AMJ
ISSN: 0005-2523

ISSN: 0005-2523
Volume 63, Issue 03, March, 2023

A comparative study examining the effect of intravenous injection of two doses of ondansetron on nausea and vomiting, pruritus, and shivering after intrathecal injection of fentanyl in lower limb orthopedic surgeries

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Keywords:
Ondansetron, Fentanyl, nausea and vomiting, Pruritus, Shivering, Orthopedic Surgery

ABSTRACT

Nausea and vomiting, pruritus, and shivering are among the most common complications induced by the administration of intrathecal opioids after surgery. Considering that the interaction between opioids and 5-hydroxytryptamine type 3 (5-HT3) receptors can play a significant role in causing these complications, this study aimed at evaluating the effect of ondansetron as a 5-HT3 receptor antagonist on reducing the incidence of nausea and vomiting, pruritus, and shivering after intrathecal injection of fentanyl in orthopedic surgeries. The present triple-blind, randomized, controlled, clinical trial was conducted on 90 patients that were candidates for lower limb orthopedic surgeries. Thirty minutes after spinal anesthesia, 4 mg of ondansetron, 8 mg of ondansetron, and 4 CC of distilled water (as a placebo) were intravenously administered to the patients in the first, second, and third groups, respectively. During 4 hours after surgery, the incidence and severity of postoperative nausea and vomiting (PONV), pruritus, and shivering were recorded. The results of the present study revealed that the incidence of PONV, pruritus, and shivering in the control group with the values of 53.3%, 20%, and 43.3%, respectively was significantly higher than their incidence in the ondansetron-4mg group with the values of 23.3%, 6.7%, and 23.3%, respectively and ondansetron-8mg group with the values of 16.7%, 10%, and 20%, respectively (P-value<0.05). Moreover, the severity and incidence of these complications were not significantly different between the two ondansetron doses (P-value>0.05). According to the results of the present study, the preventive administration of ondansetron can significantly reduce the incidence of PONV, pruritus, and shivering after surgery; however, there was no significant difference in the administration of its various doses.

1. Introduction

In orthopedic surgeries, the choice of anesthesia technique is a crucial challenge for anesthesiologists in terms of sufficient analgesia along with rapid movement recovery for the patient. Neuraxial block is the technique of choice in many cases as it provides sufficient muscle relaxation and analgesia during and after surgery, and at the same time prevents any post-operative delay in recovery [1]. In this regard, fentanyl is used as an intraspinal or epidural adjuvant because it is an effective factor for faster onset of action and prolonged duration of sensory block and analgesia after surgery. The mentioned features have made it one of the most common neuraxial drugs [2]. However, nausea, vomiting, pruritus, and shivering are relatively common complications of using opioids (such as fentanyl), and about 30-90% of these complications have been reported to depend on the type and dose of opioids used [3], [4].

In fact, opioids can increase the rate of post-operative nausea and vomiting (PONV) by several mechanisms such as the direct effect on the receptors of the vomiting center in the brain stem, sensitizing the vestibule to motion-induced vomiting, increasing digestive secretions, reducing gastric movements, and the effect of gastric emptying [5]. Although the main cause is unidentified, among the proposed mechanisms, the effect of drugs and toxins absorbed through the blood on chemoreceptors in the trigger zone can be of great importance. The antagonist agents of these receptors are able to reduce and control nausea and vomiting [6-8].

In addition, although several mechanisms have been hypothesized for the incidence of pruritus and shivering, the pathogenesis caused by opioids is still not fully understood. It seems that the μ-opioid receptor system plays a major role in the incidence of pruritus. Many therapeutic strategies have been tried in the management of opioid-induced pruritus; however, none have been completely satisfactory. According to previous reports, treatment with serotonin (5-hydroxytryptamine or 5-HT) antagonist has a documented effect [9]. Moreover, as mechanisms with mediators such as norepinephrine, dopamine, prostaglandin E1, and 5-HT are used in regulating the threshold of shivering and vasoconstriction, it seems that drugs acting on these mediators can also be effective in managing shivering [10].

