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ORIGINAL ARTICLE

Effect of ondansetron on post-dural puncture headache (PDPH) in parturients undergoing cesarean section: a double-blind randomized placebo-controlled study

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Abstract
Purpose One of the most exhausting complications of spinal anesthesia, especially in parturients, is post-dural puncture headache (PDPH). This headache is not responsive to the usual pain killers. Ondansetron is a 5-HT_3 receptor antagonist which is generally used for the prophylactic management of nausea and vomiting; however, studies have found that ondansetron might decrease the incidence of PDPH. Therefore, we aimed to evalute the effect of ondansetron on decreasing the incidence of PDPH.
Methods In this double-blind randomized placebo-controlled clinical trial, 210 parturients who underwent elective cesarean section under spinal anesthesia were randomly allocated to two groups. The intervention group received 0.15 mg/kg ondansetron, while the control group received 5 ml normal saline. Heart rate and mean arterial pressure (MAP) were recorded during surgery. Furthermore, postoperative nausea and vomiting (PONV) and PDPH in the two groups were noted by an anesthetic nurse for 3 days and compared.
Results The incidence of PDPH in the intervention group was significantly lower than in the control group ($P = 0.001$). The incidence of PONV was also significantly lower in the intervention group compared to the control group ($P < 0.05$). However, MAP was significantly higher in the intervention group compared to the control group ($P < 0.05$). No significant difference was found between the two groups regarding heart rate ($P > 0.05$).
Conclusion Ondansetron (0.15 mg/kg) appeared to reduce the incidence of PDPH, as well as the incidence of hypotension and PONV, in parturients undergoing spinal anesthesia for cesarean section.

Keywords Post-dural puncture headache · Spinal anesthesia · Parturient

Introduction

Although spinal anesthesia is the most popular anesthetic technique for cesarean section [1], it is accompanied by various complications [2] including post-dural puncture headache (PDPH) which has a significant effect on the well-being of postoperative patients [3]. Typically, this headache is accompanied by throbbing, photophobia, and blurred vision aggravated by the upright position, and does not respond to minor pain killers [4]. Unfortunately, the incidence of PDPH is higher in parturients compared to other patients due to their gender and age [5, 6]. Therefore, treatment or prophylactic management of PDPH is very important for obstetric anesthesiologists.

In order to select the best treatment option, or for prophylactic management of PDPH, the mechanism of PDPH should be taken into account [7, 8]. The exact mechanism is not clear; however, leakage of cerebrospinal fluid (CSF) from the dural hole is the traditional theory. This leakage causes traction on the pain-sensitive meningeal vasculature because of depletion of the cushion effect from CSF. Therefore, when the patient is upright, gravitational traction on the pain-sensitive vasculature induces headache [9, 10]. A new theory states that CSF leakage and lowering of CSF volume lead to a compensatory mechanism, i.e., intracerebral venodilatation that is responsible for PDPH [11, 12].

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Some studies reported that ondansetron induced migraine headaches in parturients [13, 14]. When ondansetron was used for prophylactic management of nausea and vomiting in parturients who underwent cesarean section under spinal anesthesia with a mixture of heavy bupivacaine and meperidine at our center, the incidence of PDPH decreased. Hence, the present study aims to evaluate the prophylactic effect of intravenous ondansetron on decreasing the incidence of PDPH in parturients undergoing elective cesarean section under spinal anesthesia.

Materials and methods

After approval from the Institutional Ethics Committee and obtaining written informed consent, this single-center double-blind placebo-controlled parallel-group with balanced randomization clinical trial (IRCT2013092111662N3) was conducted in the operating theater of the Department of Obstetrics and Gynecology at Hazrat-e-Zainab Hospital, Shiraz, Iran from January to October 2013.

The eligible participants were all parturients aged between 20 and 40 years, who were candidates for elective cesarean section under spinal anesthesia. The exclusion criteria were having a history of cardiovascular disorders, migraine headache, taking selective serotonin reuptake inhibitors, hypersensitivity to ondansetron and local anesthetic drugs, and having contraindication for spinal anesthesia.

