RESEARCH ARTICLE

Efficacy of Granisetron on Attenuation of Hemodynamic Responses of Parturients Undergoing Elective Cesarean Delivery under Spinal Anesthesia

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Background: Maternal bradycardia and hypotension are the most common intraoperative complications after spinal anesthesia during cesarean delivery. Prophylactic administration of ondansetron has been reported to provide a protective effect. In this study we evaluated the effect of intravenous granisetron, another serotonin 5-HT3 receptor antagonist, on prevention of these complications.

Methods: Thirty-four ASA class I-II patients undergoing elective cesarean section under spinal anesthesia were randomly allocated into two equal groups, control saline (n=17) or granisetron groups (n=17). After insertion of standard monitorings,5ml/kg lactated Ringer's solution was infused over 15 minutes. In saline group 3ml of 0.9% saline and in granisetrone 3mg (3ml) granisetron was injected intravenously five minutes before spinal anesthesia. Systolic and diastolic blood pressure and heart rate were all recorded every two minutes during first twenty minutes and then every five minutes until the end of surgery and compared between the groups.

Results: Demographic data and median of sensory block level were not statistically different between the groups. There was no statistical difference between the study groups regarding the systolic, diastolic and heart rate at measured points except at second minutes after spinal anesthesia that was lower in saline group (P=0.01).

Conclusion: This study showed that intravenous granisetron has little protective effect on attenuation of hemodynamic responses of parturients undergoing elective cesarean section under spinal anesthesia.

Keywords: cesarean section; granisetron; hemodynamic response; spinal anesthesia

Spinal anesthesia is the most popular form of anaesthesia for caesarean delivery which is frequently associated with hypotension and bradycardia. Bradycardia results from sympathetic block and relative parasympathetic dominance, increased baroreceptor activity, or induction of the Bezold Jarisch Reflex (BJR) while, hypotension results primarily from decreased vascular resistance with an incidence as high as 50-80%. Although there is no single definition for hypotension, most authors agree that hypotension is present when the systolic blood pressure (SBP) decreases to <100 mmHg or when there is a reduction from baseline of <20–30% [1-4].

Serotonin (5-hydroxytryptamine [5-HT3]), a biologic amine found in the brain and spinal cord, plays a part in neurotransmission. Previous studies showed that ondansetron, a highly effective and specific 5-HT3 receptor antagonist, can block the binding of 5-HT from activated platelets to 5-HT3 receptors then alleviates the Bezold-Jarisch reflex (BJR) triggered by 5-H and thus suppresses further expansion of peripheral vessels and increases blood return to the heart [5-8].

It has been demonstrated that ondansetron treatment preloading with crystalloid or colloid infusion reduces maternal hypotension in parturient women undergoing cesarean delivery [9-14].

The aim of our study is to evaluate the efficacy of granisetron, another drug of 5-HT3 receptor inhibitors, on reducing hemodynamic response to subarachnoid block in pregnant patients who go under spinal anesthesia for elective cesarean delivery.

Methods

This randomized double blinded controlled trial was performed in Dr. Shariati Hospital of Tehran University of Medical Sciences since March to September of 2016.The study protocol conformed to the ethical guidelines of the 1989 Declaration of Helsinki and ethical approval was provided by the Ethical Committee of Tehran University of Medical Sciences, Tehran, Islamic Republic of IRAN, protocol number 115 on 20 January 2016.

Thirty-four pregnant women aged 18-45 years, who were scheduled for elective cesarean section (CS) under spinal anesthesia, were included and informed consent was obtained separately before surgery. Patients were randomly

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allocated into two equal groups, granisetron (n=17) or control saline group (n=17). Randomization was done by means of computer-generated codes and was concealed until interactions were assigned. Exclusion criteria included any contraindications to spinal anaesthesia, BMI at term >35 kg/m2, history of allergy to ondansetron, hypertension or other cardiovascular disease and requirement for blood transfusion during surgery.