Therefore, it seems that the common denominator of the therapeutic mechanism of these complications is serotonin or 5-HT receptors. These receptors exist both in the central nervous system (CNS) and in the peripheral nervous system (PNS). The stimulation of these receptors can cause both excitatory and inhibitory activities. In fact, serotonin as a natural ligand activates these receptors. The 5-HT3 receptor is structurally and functionally different from the other two serotonin receptors (G protein-coupled). The binding of serotonin as a neurotransmitter to the 5-HT3 receptor causes the excitatory response in neurons and makes the ion channel to open. This 5-HT3 receptor is closely associated with nicotinic and acetylcholine receptors and has a wide distribution in the CNS and PNS, thereby controlling physiological activity and biological and neurological behaviors such as anger, anxiety, appetite, nausea, vomiting, pruritus, shivering, etc. [7], [11- 13].

In this regard, ondansetron is the first receptor antagonist of 5-HT3 receptors, which is used alone or in combination with other low-cost drugs to reduce the incidence of PONV, pruritus, or shivering [14- 17]. The mechanism of action of ondansetron is attributed to the blocking of serotonin receptors (5-HT1, 5HT2, 5-HT3) that lead to the interruption of Bezold-Jarisch cardiac inhibitory reflex from chemical receptors. The reflex appears as a paradoxical reaction to a sudden drop in blood pressure and further destroys the

ISSN: 0005-2523
Volume 63, Issue 03, March, 2023

compensatory mechanisms of the blood circulation system [10]. Moreover, many studies have been conducted addressing the role of ondansetron in controlling PONV, pruritus, shivering, and other complications after various surgeries and reported different results regarding the effect of this drug on each of these complications. The obtained controversial findings can be attributed to the fact that these studies were conducted in different types of surgeries using various doses of the drug [14- 23].

Considering the necessity of obtaining early rehabilitation and offering physical therapy after all types of orthopedic surgeries, it is essential to control and treat any post-operative complications such as nausea, vomiting, pain, pruritus, shivering, etc. Therefore, this study aimed at evaluating the effect of the intravenous injection of 4 and 8 mg doses of ondansetron on nausea, vomiting, pruritus, and shivering after intrathecal fentanyl injection in lower limb orthopedic surgeries.

2. Methods

The present study was a triple-blind, randomized, controlled clinical trial. The study population included all patients that referred to Kashani Hospital of Isfahan in 2021 and were candidates for orthopedic surgery of the lower limb with spinal anesthesia.

From the mentioned population, the sample size was estimated to be 30 cases in each group at the confidence level of 95%, the test power of 80%, and considering the results of previous studies [18] revealing the mean and standard deviation of sedation in two groups receiving two doses of ondansetron equal to 3.75±2.50 and 2.30±2.12, respectively.

The inclusion criteria in this study consisted of patients that were candidates for sub-spinal lower limb orthopedic surgery within the age range of 18-65 years and the ASA physical status of I or II. The non-inclusion criteria comprised the need for emergency surgery, pregnancy or breastfeeding, smoking and drug addiction, high ICP, sensitivity to ondansetron, presence of skin infection at the injection site, history of coagulation disorders, history of migraine, history of gastrointestinal diseases, history of taking psychotropic drugs, and anti-nausea consumption in the last 24 hours. The exclusion criteria included the incidence of excessive intraoperative bleeding (more than 500 cc), change of anesthesia plan, incidence of hypotension (more than 20% of the initial pressure), and increase in the duration of the surgery to more than 3 hours. In case of the incidence of any of these criteria, the patient was excluded from the study and replaced with another sample.

After obtaining the code of ethics from the ethics committee of Isfahan University of Medical Sciences (Approval code: IR.MUI.MED.REC.1401.182), the clinical trial code from the clinical trial site (approval code: IRCT20160307026950N47), and written consent from eligible patients, 90 patients were randomly selected (Fig. 1) and then divided into three groups using the random allocation software. At the beginning of the study, the patients' basic and clinical information including age, gender, height, weight, body mass index (BMI), and past medical history were recorded.