The eligible parturients were randomly assigned to two groups through block randomization using computerized random numbers. Each block had six numbers, and randomization was performed by a research coordinator who had no role in the study. Each of the patients (1:1 allocation ratio) were assigned to one of the two parallel groups to receive either intravenous (IV) ondansetron 0.15 mg/kg diluted in 5 ml normal saline (interventional group), or IV normal saline 5 ml (control group) 5 min before spinal anesthesia. The placebo syringe and the ondansetron syringe were both 5-ml syringes that were labeled A (control) and B (intervention). The content of both syringes (normal saline and ondansetron diluted in normal saline) were clear and similar in volume. The syringes were prepared by an anesthetic nurse who had no role in the clinical running of the study and data collection.

In the operation theater, standard monitors such as non-invasive blood pressure (BP), electrocardiogram, and pulse oximetry were attached to the parturients. An 18-gauge IV cannula was then inserted and all the patients received Ringer's solution 20 ml/kg over 30 min. Later, the parturients in the intervention group received IV ondansetron 0.15 mg/kg diluted in 5 ml of normal saline over 1 min, 5 min before spinal anesthesia. The parturients in the control group received 5 ml normal saline (as the placebo) over 1 min, 5 min before spinal anesthesia.

Spinal anesthesia was performed at L3-4 or L4-5 while sitting using a 25-gauge Quincke spinal needle. After confirmation of CSF fluid through the spinal needle, 2 ml of 0.5 % hyperbaric bupivacaine was administered. Then, the parturients were immediately placed in the supine position with 15° left tilt.

The incidence of PDPH was the primary outcome in relation to the possibility of the effectiveness of ondansetron in the prophylactic management of PDPH. PDPH is defined as a headache, which is throbbing in nature, is located in the frontal and/or the occipital region, and is usually accompanied by photophobia, double vision, blurred vision, dizziness, tinnitus, decreased hearing, nausea, and vomiting; it is aggravated in the upright position and is relieved by recumbency. Although parturients with a history of migraine were excluded from the study, PDPH was differentiated from migraine headache by response to change in body position. The headache of a patient with PDPH worsens in the upright position and improves after lying down.

Postoperatively, all the study participants were questioned daily about the presence of a headache and any accompanying symptoms by an anesthetist nurse who was blinded to the study groups. The parturients were asked to sit in their beds for 5 min and were then asked how they felt; if they complained about PDPH, they were asked to rate their headache on a three-point scale (mild, moderate, severe). Mild PDPH was treated conservatively with bed rest and hydration. In addition to bed rest and hydration, a rescue analgesic was also started for moderate and severe PDPH. If the parturients could not tolerate oral feeding, they received paracetamol 15 mg/kg Q6 h; however, if they could tolerate oral feeding, they received Novafen (acetaminophen, ibuprofen, and caffeine) one capsule Q8 h as a rescue analgesic. Furthermore, all the patients in both groups received a diclofenac sodium suppository 100 mg, Q12 h to control postoperative pain.

The secondary outcome of this study was the incidence of postoperative nausea and vomiting (PONV). The patients were asked to grade their nausea and vomiting according to a three-point scale where 0 = no nausea or vomiting, 1 = nausea only, and 2 = nausea and/or vomiting. The secondary outcome of the study was mean arterial pressure (MAP), and heart rate was recorded non-invasively every 5 min during the cesarean section.

An independent expertreviewed the unblinded data and followed the parturients in the intervention group during the trial to record migraine headaches, and other possible ondansetron complications. However, after starting the trial, no changes occurred in the study method due to ondansetron complications.