On arrival to the operating room, standard monitoring was applied to all patients including electrocardiogram, noninvasive arterial blood pressure (NIBP) and pulse oximeter. An 18-gauge intravenous catheter was placed on the dorsum of non-dominant hand of the patients and 5 ml/kg lactated Ringer's solution was infused over 15 minutes before spinal anesthesia.

Patients received no premedication and prepared solution (granisetrone 3mg or saline) with the same volume (3ml) were injected intravenously five minutes performing spinal anesthesia by anesthesiologist who was blinded to the allocation. All patients were blocked in the lateral position in which a 25guage Quincke needle was inserted by midline approach into the L3-4 or L4-5 interspaces and after ensuring the correct position of the needle, 12mg of hypertonic 0.5 % bupivacaine was injected. Patients were immediately placed in the supine position after the block. A resident of anesthesiology, blinded to the study solutions, measured hemodynamic parameters including heart rate (HR), systolic (SBP), diastolic (DBP) and mean arterial pressure (MAP) at time of spinal drug administration and at 2minutes intervals up to 20 min, followed by 5minutes intervals until the end of surgery. Upper sensory levels were also assessed at 5-min intervals. In case of SBP <100 mmHg or DBP <60 mmHg, 50 µg intravenous phenylephrine was administered and HR <50 beats/min was treated with intravenous atropine 0.5 mg. In patients with partial block and pain, fentanyl was injected as rescue medication.

Statistical analysis

A sample size of 15 patients in each group will be sufficient in order to detect a 10 mmHg difference in MAP between groups with 80% power and 5% probability of type I error. Consuming that 10% of patients may drop out of the study due to different reason the sample size as increased to 17 patients in each group. Statistical analysis was performed using SPSS package (version 23, SPSS, Chicago, IL). Normality of distribution of data was tested by the Kolmogorov-Simirnov test. Data were analyzed with independent sample t-test, chi-square and Mann-Whitney U test when appropriate. Two tailed P<0.05 was considered significant.

Results

Demographic data and median of sensory block level were not statistically different between the study groups (Table1).

Duration of surgery and anesthesia were 49.2± 11.5 and 88.1±3.6 minutes in granisetrone and 52.3± 10 and 80.2±6.5 minutes in control saline group respectively (P=0.3 and P=0.2).

Three patients in granisetron and two in saline group received atropine (P=0.5). Nine patients in saline and eight patients in granisetrone group received phenylephrine for hypotension (P=0.49).

The amount of total phenylephrine consumption was 450µg and 400µg in saline and granisetrone group respectively (P=0.5). Two patients in each group received 50µg fentanyl as rescue medication for pain (P=0.6).

There was no statistical difference in systolic, diastolic, MAP and heart rate between the study groups at time measured points except at second minutes that MAP was lower in saline group (P=0.01) (Figures 1-4).

Total bleeding was 850ml and 900 ml in granisetrone and saline group respectively and there was no need for blood transfusion (P=0.23).

Figure 1- Comparison of systolic blood pressure between the study groups.