Then, all patients received 5 cc/Kg of normal saline in the admission room, then entered the operating room, and were placed on the operating bed. After connection, the results of monitoring including ECG, pulse oximetry, non-invasive blood pressure, and heart rate (HR) were recorded. All patients were subjected to spinal anesthesia in the sitting position at the vertebral levels (L5-L4) or (S1-L5) with a No. 24 needle with 25 µg of fentanyl and 12.5 mg of Marcaine. Then, 30 minutes after spinal anesthesia, the first, second, and third groups intravenously received 4 mg of ondansetron, 8 mg of ondansetron, and 4 CC of distilled water (as a placebo), respectively.

In order to comply with the conditions of blinding, all the drugs with similar syringes were brought to the same volume, coded with A, B, and C labels, and daily given to the researcher, who prescribed them without knowing the type of drug. In addition, the patient and the data collector as well as the statistician were not aware of the type of the intervention in either of the three groups.

Patients' hemodynamic parameters including systolic and diastolic blood pressure (SBP, DBP), HR, respiratory rate (RR), and oxygen saturation percentage (SpO2) were evaluated and recorded regularly during 4 hours (every 5 minutes to 15 minutes, then every 15 minutes until the end of the surgery, and every 15 minutes after surgery).

In addition, the incidence and severity of postoperative nausea and vomiting (PONV), pruritus (according to a score from 0 to 10), and shivering (according to the score as follows: 0: no shivering, 1: peripheral cyanosis or vasoconstriction, 2: tremors and movements of a muscle group, 3: tremors and clear shaking movements of more than one muscle, and 4: severe and full body tremors) were recorded over 4 hours after surgery. Finally, the patients' satisfaction was questioned and recorded based on the VAS scale from 0 (no satisfaction) to 10 (complete satisfaction).

Statistical method:

The collected information was entered into SPSS software (Ver. 26). N (%) was used to display qualitative data while means ± standard deviation (SD) or median [interquartile range (IQR)] was used for presenting quantitative data. According to the results of the Kolmogorov-Smirnov test indicating the normal data distribution, one-way analysis of variance (ANOVA) was used to compare the mean of the quantitative data among the three groups. Moreover, Tukey's post-hoc test was used to perform the pairwise comparisons. The repeated measures ANOVA was used to compare the changes in the hemodynamic parameters in each of the groups over time. Chi-squared test was also used to compare the frequency distribution of qualitative data among three groups. The significance level of less than 0.05 was considered in all analyses.

3. Results

In the present study, the ondansetron-4 mg group consisted of 66.7% male and 33.3% female patients with the mean age of 46.39±15.84 years, the ondansetron-8 mg group comprised 80% male and 20% female patients with the mean age of 41.41±13.32 years, and the control group included 53.3% male and 46.7% female patients with the mean age of 44.97±16.73 years. The three studied groups were not significantly different from each other in terms of age, gender, height, weight, BMI, past medical history, and duration of surgery (P-value>0.05).

Table I. Comparison of patients' demographic and clinical characteristics between three groups

Characteristics	Ondansetron-4 group (N=30)	Ondansetron-8 group (N=30)	Control group (N=30)	P-value[1]
Age; year	46.39±15.84	41.41±13.32	44.97±16.73	0.453*
Sex				
Male	20(66.7%)	24(80.0%)	16(53.3%)	0.091**
Female	10(33.3%)	6(20.0%)	14(46.7%)	
Weight; kg	76.85±11.67	73.68±12.47	71.35±13.42	0.309*
Height; cm	172.36±9.06	172.45±9.84	168.68±10.09	0.349*
BMI; kg/m^2	26.65±3.59	25.24±3.83	24.99±3.59	0.280*
Past medical history				
Non	20(66.7%)	20(71.4%)	18(64.3%)	0.826**

ISSN: 0005-2523
Volume 63, Issue 03, March, 2023

DM	7(23.3%)	4(14.3%)	5(17.9%)	
HTN	1(3.3%)	3(10.7%)	2(7.1%)	
Other	2(6.7%)	1(3.6%)	3(10.7%)	
Duration of surgery; minute	92.78±35.47	84.00±34.92	80.36±18.80	0.088*

*: The significance level of the ANOVA comparing the mean of the variable between the three groups
**: The significance level of the Chi-Squared test comparing the frequently distribution of the variables between the three groups

Moreover, none of the hemodynamic parameters were significantly different among the three studied groups at any of the investigated times (P-value>0.05). Over time, the changes of these parameters were not significant in any of the three groups within 4 hours of surgery (Fig. 1).

