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Efficacy of Intravenous Ondansetron on Hemodynamic Complications in Women Undergoing Spinal Anesthesia for Cesarean Section: A Randomized Placebo Controlled Clinical Trial

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Abstract

Background: Several methods are used for the prevention or decreasing the incidence of spinal anesthesia hemodynamic complications. Ondansetron is a 5HT3 receptor antagonist with known efficacy on preventing nausea and vomiting and probably on intrathecal opioid-induced pruritus. The present study aims to evaluate the effects of intravenous Ondansetron on the attenuation of blood pressure and heart rate, by 5HT3 blocking in vagal nerve endings and effect on Bezold Jarish reflex. **Material and Methods:** 102 candidates for elective cesarean section were randomized into 2 groups of 51 cases, the Ondansetron group received 4mg Ondansetron intravenously before performing spinal anesthesia, and placebo group received 2cc sterile water. Hypotension was defined: Systolic blood pressure less than 100 MmHg or fall more than 20% from primary BP which was treated by administration of Ephedrine in case of any. In both groups, Ondansetron effect was studied on hypotension occurrence, bradycardia, consumed Ephedrine amount, pruritus, nausea and vomiting. **Results:** There were no statistically significant differences in systolic/diastolic blood pressure, Mean Arterial Pressure, heart rate and pruritus in both groups (P=0.081).Nausea and vomiting in the first 10 minutes after spinal anesthesia were lesser in Ondansetron group (P= 0.001). Mean consumed Ephedrine was significantly lesser in Ondansetron group. (5.8 mg in ondansetron and 10.7 mg in placebo group, P=0.009). **Conclusion:** Ondansetron given intravenously with antiemetic dose (4 mg) decreases mean consumed Ephedrine and nausea and vomiting after spinal anesthesia, but does not have an influence on blood pressure, heart rate and pruritus. **[GMJ. 2016;5(1):13-18]**

Keywords: Anesthesia; Spinal; Cesarean Section; Hemodynamics; Ondansetron

Introduction

About 30% of all deliveries are performed by cesarean section and this rate is progressively rising in many parts of the world. Technique of anesthesia for Cesarean surgeries depends on the urgency of cesarean section, the desire and condition of mother [1-7]. The use of general anesthesia has fallen dramatically in the past few decades and neuraxial anesthetics have become the most commonly used techniques. Neuraxial techniques

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are largely safe and effective, but despite their benefits, complications with spinal anesthesia, such as cardiovascular or pulmonary side effects are seen [1-3, 8-10]. Resources have noted different incidences of hypotension [up to 80%] after spinal anesthesia [4].

Probably, the reduction in vascular resistance by sympathetic nerve blockade is the main reason for hypotension. Relative dominance of parasympathetic system, activation of Bezold Jarish reflex (BJR) and increased baroreceptor activity may lead to bradycardia and some degrees of hypotension. The responsible receptors for BJR are mechanoreceptors located in the heart walls which participate in systemic responses to hyper- and hypovolemia. They also include chemoreceptors sensitive to serotonin (5-HT3 receptors) [11]. Several studies have shown that BJR could be reduced by 5-HT3 antagonists [12-15].

Ondansetron is an exclusive 5-HT3 antagonist which is usually recommended for the prevention and treatment of nausea and vomiting during and after surgery which can block the binding of 5-HT from activated platelets to 5-HT3 receptors then alleviates the BJR triggered by 5-HT and thus suppresses further expansion of peripheral vessels and increases blood return to the heart. Injection of these drugs into the preoptic hypothalamus in cats resulted in vasodilatation [16]. Many methods have been investigated for preventing hemodynamic complications during spinal anesthesia for cesarean delivery, but no single technique has proven to be effective and reliable. Although several studies have shown the effectiveness of Ondansetron in reducing nausea and vomiting and the attenuation of hemodynamics, there are some inconclusive results. Ondansetron was shown to attenuate arterial blood pressure drop due to spinal anesthesia in general surgery population in a study by Owczuk et al. [3] and in obstetrical population in a study by Sahoo et al. [15]. However, it was not shown to decrease this risk in obstetrical population in a study by Ortiz-Gómez et al. [17] for which, possible reasons include the specific population and the anesthetic technique. Additionally, the administration of higher doses of Ondansetron (>5mg) might cause light lactate acidosis in the fetuses relative to the reduced BEecf value. Therefore, the application of appropriate concentration of Ondansetron during cesarean delivery is important to the health and safety of mother and fetus [18]. This clinical trial was designed and performed aiming to evaluate the effects of lower doses of intravenous Ondansetron on hypotension and heart rate in women undergoing spinal anesthesia cesarean section deliveries.