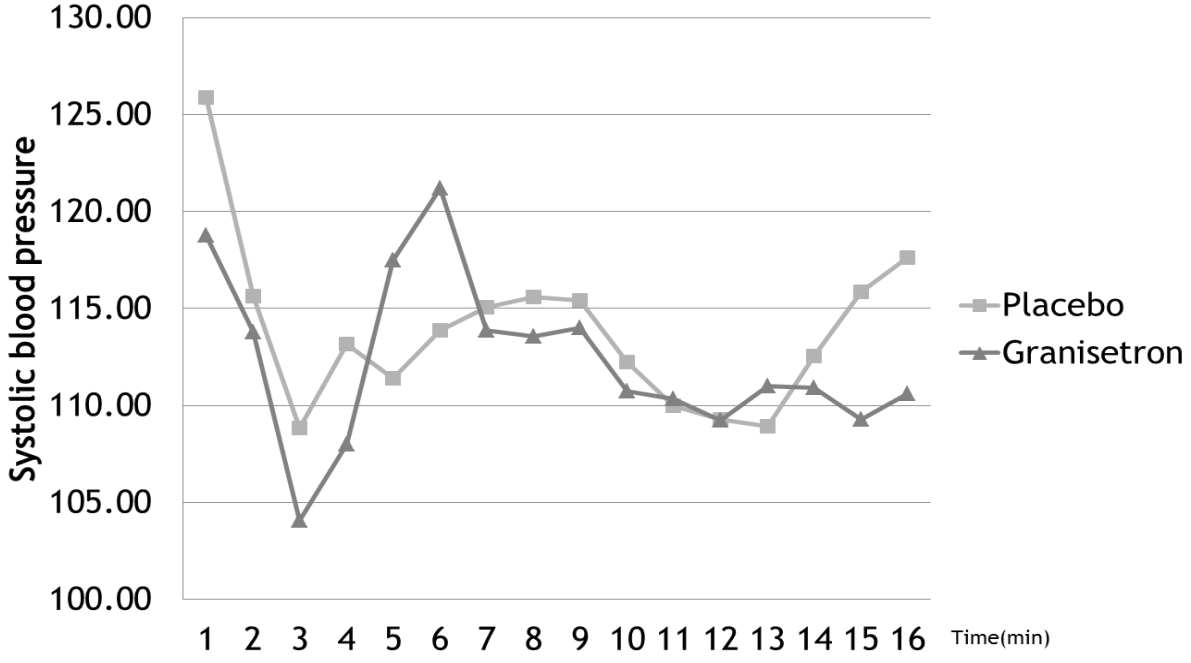

Figure2- Comparison of diastolic blood pressure between the study groups.

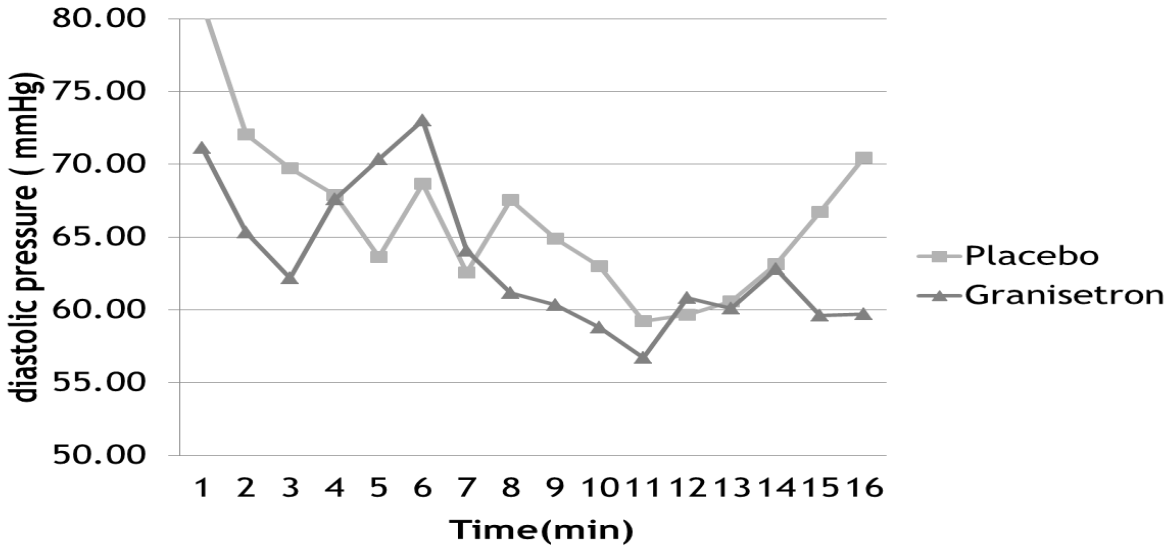

Figure3- Comparison of mean arterial blood pressure between the study groups.