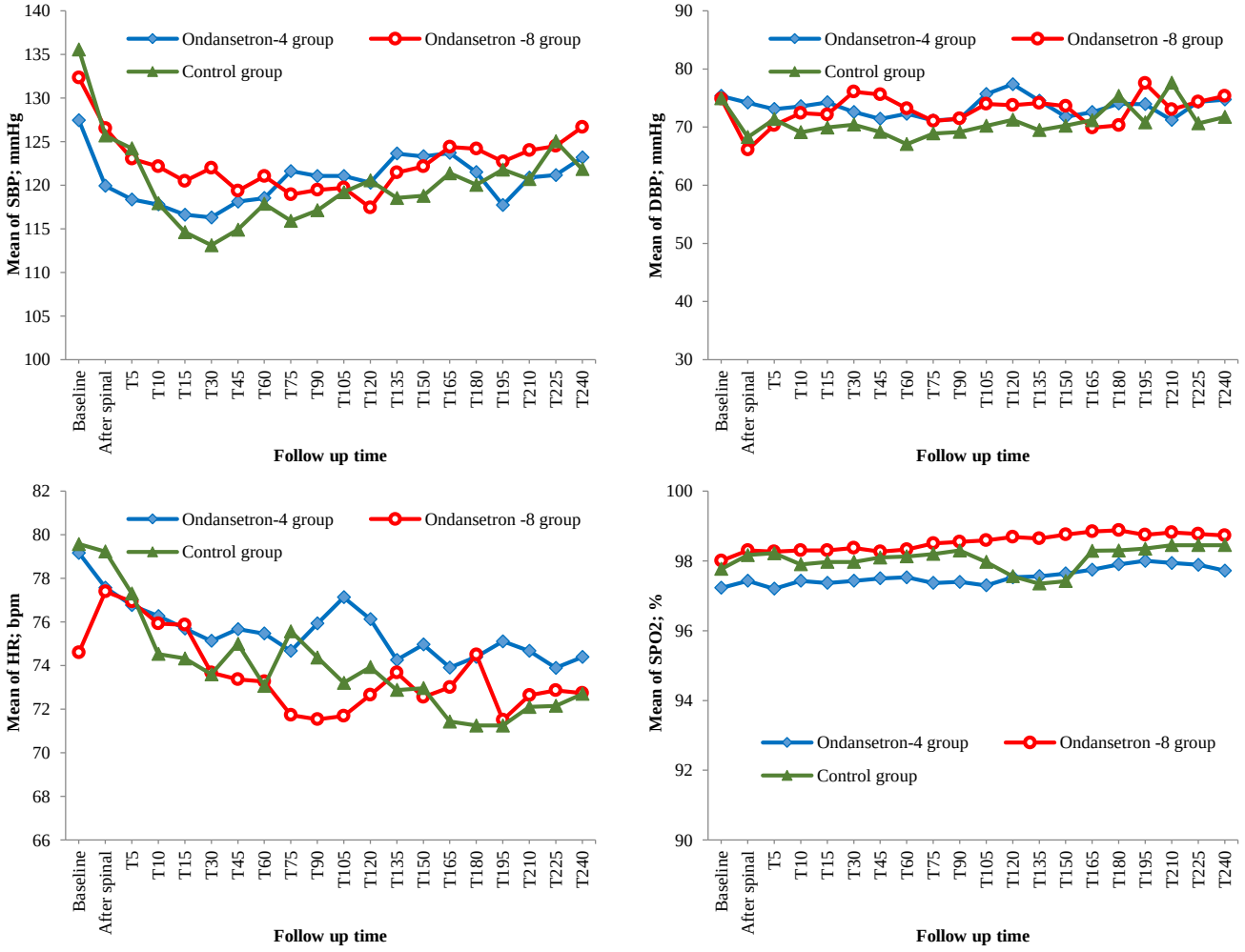

Fig. 1: Line chart of the hemodynamic parameters mean in follow-up times for the three groups

