Original Article

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A Comparison of the Effect of Ondansetron and Propofol on Intrathecal Opioid-Induced itch in Elective Cesarean Section

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ABSTRACT

BACKGROUND AND OBJECTIVE: Itch is one of the most common and uncomfortable side effects of neuraxial anesthesia. Its incidence is higher especially in cesarean section. The aim of this study was to compare the effect of ondansetron and propofol at doses lower than the hypnotic dose on the treatment of itch induced by intrathecal fentanyl in cesarean section.

METHODS: In this prospective study, 90 patients with American Society of Anesthesiologists (ASA) class I and class II with an average age of 30 years and first time cesarean section underwent intra-spinal anesthesia with 25 µg fentanyl and 10 mg bupivacaine 0.5%. Women were randomly divided into two groups of 45. One group received 4 mg ondansetron and another group received 10 mg propofol at first and then 10 µg/kg / min through infusion. The incidence and severity of itch were recorded on the basis of the visual scoring system during operation and during recovery.

FINDINGS: The highest incidence of itch was 30 to 60 minutes after injection. The incidence of itch during surgery was 2.22% and 7.26%, and during recovery was 7.6% and 8.8%, in the ondansetron and propofol groups, respectively (p=0.5, p=0.4). The mean itch severity scores during surgery were 1.85±0.69 and 1.66±0.81, and during the recovery were 1.33±0.57 and 1.25±0.5, in the ondansetron and propofol groups, respectively (p=0.65) (p=0.84).

CONCLUSION: Based on the results of this study, ondansetron and propofol at doses lower than the hypnotic dose were well tolerated. Considering the effect of both drugs on the treatment of itch caused by intrathecal fentanyl, both of them can be used clinically.

KEY WORDS: *Itch, Ondansetron, Propofol, Opiate, Caesarean section.*

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Introduction

Neuraxial injection of opioids provides adequate analgesia in various surgeries. However, the use of opiates for intra-spinal anesthesia has side effects such as pruritus, nausea and vomiting (1, 2). The incidence of pruritus is about 30 to 100%, reporting it as the most common complication of neuraxial injection of opioids (3). The incidence of pruritus ranges from 83% in postpartum women to 69% in non-pregnant patients, including men and women (4–7).

In pregnant women, neuraxial opioid-induced pruritus is more frequent than other causes (8, 9). The higher incidence of neuraxial opioid-induced pruritus among women can be attributed to interference of estrogen with opioid receptors (10, 11). Pruritus is most commonly observed in the trunk, nose, around the eyes, and on the face in areas innervated by trigeminal nerve (12).

This condition begins shortly after neuraxial injection of opioids. This period depends on the type and dosage of the opioid (13). Neuraxial opioid-induced pruritus is still a major issue and naloxone is used in this case. Several drugs with different effects have been used for this purpose, including: 5-HT3 receptor antagonists, opioid antagonists, propofol, nonsteroidal anti-inflammatory drugs and droperidol (14). 5HT is a biological amine that acts as a neurotransmitter in the brain and spinal cord (15). The contrast between opioids and the 5-hydroxytryptamine type 3 (5-HT3) receptors plays an important role in causing pruritus after the administration of neuraxial opioid. For this reason, it seems that the preventive use of 5-hydroxytryptamine type 3 receptors antagonist is effective in the treatment of neuraxial opioid-induced pruritus. There are contradictions in the use of 5-HT3 receptor antagonists to prevent pruritus after neuraxial opioid use (16).

5-HT3 antagonists are antiemetic drugs with less side effects. This drug does not have sedative effects, restlessness, and extrapyramidal complications observed in other common antiemetic drugs. Ondansetron is the first 5-HT3 receptor antagonist to be used alone or with other low-cost drugs (17-22). Propofol is currently the most commonly used intravenous anesthetic drug used in anesthetics (23). Values less than the dose necessary for the hypnotic effect of propofol in reducing cholestatic pruritus and the treatment of pruritus caused by intravenous injection of opioids is as effective as naloxone, although not all previous studies support this effect of propofol (24). Et al., found that 8 mg of ondansetron had no effect on the pruritus caused by intrathecal fentanyl (25). In a study, Hirmanpour et al. found that ondansetron and propofol at doses lower than those that produce hypnosis could be used in the treatment of pruritus caused by intrathecal fentanyl (26).

Beilin et al. successfully used propofol at doses lower than those that produce hypnosis in the treatment of pruritus in patients receiving intrauterine morphine (27). Sometimes this complication has a lot of dissatisfaction and clotting in pregnant patients during cesarean section.