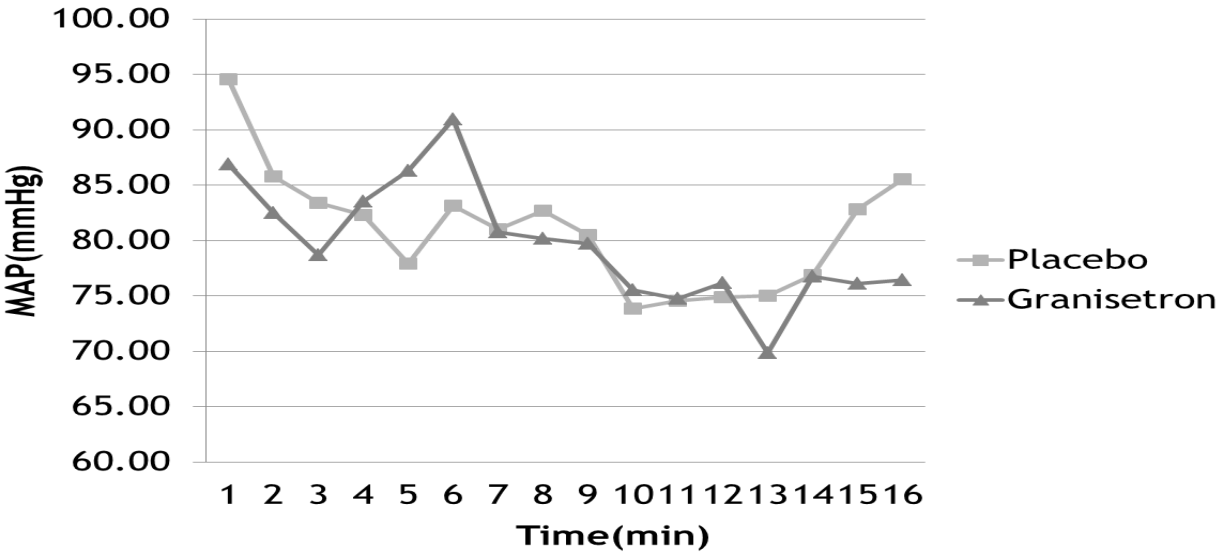

Figure4- Comparison of heart rate between the study groups.