Materials and Methods

This Double-blind placebo controlled randomized clinical trial was designed and performed on healthy pregnant women (ASA class I, II), aged 15-45 years with single fetus who were candidate for elective Cesarean section under spinal anesthesia and were referred to Besat University Hospital (Hamedan, Iran) during 2011-2012.

Before recruitment of first subject, study protocol was approved by local ethics committee of Hamedan University of Medical Sciences and was registered in Iranian registry of clinical trials (RCT Code: IRCT201111138090N1). The study has been performed in accordance with the ethical standards of the 1964 Declaration of Helsinki. All patients signed the informed consent forms prior to recruitment in the study.

Sample size was estimated to be 51 per group using two-sample comparison of proportions Test.Exclusion criteria included hypertension, body mass index (BMI) more than 35 kg/m^2, motion sickness, cardiovascular disease, liver disease, history of migraines or epilepsy, consumption of any medication that affect blood pressure or heart rate or affect the serotonin receptors, allergy to study medications and failure of spinal anesthesia. Therefor, 102 patients were included in the study and randomly divided into two groups of 51 cases using randomized blocks.

Prior to the surgery, all patients received 300 ml of normal saline intravenously. Systolic blood pressure (SBP), Diastolic blood pressure (DBP), mean arterial blood pressure (MAP) and heart rate (HR) were measured and recorded. These parameters were measured right after performing spinal anesthesia

as well, and every 3 minutes during the first 10 minutes and then every 5 minutes until 30 minutes afterwards. Patients were also asked about Pruritus, retching, nausea and vomiting every 10 minutes.

Before performing spinal anesthesia, 4 mg Ondansetron IV or equivalent distilled water was injected over 30 seconds by an anesthesia technician who was blind to the study. Spinal anesthesia was performed in a sitting position, using 10 mg of 0.5% bupivacaine and 5 mcg Sufentanil through a Quinque 25 needle in L4-L5 or L3-L4 space. The procedure was performed by an anesthesiologist who was blind to the assigned group of patients.

In the case of SBP <90 mmhg, 10-5 mg IV Ephedrine was injected and total Ephedrine consumption for each patient was recorded. Severe nausea and vomiting was managed by Metoclopramide injection of 1 x (mg 10) intravenously.

In order to ensure blindness, all syringes have the same volume and were labelled as 1 and 2. Anesthesiologists who were responsible for recording the variables and analyzing data were blind to patient group assignment.

Data were transferred into SPSS software version 18.0. Inter-group comparisons were performed using analysis of variance or the Kruskal-Wallis test as appropriate and the Tamhane and Bonferroni procedures were used for post-hoc test, while the paired sample t-test was used to compare the mean differences with baseline values within groups. The chi-squared and Fisher's exact tests were used for categorical data. Changes in SBP, DBP, MAP, and HR at all-time points after spinal anesthesia were analyzed by using the two-way analysis of variance (ANOVA). $P<0.05$ was considered to be statistically significant.

Results

One hundred and two healthy pregnant women aged 22-33 years with single fetus candidates for elective cesarean section under spinal anesthetic technique were enrolled. The average age of patients and their mean weight were compared showed no significant statistical difference between the two groups (Table 1).

Nausea and vomiting in the Ondansetron group during the first 10 minutes after spinal anesthesia were seen in 17 patients of control group (33.3%) and 4 (7.8%) cases of Ondansetron group. This difference is statistically significant (P=0.001). Over the next few minutes of surgery, the incidence of nausea and vomiting between the two groups was not statistically significant (Table 1).

Pruritus was seen in the first 10 minutes, second 10 minutes and third 10 minutes after spinal anesthesia in 27 patients of Ondansetron group and in 31 patients of the control group. There was no significant difference between the two groups about pruritus incidence (Table 1).

Average consumption of Ephedrine was 10.7mg in Ondansetron group, and in control group this amount was 5.8 mg. The lower amount of total Ephedrine consumption in intervention group was statistically significant (P =0.009) in comparison to control group (Table 1).