The Evaluation of the incidence of each of the complications of PONV, pruritus, and shivering revealed that the incidences of PONV, pruritus, and shivering in the control group with the values of 53.3%, 20%, and 43.3%, respectively were significantly more than those of the ondansetron-4 mg group with the values of 23.3%, 6.7%, and 23.3%, respectively and the ondansetron-8 mg group with the values of 16.7%, 10%, and 20%, respectively (P-value<0.05). Although the incidence of these complications in the ondansetron-8 mg group was lower than their incidence in the ondansetron-4 mg group, this difference was not statistically

significant (P-value>0.05). Furthermore, the severity of these three complications was not significantly different among the three groups (P-value>0.05). Besides, there was no significant difference in patients' satisfaction among the three groups (P-value>0.05) (Table 2).

Table 2. Comparison of the incidence and severity of complications and patients' satisfaction among the three groups

Complication	Ondansetron-4 group (N=30)	Ondansetron-8 group (N=30)	Control group (N=30)	P-value
Adverse effect				
PONV	7(23.3%)[b]	5(16.7%)[b]	16(53.3%)[a]	0.015**
PONV severity	3.00[1.00-3.00]	2.00[1.00-2.00]	3.00[1.00-3.00]	0.597*
Pruritus	2(6.7%)[b]	3(10%)[b]	6(20%)[a]	0.026**
Pruritus severity	2.00[2.00-3.00]	2.00[1.00-2.00]	3.00[2.00-3.00]	0.425*
Shivering	7(23.3%)[b]	6(20%)[b]	13(43.3%)[a]	0.038**
Shivering severity	1.00[0.00-2.00]	1.00[0.00-2.00]	1.00[0.00-3.00]	0.794*
Patients' satisfaction	8.69±1.65	8.95±1.20	9.29±0.98	0.240*

PONV: Postoperative nausea and vomiting Data shown as n (%) or median [IQR]

*The significance level of the ANOVA comparing the mean of the variables among the three groups. Then, Tukey's post-hoc test was used to compare two groups.

The similar letters indicate the non-significant differences, and non- similar letters indicate the significant differences among groups.

** The significance level of the Chi-squared test comparing the frequency distribution of the variables among the three groups

4. Discussion

The results of the present study showed that as compared with the control group, the administration of ondansetron after intrathecal fentanyl injection significantly reduced the incidence of PONV, pruritus, and shivering after lower limb orthopedic surgeries; however, there was no significant change in the severity of these complications among the three groups. In addition, there was no significant difference between the two doses of ondansetron in terms of the incidence and severity of these three complications. In fact, it can be stated that increasing the dose of this drug cannot have a significant role in reducing the incidence and severity of complications after surgery, and it is only possible that increasing the dose of the drug can slightly disturb the patients' hemodynamic stability during and after surgery. [23] evaluated the effectiveness of ondansetron along with fentanyl in pain relief pumps after hip and knee replacement surgery and figured out that ondansetron could control the incidence and severity of PONV and helped reduce these complications after surgery. The findings of the mentioned study were consistent with those of the present study.

[22] also showed that the administration of ondansetron together with propofol alone effectively reduced the incidence of vomiting but did not have a significant effect on the incidence of nausea in any of the three types of general anesthesia (administration of sevoflurane alone, propofol alone, or the combination of sevoflurane and propofol). In fact, the effect of the use of opioids in anesthesia was also taken into account in their study, and it was revealed that the type of opioids used could be effective in the incidence of complications after surgery. The difference between their study and this study is that we used the same protocol for spinal anesthesia in all three groups, as a result of which the role of narcotic drugs were removed.