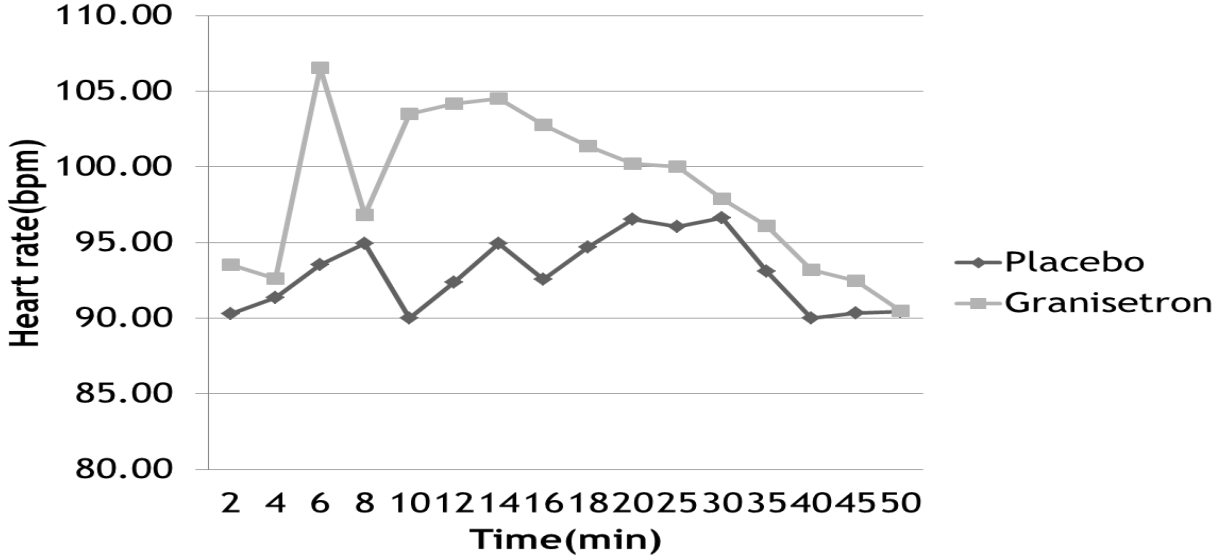

Table 1- Comparing demographic data and level of sensory block between the study groups

Variable	Granisetrone group (n=17)	Saline group(n=17)
Age (year)	30.8±8.5	31.2±6.5
Weight (kg)	71.8±6.4	73.1±7.4
Height (cm)	154.8±7.9	156.1±3.4
ASA class I/II(n)	14/3	13/4
Median of sensory block level	T4(T5-T10)	T4(T4-T10)

Data are presented as mean ± SD, number of patients (n), median (range), P> 0.05

Discussion

This study showed that granisetrone 3mg intravenously has little protective effect on reducing spinal anesthesia induced hemodynamic responses during CS compared to saline control group.

Regional anesthesia is a safe method for cesarean delivery because pregnancy induced physiologic changes increase chance of difficult intubation however, it has own set of complications including hypotension and bradycardia [15-16].

Different techniques have been studied for prevention of these complications. Some studies compared crystalloid preloading to colloid preloading and others tested preloading to co-loading. Physical methods like lower leg compression have been tested too but, these methods vary in their effectiveness [17-19].

Many studies compared use of pharmacological drugs including ephedrine, phenylephrine, 5-HT3 antagonists and other drugs with fluid loading however, none of them is effective alone to prevent hypotension [3-19].

Sahoo et al studied 52 patients undergoing CS. They administered 4mg ondansetron and preloaded them with crystalloid at dose of 20ml/kg over a period of 30 minutes. They concluded that prophylaxis with intravenous 4 mg ondansetron is effective against spinal anesthesia induced hypotension. In contrast to our study, we found no effective protection of granisetron on spinal induced hemodynamic response of parturient that may be due to different type of drug and less volume preload [7].

In a study by Owczuk et al on 71 patients, they administered 8 mg of ondansetron to one group, and saline as placebo to other Group. They gave maximum of 200 ml of normal saline during the study period and found that systolic blood pressure was higher in ondansetron group. They found no difference in heart rate between two groups that was similar to our study [9].

Ortiz-Go´mez et al conducted a study on 128 healthy pregnant women scheduled for elective caesarean delivery under spinal anaesthesia. They administered three different doses of ondansetron 2, 4 or 8 mg intravenously before induction of spinal anaesthesia and concluded that it had little effect on the incidence of hypotension in these groups of patients that was similar to our study [10].

Our limitations were small sample size,using just one dose of drug and less volume preload before the spinal block administration. We recommend further studies with larger sample size and different doses of granisetron to evaluate the effect of it on reducing hemodynamic responses and also on postoperative nausea, vomiting and shivering in pregnant patients undergoing spinal anesthesia for cesarean delivery.

