its incidence and severity was higher in control group (p=0.035) (Table 4). The considerable fact was the correlation between headache severity and nausea (p=0.004) and pruritus severity and nausea (p=0.005) in case group.

Table 1. Demographic characteristics of patients' in two groups

Variable	Case	Control	*p*-value
Age* (year)	52.59±9.70	55.01±10.47	0.147
Weight* (kg)	72.14±9.33	70.64±11.11	0.162
Height* (Cm)	165.14±8.74	163.14±9.10	0.132
Gender #			
Female	17.0	13.0	0.441
Male	83.0	87.0	
ASA class #			
I	15.0	14.0	
II	33.6	31.0	0.981
III	51.4	52.0	

* Data expressed by mean ± standard deviation
\# Data expressed by percent

Table 2. Distribution frequency of pruritus site in two groups

Pruritus site	Above T_6 dermatomes		T_6-L_1		L_1 Below dermatomes	
Pruritus severity	Case	Control	Case	Control	Case	Control
Mild	29	27	11	30	9	14
Sever and need treatment	5	12	2	14	1	6
p-value	0.570		0.001		0.001	

Table 3. Incidence and severity of nauseas in two group

Nausea	Case	Control
Does not exist	90.0	62.0
Mild	8.0	28.0
Moderate and need treatment	1.0	8.0
Severe with vomiting	1.0	2.0

Table 4. Frequency of headache and its severity in two groups (percent)

Group / Headache severity	Case	Control
0	88.0	77.0
1-2	5.0	10.0
3-4	4.0	4.0
5-6	1.0	3.0
7-8	2.0	4.0
9-10	0	2.0

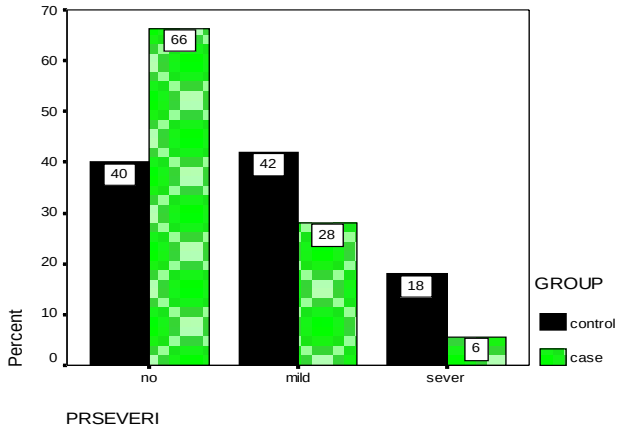

Figure 1. Frequency and intensity of pruritus in two groups

Discussion

Opioids are effective drugs for reliving acute and chronic pain. Using them in spinal anesthesia increase duration and strength of analgesia [9, 10]. The incidence of opioids-induced pruritus depends on its kind and method of administration [11, 12]. Pruritus occurred in 2-10% of patients who received systemic opioid. The risk of pruritus increased significantly if opioid administrated by epidural or intrathecal method. The highest incidence of pruritus occur with intrathecal morphine (up to 100%) [11-14].

The incidence of pruritus after intrathecal fentanyl was reported 60-100% [1, 2]. The incidence of pruritus in our study was 60% in control group and 34% in case group. The incidence of pruritus increased with higher does [13]. Pregnant women have the highest sensitivity [5, 13, 14], which could be because of reaction between estrogens and opioids receptors [14]. Delta receptors cause disorder in mechanical receptors function and produce inflammation [15]. Varied mechanism was suggested to explain opioids- induced pruritus. Opioids that are used in central nervous system (like epidural, intracisternal, intraspinal, or intrathecal) induce a pruritus which probably does not relate to histamine, but central μ-opiate-receptors are involved in it. In this mechanism, posterior section of middle cerebral is the main place of opioids activity and inducing pruritus [16, 17]. There are also other hypotheses about mechanism of opiates-induced pruritus. In a study with radioactive material researchers found that pruritus in face area occurred before opioids reach brainstem [18, 19]. Therefore, they stated that opioids produce pruritus by changing neural pathways in injection site [20]. In pregnant women, because of high blood pressure and different maneuvers perform for them, opioids reached middle cerebral by the time pruritus occur [21-23], this could be one of the reasons for higher incidence of pruritus in pregnant women [24].

5-HT_3 receptor antagonist like ondansetron and dolasetron effects on preventing opioids-induced pruritus is controversial. Some investigators reported positive effects and some other reported its inefficiency [12, 25-27]. Studies that indicated positive effects for 5-HT_3 receptor antagonist, reported that ondansetron decrease opioids- induced pruritus in orthopedic patients from 70% to 30% [3]. In Latrou et al. study prophylactic ondansetron and dolasetron reduce the incidence of pruritus in non pregnant patients. The incidence of pruritus in ondansetron group was 34%, in dolasetron group 20% and in control group 66%. Kyriakides et al. reported that the frequency of skin lesions around nose due to pruritus in patients who received alfentanil reduce 39% with prophylactic ondansetron [13]. Ondansetron decreased the severity of pruritus due to intrathecal morphine after cesarean section by 80% [4]. Yeh et al. showed that the frequency of pruritus in women who had elective cesarean section and received prophylactic ondansetron decrease from 85% to 25% [5]. In contrast, other authors reported no effect for prophylactic ondansetron in preventing pruritus caused by intrathecal fentanyl [26]. Present study showed that ondansetron reduce incidence and severity of fentanyl-induced pruritus, although pruritus still occurred in 34% of patients and it was severe in 6% of patients. There was no difference between two genders for pruritus incidence.