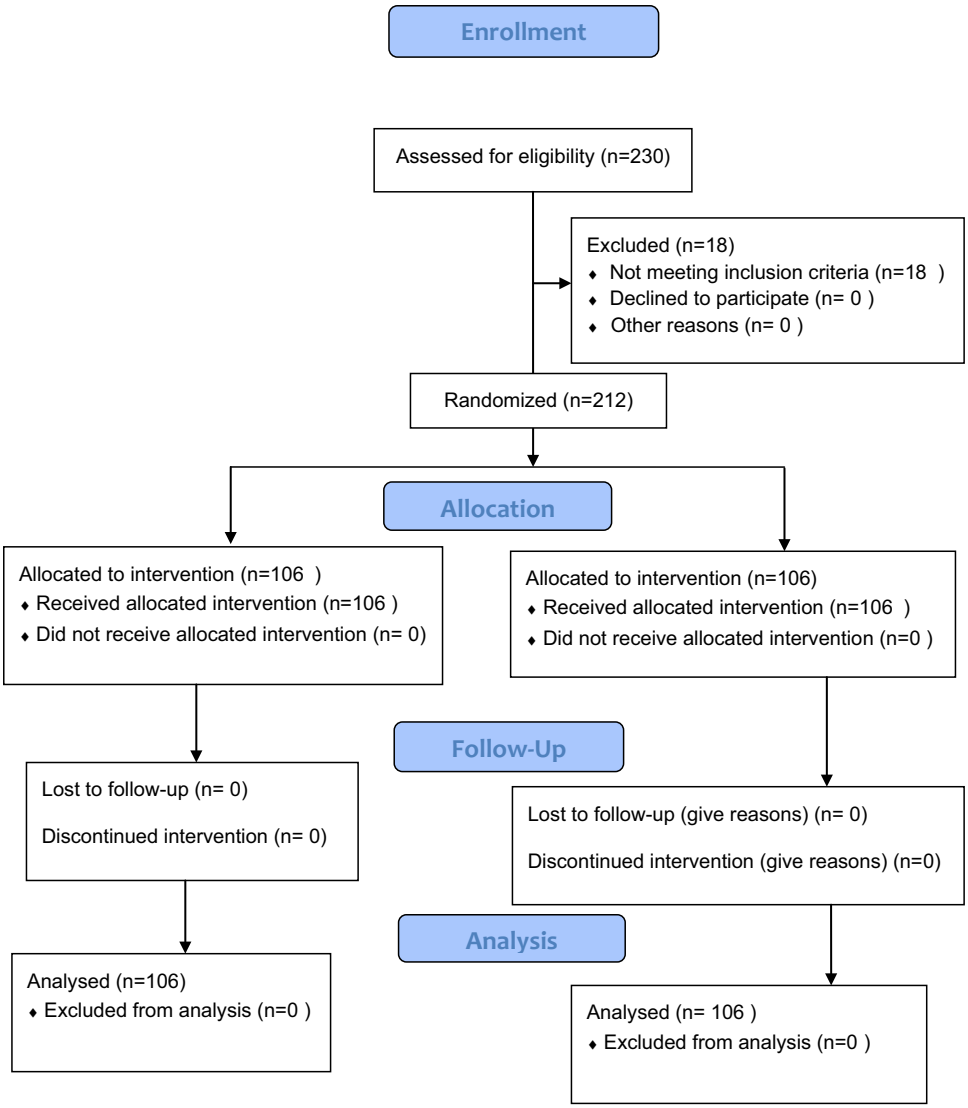

Fig. 1 Flowchart of patients according to consort guidelines

Statistical analysis

If a Quincke needle is used for spinal anesthesia, the incidence of PDPH is estimated as 25 %. Therefore, to decrease the incidence of PDPH to 10 % with a power of 80 %, and α level of 0.05, a 210-subject sample size (105 in each group) was determined for the study. The study data were prospectively transferred into a computer database for further analysis by SPSS for Windows, Version 20.0 (SPSS Inc., Chicago, IL, USA). The numerical variables, such as age, weight, body mass index, and height were normally distributed and compared between the two groups using Student's independent sample *t* test. Furthermore, the categorical variables, such as PDPH and PONV were compared between the two groups using chi-squared test. The repeated measures ANOVA test was used for intra-group comparison of the numerical variables, such as MAP and heart rate. The data were reported as mean ± SD. A two-sided *P* value of <0.05 was considered statistically significant.

Results

Of the 230 parturients scheduled for elective cesarean section from January to October 2013, 210 fulfilled the study criteria. Twenty parturients were excluded from the study due to refusing spinal anesthesia ($n = 10$), having a definite diagnosis of migraine headache ($n = 6$), and suffering from valvular heart disease ($n = 4$). Finally, 212 parturients were enrolled into the study and were randomly allocated to a control or an intervention group (Fig. 1).

The results revealed no significant differences between the two groups regarding demographic characteristics ($P > 0.05$) (Table 1).

Table 1 Demographic characteristics in the control (A) and intervention (B) groups

	Group A	Group B	*P* value
Age (years)	25.12 ± 2.05	24.11 ± 1.98	0.41
Height (m)	1.58 ± 0.35	1.61 ± 0.12	0.30
Weight (kg)	79.13 ± 3.11	80.32 ± 2.98	0.56
Body mass index (kg/m^2)	28.20 ± 1.71	29.18 ± 1.4	0.23

Data are mean ± standard deviation

However, MAP was significantly higher in the intervention group compared to the control group during surgery ($P = 0.01$) (Fig. 2). Nevertheless, no significant difference was noted between the two groups regarding heart rate during surgery ($P = 0.23$) (Fig. 3).