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References

1. Liu SS, McDonald SB. Current issues in spinal anesthesia. Anesthesiology 2001; 94(5):888–906.
2. Carpenter RL, Caplan RA, Brown DL, Stephenson C, Wu R. Incidence and risk factors for side effects of spinal anesthesia. Anesthesiology 1992; 76(6):906–16.
3. Stewart A, Fernando R, McDonald S, Hignett R, Jones T, Columb M. The dose-dependent effects of phenylephrine for elective cesarean delivery under spinal anesthesia. Anesth Analg. 2010; 111(5): 1230-7.
4. Cyna AM, Andrew M, Emmett RS, Middleton P, Simmons SW. Techniques for preventing hypotension during spinal anaesthesia for caesarean section. Cochrane Database Syst Rev. 2006; (4):CD002251.
5. Aviado DM, Guevara Aviado D. The Bezold-Jarisch reflex: a historical perspective of cardiopulmonary reflexes. Ann N Y Acad Sci. 2001; 940:48–58.
6. Campagna JA, Cartner C. Clinical relevance of Bezold Jarisch reflex. Anesthesiology. 2003; 98(5):1250-60.
7. Sahoo T, SenDasgupta C, Goswami A, Hazra A. Reduction in spinal-induced hypotension with ondansetron in parturients undergoing caesarean section: A double-blind randomised, placebo-controlled study. Int J Obstet Anesth. 2012; 21(1): 24-8.
8. Wang Q, Zhuo L, Shen MK, Yu YY, Yu JJ, Wang M. Ondansetron Preloading with Crystalloid Infusion Reduces Maternal Hypotension during Cesarean Delivery. Am J Perinatol. 2014; 31(10): 913-22.
9. Owczuk R, Wenski W, Polak-Krzeminska A, Twardowski P, Arszułowicz 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.
10. 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 hemodynamics during elective caesarean delivery under spinal anaesthesia: a double-blind, randomised, placebo-controlled trial. Int J Obstet Anesth. 2014; 23(2):138-43.
11. Marashi SM, Soltani-Omid S, Mohammadi SS, Aghajani Y, Movafegh A. Comparing two different doses of intravenous ondansetron with placebo on attenuation of spinal-induced hypotension and shivering. Anesth Pain Med. 2014; 4(2):e12055.
12. Khalifa OS. A comparative study of prophylactic intravenous granisetron, ondansetron, and ephedrine in attenuating hypotension and its effect on motor and sensory block in elective cesarean section under spinal anesthesia. Ain-Shams J Anesthesiol. 2015; 8(2):166-172.
13. Abbas N, Shah SAR, Naqvi SS. Role of prophylactic ondansetron for prevention of spinal anesthesia induced hypotension in lower segment cesarean section. Pak Armed Forces Med J 2016; 66(6):790-94.
14. Tubog TD, Kane, TD, Pugh MA. Effects of Ondansetron on Attenuating Spinal Anesthesia–Induced Hypotension and Bradycardia in Obstetric and Nonobstetric Subjects: A Systematic Review and Meta-Analysis. AANA Journal; 2017: 85(2):113-122.
15. Yeoh SB, Leong SB, Heng AST. Anaesthesia for lower-segment

caesarean section. Indian J Anaesth. 2010; 54(5): 409–14.
16. Agarwal A, Kishore K. Complications and Controversies of Regional Anaesthesia : A Review. Indian J Anaesth. 2009; 53(5): 543-53.
17. Tamilselvan P, Fernando R, Bray J, Sodhi M, Columb M. The effects of crystalloid and colloid preload on cardiac output in the parturient undergoing planned cesarean delivery under spinal anesthesia: a randomized trial. Anesth Analg. 2009; 109(6): 1916-21.
18. Gunusen I, Karaman S, Ertugrul V, Firat V. Effects of fluid preload (crystalloid or colloid) compared with crystalloid co-load plus ephedrine infusion on hypotension and neonatal outcome during spinal anaesthesia for caesarean delivery. Anaesth Intensive Care. 2010; 38(4): 647-53.
19. Chohedri AB, Khojeste L, Shahbazi S, Alahyari E. Ephedrine for prevention hypotension; comparison between intravenous,intramuscular and oral administration during spinal anesthesia for elective Cesarean section. Professional Med J. 2007; 14(4): 610-5.