Table 1. Demographics and Outcome Measures Compared in Both Groups

	Ondansetron group (N=51)	Placebo group (N=51)	P-value
Mean age (years)	28.5 ±4	27.8±4.2	0.65
Mean weight (kg)	73.5 ±11	76.1±10.9	0.37
Nauseas and vomiting*	4 (7.8%)	17 (33.3%)	0.001
Pruritus	27 (52%)	31 (60%)	0.067
Mean Ephedrine consumption (mg)	10.7 ±2.1	5.8±1.1	0.009

* during the first 10 minutes after spinal anesthesia

The average SBP, DBP and MAP before spinal anesthesia and also at different times after induction in both groups are demonstrated in Table 2. These parameters were measured and analyzed in both groups; however, they show no significant difference statistically (P= 0.081) (Table 2).
The mean heart rate during different moments in the two groups was almost identical, and the differences were not statistically significant (Table 2).

Discussion

The hemodynamic changes may have serious complications such as heart failure. One of the important issues regarding anesthesia in pregnant women is preventing maternal hypotension. Placental perfusion and fetal oxygenation have direct association with maternal blood pressure Thus, maternal hypotension can lead to decrease fetal oxygenation and this is manifested with abnormal fetal heart rate [4]. Different techniques and methods are evaluated to prevent or reduce the occurrence of hemodynamic changes during spinal anesthesia such as intravenous fluids, Atropine, Ephedrine and Phenylephrine and placing the patient in Trendelenburge position [3]. Intravenous administration of Ondansetron is one of the methods currently used to treat nauseas and vomiting caused by spinal or epidural anesthesia but can cause hemodynamic complications by blocking the binding of 5-HT from activated platelets to 5-HT3 receptors. It alleviates the BJR triggered by 5-HT and thus suppresses further expansion of peripheral vessels and increases blood return to the heart [7]. In our study we found that the administration of 4 mg Ondansetron intravenously before spinal anesthesia in pregnant women undergoing elective cesarean section did not prevent the occurrence of intraoperative hypotension but it reduced the occurrence of nausea and vomiting along with total Ephedrine consumption. Although reduced occurrence of nausea and vomiting with administration of Ondansetron has been reported in several studies as well as the present study, our findings are not consistent with some previously done studies on hemodynamic changes [15, 18]. The differences between these studies

Table 2. changes of hemodynamic variables at different times

	Ondansetron (N=51)		**placebo (N=51)**		**P-value**
Mean Systolic blood pressure		SD		SD	
Before	118	19	117	18.7	
During first 10 minutes	109	18.1	109	18.1	0.43
30 minutes after induction	93	15.5	98	16	
Mean Diastolic blood pressure					
before	70	11	68	9.7	
During first 10 minutes	63	10.1	63	10.1	0.26
30 minutes after induction	59	9.5	54	9	
Mean arterial pressure					
before	85	14	82	13.7	
During first 10 minutes	75	12	75	12	0.91
30 minutes after induction	75	12	73	12.1	
Mean Heart rate					
before	97	16.1	99	16.6	
During first 10 minutes	94	15.6	97	16.1	0.87
30 minutes after induction	93	15.1	98	16	

may be attributed to different methods used for surgery, Ondansetron loading and anesthesia during the study period.

In the present study and during the first 10 minutes after spinal anesthesia, nausea and vomiting in the Ondansetron group occurred more in control group than Ondansetron group; more recent studies have confirmed this role of Ondansetron such as the study which was conducted in 2006 and revealed that Ondansetron is more effective than Droperidol or placebo in preventing nausea and vomiting induced by intrathecal Morphine [10].

Average consumption of Ephedrine was compared in these two groups. The total amount of Ephedrine consumed in Ondansetron group was 5.8 mg and in the control group it was 10.7 mg. A statistically significant difference was noted here in the mean Ephedrine consumption in both groups (P=0.009). However, this issue needs to be further investigated through future studies.

The effects of serotonin antagonists such as Ondansetron in the prevention of pruritus associated with intrathecal drug are studied and different results are obtained. In some studies, for example, the study on comparing the effects of Nalbuphine and Ondansetron with placebo which was carried out in this field conclusively showed that the effect of Ondansetron was far more effective than placebo in preventing pruritus [15]. But the study of prophylactic Ondansetron administration in 2007 compared with placebo did not reduce the incidence of pruritus [14]. In the present study, the prophylactic administration of Ondansetron had no effect on the incidence of pruritus associated with intrathecal drug administration which is consistent with the latter research.

As the duration and type of the surgery, as well as blood loss and maintenance fluids could influence the results of such studies, the effect of Ondansetron on the parameters examined in this study such as HR, MAP, DBP, SBP and pruritus needs to be further investigated in future studies with higher doses of Ondansetron than antiemetic dosage (8 mg). Larger sample size and different groups of patients undergoing surgery can be studied. Moreover, the application of appropriate concentration of Ondansetron during cesarean delivery for ensuring the health and safety of the mother and fetus can be considered in prospecting studies.