Considering the abovementioned issues and the different results obtained in previous studies, further studies on this issue could be useful. The aim of this study is to compare the effect of ondansetron and propofol at doses lower than those that produce hypnosis in the treatment of pruritus induced by intrathecal fentanyl in cesarean section.

Methods

This randomized clinical trial study was approved by the Ethics Committee of Urmia University of Medical Sciences with the code IR.UMSU.REC.13950299.171 and with the registration number of the clinical trial IRCT: 2017041527677N7. An informed consent was obtained from the 90 female patients based on the study by Hirmanpour et al. (26), (45 people in each group). People aged 20 to 40, American Society of Anesthesiologists (ASA) Class I and II, elective cesarean section, cesarean section with spinal anesthesia entered the study.

People with history of a disease associated with pruritus of the skin and any complaints of pruritus before surgery, onset of pruritus before closure of the umbilical cord, allergy to drugs, preeclampsia, eclampsia, and those who used anti-nausea during the last 24 hours were excluded from the study. In the operating room, patients were first monitored by non-invasive pressure indicator, electrocardiogram, and pulse oximetry. All patients received 5 – 7 ml / kg (max. 1500 ml) of normal saline prior to any intervention (28).

The spinal anesthesia was performed by the needle number 25 (EXEL) in sitting position of the third and fourth intervertebral space, and 10 mg of hyperbaric bupivacaine plus 25 µg of fentanyl was injected into the subarea of the conoid. Patients were placed in the position behind the back and hypotension was

prevented. The patient's bed was rotated 15 to 20 degrees to the left to prevent the aortocaval pressure by the uterus. Oxygen was administered to patients at a rate of 6 liters per minute by a mask.

Based on random numbers, one group was administered with 4 mg intravenous ondansetron, immediately after closure of the umbilical cord and the other group intravenously received propofol at a single dose of 10 mg and then with 10 µg per kg body weight per minute by the second person. Every 3 minutes until the first half hour and then every 5 minutes until the end of the operation, the blood pressure of the patients was measured and if the systolic blood pressure reached below 100 mmHg or up to 20% more than of the initial systolic blood pressure, further pressure loss was prevented by increasing the rate of normal saline infusion and using 5–10 mg intravenous ephedrine. The incidence of pruritus and its severity, nausea and vomiting during and after operation was reviewed and recorded in the recovery and compared in two groups. In the case of severe pruritus with a number greater than 2, naloxone at a dose of 0.33 µg/kg bodyweight was used for intravenous treatment. Patients were given a complete explanation and training for the severity of pruritus based on the visual analog scale (VAS). Zero: no pruritus, 1-3: low pruritus, 3-7: average pruritus and 7-10: severe pruritus were shown on the ruler and pruritus score was considered as follows: zero = no pruritus, 1 = low pruritus, 2 = average pruritus, 3 = severe pruritus (29).

To compare the frequency in the two groups, Chi-square test was used (if necessary, Fisher test) and for comparing the means, T-test was used (if necessary, Mann-Whitney) and $p<0.05$ were considered significant.

Results

Patients in the two study groups did not have a statistically significant difference in demographic characteristics (Table 1). The highest incidence of pruritus was from 30 to 60 minutes after injection. Of the 45 patients, 10 (22.2%) patients in the ondansetron group and 12 (26.7%) patients in the propofol group had pruritus during the procedure. Considering the sample size and type 1 error with alpha 0.05, and according to the ratio of pruritus in the study group (22.2% to 26.7%), the power of the statistical test in this study was 66%. Three (6.7%) patients in the ondansetron group, and four (8.9%) patients in propofol groups had pruritus in recovery (p=0.41) (p=0.5) (Table 2).

Table 1. Demographic characteristics of patients in the two groups

Group / Variable	Propofol Mean±SD	Ondansetron	P-value
Age (year)	32.42±6.21	32.78±5.67	0.23
Height(centimeters)	159.61±3.83	160.02±3.25	0.12
Weight (kg)	83.73±7.69	84.02±8.07	0.36
BMI (Kg/m^2)	33.9±3.23	32.85±3.44	0.9
Operation duration (min)	89.9±11.93	88.07±8.28	0.29

Table 2. Distribution of absolute and relative frequency of pruritus during surgery and recovery in the two groups

Group / Variable	Ondansetron N(%)	Propofol N(%)	P-value
Pruritus during surgery	10(22.2)	12(26.7)	0.4
Pruritus in recovery	3(6.7)	4(8.9)	0.5

Comparing the severity of pruritus during the operation between the two groups, the mean severity of pruritus in the ondansetron group was 1.85±0.69 and in the propofol group was 1.66±0.81 (p = 0.65). The mean severity of pruritus in the ondansetron group was 1.33±0.57 and in the propofol group was 1.25±0.5 in recovery (p=0.84).