The total incidence of PDPH was 4.71 % in the intervention group which was significantly less than the control group (20.75 %; $P = 0.001$) (Table 2). Table 2 shows the severity of PDPH between the two groups. However, none of the patients who developed PDPH in either group required an epidural blood patch to treat the PDPH.

The results showed the total incidence of PONV was less in the intervention group compared to the control group ($P < 0.0001$) (Table 3). Table 3 shows the severity of PONV in the two groups.

Discussion

The results showed that intravenous ondansetron (0.15 mg/kg) could be effective in the prophylactic management of PDPH in parturients undergoing elective cesarean section under spinal anesthesia.

Ondansetron is a selective 5-HT$_3$ receptor antagonist widely used for prophylaxis and treatment of PONV [15, 16]. However, two case reports showed that ondansetron could induce severe headaches like migraine due to 5-HT$_3$ receptors in the brain [13, 14]. It has also been shown that this headache responded well to discontinuation of ondansetron [17]. In contrast to these reports, when ondansetron

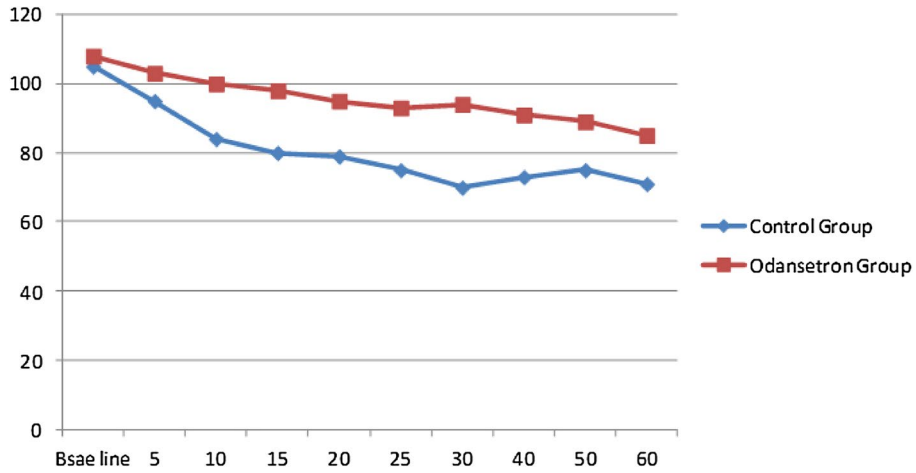

Fig. 2 Mean arterial pressure (mmHg) in both groups during surgery

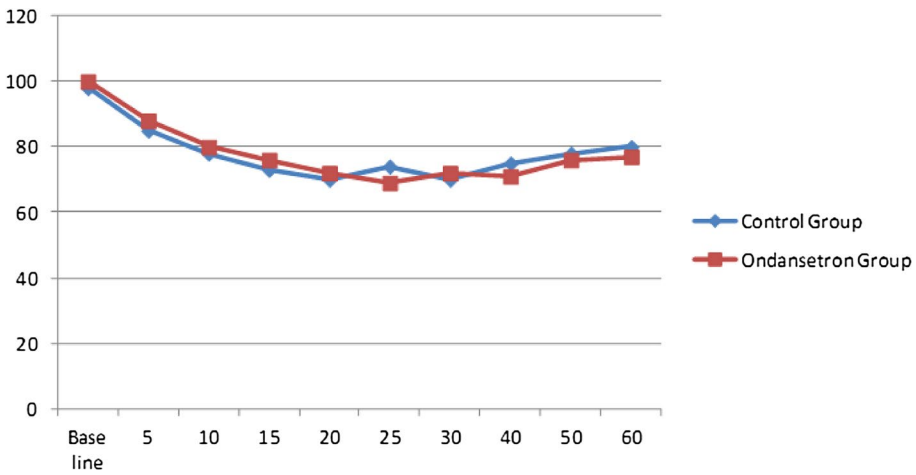

Fig. 3 Heart rate per minute in both groups during surgery

Table 2 Incidence of post-dural puncture headache (PDPH) and severity in the control (A) and intervention (B) groups