Conclusion

In conclusion, Ondansetron, given intravenously with antiemetic dose (4 mg), decreases mean consumed Ephedrine and nausea and vomiting after spinal anesthesia, but does not have an influence on BP, HR and pruritus.

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Conflict of Interest

The authors report that there was no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

References

1. ReferencesMiller RD. Anesthetic implications of concurrent diseases. In: Miller's Anesthesia. 7th ed. Philadelphia, PA: Churchill Livingston Elsevier; 2010; 1337–59.
2. Silva M, Halpern SH. Epidural analgesia for labor: Current techniques. Local Reg Anesth 2010; 3 (7):143-53.
3. Owczuk R, wojciechwenski M. Ondansetron given intravenously attenuates arterial blood pressure drop due to spinal anesthesia: Reg anesth pain med, 2008, 33(4): 332-9.
4. Halpern SH, Breen TW, Campbell DC. A multicenter, randomized, controlled trial comparing bupivacaine with ropivacaine for labor analgesia. Anesthesiology. 2003;

98:1431–5.
5. Siddik SM, Aoud MT, Kai GE. Hydroxyethylstarch 10% is superior to Ringer's solution for preloading before spinal anesthesia for caesarian section. Can J Anesthesia 2000; 47 (5):616-24.
6. Wisher D. Martindale: The Complete Drug Reference. 37th ed. Journal of the Medical Library Association : JMLA. 2012; 100(1):75-76.
7. Borgeat A, strnemann HR. Ondansetron is effective to treat spinal or epidural morphine inducdedpruritis. Anesthesiology 1999; 19 (2): 432-6.
8. Sudharma J, Birnbach D. Current Status of Obstetric Anesthesia: Improving Satisfaction and Safety. Indian J Anaesth. Oct 2009; 53(5): 608–17.
9. Somboonviboon W. Incidence and Risk factors of hypotension and bradycardia after spinal anesthesia for cesarean section. J Med associ Thai. 2008; 91(2). 181-7.
10. Brenck B, Hartmann S. Hypotension after spinal anesthesia for cesarean section. J cl in monitcomput. 2009; 23(2): 85-92.
11. Soltani-Mohammadi S; Aghajani Y; Movafegh A. Comparing Two Different Doses of Intravenous Ondansetron with Placebo on Attenuation of Spinal-induced Hypotension and Shivering. Anesth Pain Med. 4(2): e12055.
12. White CM, Chow MS, Fan C, Kluger J, Bazunga M. Efficacy of intravenous granisetron in suppressing the bradycardia and hypotension associated with a rabbit model of the Bezold-Jarisch reflex. J Clin Pharmacol. 1998; 38 (2):172–7.
13. Owczuk R, Wenski W, Polak-Krzeminska A, Twardowski P, Arszulowicz R, Dylczyk-Sommer A, et al. Ondansetron given intravenously attenuates arterial blood pressure drop due to spinal anesthesia: a double-blind, placebo-controlled study. Reg Anesth Pain Med. 2008; 33(4):332–9.
14. Kelsaka E, Baris S, Karakaya D, Sarihasan B. Comparison of Ondansetron and meperidine for prevention of shivering in patients undergoing spinal anesthesia. Reg Anesth Pain Med. 2006; 31(1):40–5.
15. Sahoo T, SenDasgupta C, Goswami A, Hazra A. Reduction in spinal-induced hypotension with Ondansetron in parturients undergoing caesarean section: a double-blind randomized, placebo-controlled study. Int J Obstet Anesth. 2012; 21(1):24–8.
16. Safavi MR, Honarmand A, Negahban M, Attari MA. Prophylactic effects of intrathecal Meperidine and intravenous Ondansetron on shivering in patients undergoing lower extremity orthopedic surgery under spinal anesthesia. J Res Pharm Pract. 2014 Jul-Sep; 3(3): 94–9.
17. Ortiz-Gómez JR, Palacio-Abizanda FJ, Morillas-Ramirez F, Fornet-Ruiz I, Lorenzo-Jiménez A, Bermejo-Albares ML. The effect of intravenous Ondansetron on maternal haemodynamics during elective caesarean delivery under spinal anaesthesia: a double-blind, randomised, placebo-controlled trial. Int J Obstet Anesth. 2014 May; 23(2):138-43.
18. Wang M, Zhuo L, Wang Q, et al. Efficacy of prophylactic intravenous Ondansetron on the prevention of hypotension during cesarean delivery: a dose-dependent study. Int J Clin Exp Med2014;7(12):5210-5216.