Ondansetron also decreased incidence of nausea and headache. The reduction in headache incidence may be due to reduction in nausea which reduce CSF leak. Other studies reported various results for ondansetron effects on nausea and vomiting. In a study in 2000, reduction in nausea and vomiting in patients with IV ondansetron was significant [4]. Another study showed that there is a correlation between IV ondansetron and incidence and intensity of nausea and vomiting [6]. However, a study conducted in 2005 showed no prophylactic effects for IV or oral ondansetron in preventing nausea and vomiting [8]. Regarding ondansetron effects on preventing headache some studies reported inefficiency while some recent studies reported that it increase incidence of headache [28].

After administration of intrathecal or epidural opioids, patients usually start to scratch around their nose and upper part of face [12, 14]. The reason could be high sensitivity of opiates receptors in brain neural ganglion especially trigeminal nerve. In our study, the most common site of pruritus was T_6-L_1. Some investigators declared that fentanyl pruritus occurred mainly around injection site [26]. This is probably because fentanyl is a lipophilic opioid and immediately absorbed by spinal cord therefore a little amount of it move upward. In contrast, morphine which is hydrophilic gradually absorbed by spinal cord and therefore has chance of moving upward to brain [29]. Wells et al. showed that prophylactic ondansetron is not effective in preventing intrathecal fentanyl- induced pruritus administrated for delivery [27]. Furthermore, ondansetron does not prevent pruritus caused by intrathecal sufentanil and morphine after cesarean section [6]. This various results probably depends on intrathecal opiod does [24]. In our study, all the patients received same does of fentanyl (25 μg). Another theory provided by Wells is that probably the efficiency of 5-HT_3 receptors antagonist depends on

bupivacaine does that is administrated with opioids [27]. In this study bupivacaine does was 10-15 mg. Bupivacaine prevents bounding of opiates with mu receptors and facilitate their bounding with kappa and delta receptors [30]. Opioids bounding with kappa receptor decrease pruritus frequency [31].

Previous studies did not show any relation between incidence of back pain, blood pressure changes, palpitation, and urinary retention with ondansetron [3, 5-8]. We found similar results. in addition duration of analgesia and time of blockade regression were similar between our two groups indicating that ondansetron does not decrease or increase analgesic effects of opioids therefore it has a preference over μ-receptors agonist or antagonist.

In conclusion although ondansetron reduced frequency and intensity of pruritus, but pruritus still occurred in patients even in severe form, so for making a decision it is recommended that patients satisfaction have also evaluated. Besides effective mechanism of ondansetron in preventing opioids-induced pruritus is not known. Ondansetron decreased pruritus in fentanyl injection site, where drug has its highest concentration, but patients received ondansetron had pruritus in upper part of T_6. This is probably due to role of 5-HT_3 receptors in inducing pruritus at injection site. The important fact was that with decrease in pruritus severity, severity of nausea and vomiting also decreased, this could be the main key for discovering exact mechanism of pruritus caused by opioids and ondansetron mechanism in preventing it. Headache also reduced in patients along with reduction in nausea and vomiting which could be due to decreasing CSF leakage following gag reflex. Further studies are required to discover mechanisms, mediators, and involve neural pathways contributed to this side effect. We based on similar studies used does of 8 mg ondansetron [5, 9]. Conducting more studies with different ondansetron dosage to find the optimal does of ondansetron, investigating other 5-HT_3 receptors agonist and comparing them with ondansetron, and finally evaluating ondansetron effects with different opioids in SA, are recommended.

Suggestions

1- It was better if we excluded patients with severe pain from study

2- Some drugs have anti- pruritus property, like diclofenac [32] that is administrated to control pain, it was better if we prepared a list of them and patients who used them would excluded from study.

3- It was better if we documented patients satisfaction so we could better decide about prophylactic effects of ondansetron

4- Patients in vascular surgery division usually have many background diseases and use different medications. It was better if we conducted our study in other surgery division like orthopedic to prevent drug interactions, and reduce the chance of existed pruritus in the ground of chronic disease.

5- It is recommended that site and severity of pruritus documented carefully in different times.

6- It is recommended that patients be follow- up for longer time

Since pruritus is a subjective finding, it was better if we evaluated an objective finding.

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Authors' Contributions

All authors had equal role in design, work, statistical analysis and manuscript writing.

Conflict of Interest

The authors declare no conflict of interest.

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