Variables [*n* (%)]	Control group ($n = 106$)	Intervention group ($n = 106$)	*P* value
Mild	8 (7.54 %)	3 (2.83 %)	0.01
Moderate	11 (10.37 %)	2 (1.88 %)	0.001
Severe	3 (2.83 %)	0 (0 %)	0.002
Total	22(20.75 %)	5 (4.71 %)	0.001

Table 3 Incidence of postoperative nausea and vomiting (PONV) in the control (A) and intervention (B) groups

Variables [*n* (%)]	Control group ($n = 106$)	Intervention group ($n = 106$)	*P* value
Nausea	21 (19.81 %)	4 (3.77 %)	0.001
Vomiting	18 (16.98 %)	2 (1.88 %)	0.002
Total PONV	39 (36.79 %)	6 (5.6 %)	0.0001

was used for the prophylactic management of PONV in parturients undergoing cesarean section under spinal anesthesia, the incidence of PDPH decreased.

There are two theories regarding the mechanisms of PDPH. The first and traditional theory states that at the time of spinal anesthesia, loss of CSF from the dura hole and a decrease in CSF pressure cause traction on the pain-sensitive intracranial structure, especially when the patient is in the upright position, and this traction results in a headache [18, 19]. However, Boezaart [20] in his study proposed a second theory stating that lowering of the CSF volume leads to a compensatory mechanism, i.e., intracerebral vasodilatation which is responsible for PDPH.

5-HT_3 receptors play an important role in many physiological processes, including vasomotor reflexes, control of gastrointestinal function, pain mechanisms, cardiovascular regulation, neuronal function, and limbic-cortical functioning [21]. Some of these processes are serotonin-mediated. Yamano et al. [22] found that hypotension and bradycardia Bezold–Jarisch reflex (BJR) could be induced by serotonin in anesthetized rats. Serotonin triggers chemoreceptors in the wall of the heart [22, 23]. Furthermore, stimulation of 5-HT_3 receptors by serotonin increases activity of the vagal nerve [22]. In another study, Owezuk et al. [24] showed that intravenous ondansetron attenuated spinal anesthesia-induced hypotension that might be caused by BJR. Moreover, another study by Sahoo et al. [25] showed that ondansetron could reduce hypotension associated with spinal anesthesia in parturients undergoing cesarean section under spinal anesthesia. They concluded that 5-HT_3 antagonists by suppressing venodilatation increased the venous returned to the heart, causing less reduction in MAP and systolic BP.

In the present study, we found that ondansetron, which is usually used for prophylactic management of nausea and vomiting, can reduce the severity of hypotension from spinal anesthesia by blocking the serotonin receptors. Ondansetron, through blocking 5-HT_3 receptors, directly suppresses venodilatation in the brain or, by maintaining MAP, indirectly prevents compensatory vasodilation in the brain through autoregulation of cerebral circulation. Therefore, this effect prevents compensatory vasodilatation of the intracerebral vessels due to CSF leakage and effectively reduces PDPH in parturients.

PONV is the second most common complaint in the postoperative period. PONV may be triggered by various pathways through centrally and peripherally located receptors [26]. There are 20 high concentrations of 5-HT_3 receptors in the central nervous system in the area postrema (chemoreceptor trigger zone) and nucleus tractus solitarius (vomiting center) [21]. 5-HT_3 antagonists, such as ondansetron, can significantly reduce the incidence of PONV. Moreover, many randomized, double-blind, controlled studies have shown the efficacy of ondansetron compared to other classes of antiemetics [27]. In the present study, ondansetron also effectively decreased the incidence of PONV.

This study had some limitations. Anesthesiologists usually use small needles for spinal anesthesia in parturients. Therefore, more studies are needed to evaluate the effect of ondansetron on the prophylactic management of PDPH. For example, a study should evaluate the effect of ondansetron on the prophylactic management of PDPH after accidental dural puncture with epidural needles. Moreover, patients need to be followed for at least one week to record delayed onset of PDPH.

In conclusion, the authors found that ondansetron (0.15 mg/kg) reduced the incidence of PDPH, as well as the incidence of hypotension and PONV, in parturients undergoing spinal anesthesia for cesarean section.

Conflict of interest No external funding and no competing interests declared.

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