12 (26.7%) patients in the ondansetron group, and 22 (48.9%) patients propofol group had nausea during the operation (p=0.02). Nausea in the recovery was reported in three (6.7%) patients in the ondansetron group and two (4.4%) patients in the propofol group (p=0.26). Four (8.9%) patients in the ondansetron group and six (13.3%) patients in the propofol group had vomiting during the operation (p = 0.37). Two (4.4%) patients in the ondansetron group and one (2.2%) patient in the propofol group had vomiting in the recovery (Table 3).

Table 3. Distribution of absolute and relative frequency of nausea and vomiting during operation and recovery in two groups

Group / Variable	Ondansetron N(%)	Propofol N(%)	P-value
Nausea during surgery	12(26.7)	22(48.9)	0.02
Nausea in recovery	3(6.7)	2(4.4)	0.26
Vomiting during surgery	4(8.9)	6(13.3)	0.37
Vomiting in recovery	2(4.4)	1(2.2)	0.5

Discussion

The results of this study showed that although single dose of ondansetron 4 mg and infusion of propofol at doses lower than those that produce hypnosis deceased the overall incidence of pruritus caused by intrathecal fentanyl injection, but the level of pruritus was not statistically different between the two groups receiving the medications during operation and in recovery. The severity of pruritus was not statistically different between the two groups. In both groups, the incidence of nausea and vomiting during operation and recovery was reduced, while nausea in the ondansetron group was lower than the propofol group and it was statistically different.

The mechanism of pruritus caused by intrathecal opioids has not yet been fully recognized. It is unlikely that opioid-induced pruritus in related to the effects of histamine release, since the use of antihistamines for the prevention and treatment of opioid-induced pruritus is inevitable (30). One of the assumptions made in this regard is the movement of the opioids to the upper part of the neuraxial system, where the pruritus center is located in medulla and is associated with the trigeminal nucleus. On the other hand, communication paths that transmit pain and pruritus are similar (13).

Hirmanpour et al. found that although the incidence of pruritus was lower in both groups, this difference was not statistically different, which is consistent with our findings. They used intravenous sufentanil and 8 mg intravenous insulin (26). Beilin et al. found that injecting 10 mg intravenous propofol was not successful in reducing pruritus, which is not consistent with the results of our study. However, the dose of propofol used in this study was one intravenous infusion and then continued infusion, which was generally successful in reducing pruritus (27). Warwick et al. examined the effect of propofol at doses lower than those that produce hypnosis in the incidence of pruritus caused by intrathecal morphine injections in a cesarean section at Milton Keynes. The dosage they used in their study was 10 mg intravenous. They concluded that this dose of propofol is not effective in the treatment of pruritus caused by intrathecal opioid, which is not consistent with our findings (5). The difference in the conclusion can be attributed to the type of opioid used and the injected propofol. Kostopanagiotou et al. examined the effect of propofol during operation in reducing postoperative morphine-induced pruritus in patients undergoing hysterectomy surgery with epidural anesthesia and with general anesthesia based on propofol or thiopental. Propofol-induced anesthesia, compared with thiopental and sevoflurane anesthesia, reduces the incidence and severity of pruritus caused by the epidural injection of 3 mg morphine with ropivacaine (31). In our study, we used the sub-arachnoid opioid that achieved the same results. The dosage of propofol used in our study was lower than that. But the similarity of the results can be attributed to the type of opioid used, which is expected to increase the incidence and severity of morphine-induced pruritus more than lipophilic opioids, as mentioned in the studies (26).

Pirat et al. in a study in Ankara, Turkey evaluated the effect of oral and injectable ondansetron on intrathecal morphine-induced pruritus (29). Sarvela et al. also examined the effect of ondansetron and tropisetron on intrathecal morphine-induced pruritus (32). Kung et al. also did a similar study (33). None of these studies found a difference in the effect of ondansetron and placebo on the incidence and severity of intrathecal opioid-induced pruritus, which is not consistent with our findings. The reason for this difference can be attributed to the type of opioid used. This study showed that ondansetron and propofol at doses lower than those that produce hypnosis were effective in the onset of intrathecal fentanyl and reduced its rate.

However, this difference was not significant between the studied groups. Given that limited studies have been conducted in this regard, it is recommended that further studies be conducted with a larger number of patients and different doses.

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