ISSN: 0005-2523
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In this respect, it can be assumed that the most important effect of ondansetron as a serotonin receptor antagonist is its anti-vomiting effect, which is applied by acting on the ends of the vagus nerves and their central receptors, thereby preventing nausea and vomiting by inhibiting the vomiting reflex centrally [14]. Furthermore, as mentioned earlier, the administration of ondansetron in this study significantly reduced the incidence of shivering in these patients.

In line with the present study, [25] showed the positive effect of ondansetron administration on reducing the incidence of shivering after caudal anesthesia in children. Moreover, other studies also revealed the effect of this drug on shivering after spinal anesthesia in other invasive procedures [19], [20], [26]. In contrast, Powell et al.'s study indicated that the administration of ondansetron with a dose of 8 mg before anesthesia was more effective than the administration of ondansetron with a dose of 4 mg in reducing shivering after anesthesia [18]. This result is contrary to the results of our study as no significant difference was found between the two doses of ondansetron. Perhaps this discrepancy can be attributed to the difference in the type of surgery, the type of anesthesia, the drug used in anesthesia, and the time of drug injection.

Moreover, consistent with the present study, [27] also showed that the administration of intravenous ondansetron for preventing pruritus caused by neuraxial morphine can reduce the severity and incidence of pruritus.

In contrast, another study indicated that the administration of intravenous ondansetron after intrathecal morphine was effective in reducing the amount and severity of PONV; however, it did not have a significant effect on pruritus [28]. [21] also revealed that there was no significant difference between the administration of ondansetron 4 mg and propofol 10 mg in the incidence of pruritus caused by intrathecal fentanyl injection during and after elective cesarean section. [29] also concluded that the administration of 8 mg of ondansetron after intrathecal sufentanil cannot reduce the incidence of pruritus after surgery. Previous studies reported that central causes of pruritus, as compared with peripheral ones, are of higher significance. IT opioid-induced pruritus can be attributed to not only the cephalad spread of drug within the cerebrospinal fluid but also its action on central serotonin type 3 receptors in the medulla and spinal cord and the μ receptors in the medulla. Consequently, opioids not inducing peripheral histamine release can result in pruritus [9], [30], [31].

Therefore, the insignificant effect of ondansetron on pruritus in the mentioned studies may be ascribed to the difference in the type of surgery, the multiple mechanisms of pruritus, the administration of intrathecal sufentanil that may cause more pruritus than other intrathecal opioids, or the failure of ondansetron to reach the suitable central serotonin receptors.

Conceivably, the most important strengths of this study are as follows: Firstly, the comparison of two different doses of ondansetron after intrathecal fentanyl administration was performed. Secondly, all patients were under spinal anesthesia, intrathecal fentanyl was administered, and different types of opioids were not used. Thirdly, patients with the history of gastrointestinal diseases, pregnancy, smoking, extended surgery, and use of inhalant gases were not included in the study so that the factors related to increased risk of nausea and vomiting were controlled as much as possible. However, the small size of the sample, the non-examination of different types of drugs in intrathecal administration, and the impossibility of recording the patients' central body temperature can be mentioned among the weak points of this study. Finally, it is suggested to conduct future studies with a larger sample size comparing various types of drugs.

5. Conclusion

The results of the present study revealed that although the administration of 4 and 8 mg of ondansetron, after intrathecal fentanyl injection, as compared with the control group, caused a significant reduction in the incidence of PONV, pruritus, and shivering after lower limb orthopedic surgeries, no significant difference was found between the two studied doses.

An appropriate sample size of spinal anesthesia patients, with regular and accurate measurement, in four stages is the strength of the study, and the lack of calculation of other biochemical markers is considered a weakness. It is suggested that other researchers carry out our study in wider aspects.

6. Acknowledge

This research is extracted from the dissertation of the Specialist Doctorate of Medicine, which was approved by the Research Deputy of the Faculty of Medicine at No. 3401244 with the support of the mentioned deputy. Hereby, the authors appreciate all those who helped carry out the research.

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