Egyptian Journal of Anaesthesia (2013) **29**, 369–374

Egyptian Society of Anesthesiologists

Egyptian Journal of Anaesthesia

www.elsevier.com/locate/egja
www.sciencedirect.com

Research Article

Effects of intravenous ondansetron and granisetron on hemodynamic changes and motor and sensory blockade induced by spinal anesthesia in parturients undergoing cesarean section

Manal M. Rashad *, Manal S. Farmawy

Department of Anesthesia and Intensive Care, Faculty of Medicine, Zagazig University, Egypt

Received 5 February 2013; revised 24 March 2013; accepted 12 April 2013
Available online 20 June 2013

KEYWORDS

Ondansetron;
Granisetron;
Spinal anesthesia;
5-HT;
Cesarean section

Abstract *Background:* Spinal anesthesia has many advantages for cesarean section parturients, but hypotension is considered the most frequent complication and can be managed by different interventions. One of these interventions is to give a serotonin receptor antagonist prior to spinal anesthesia.
Objectives: To compare between two serotonin receptor antagonists on the hemodynamics, sensory, and motor blockade induced by intrathecal bupivacaine in parturients undergoing cesarean section.
Patients and methods: Sixty patients undergoing elective cesarean section under spinal anesthesia by intrathecal bupivacaine were randomly divided into three groups (20 pregnant females of ASA I–II physical status in each group). Group O received intravenous 4 mg ondansetron diluted in 10 ml normal saline and injected over 1 min, 5 min before spinal anesthesia, group G given intravenous 1 mg granisetron by the same route and group S given 10 ml normal saline. Mean arterial blood pressure, heart rate, vasopressor use, sensory, and motor blockade were assessed.
Results: Decreases in mean arterial pressure were significantly lower in group O than groups G and S with lower vasopressor use ($P < 0.05$), while there was significant faster sensory recovery in group G than groups O and S ($P < 0.05$). Actually, there were significant decrease in the incidence of nausea in groups O and G than group S ($P = 0.008$).
Conclusion: In parturient females undergoing elective cesarean section, intravenous 4 mg ondansetron before subarachnoid block significantly decreased both the hypotension and the doses of vaso-

* Corresponding author. Tel.: +20 1005671564.
E-mail addresses: mannola1972@gmail.com, mervatassy@yahoo.com (M.M. Rashad).

Peer review under responsibility of Egyptian Society of Anesthesiologists.

Production and hosting by Elsevier

 http://dx.doi.org/10.1016/j.egja.2013.04.004

pressor used, while intravenous 1 mg granisetron prior to subarachnoid block induced faster sensory recovery compared to both the ondansetron and the saline groups, with no significant differences between the later two groups.

1. Introduction

Many anesthetists prefer to give spinal anesthesia for women who will undergo cesarean section due to many advantages like avoiding risks of general anesthesia, for better postoperative pain relief and also for keeping the woman awake to see her baby just after birth [1]. Although this can be achieved by spinal or epidural anesthesia, spinal anesthesia is a simple technique with low failure rate, rapid onset, and low drug dose [2].

On the other hand, the anesthetist is facing certain problems after giving spinal anesthesia like hypotension, bradycardia, and failure of block. But hypotension represents incidence of about 55–100%, so it is the most frequent complication [3,4]. Moreover, hypotension is hazardous for the mother and the baby as it can cause loss of consciousness, aspiration, and even cardiac arrest for the mother and placental hypoperfusion, which can lead to fetal problems [5].

There are several methods to minimize maternal hypotension after spinal anesthesia like fluids, medications, and physical methods like positioning, leg bindings, etc. [1].

This study concentrated on two medications, which can minimize the occurrence of maternal hypotension after spinal anesthesia. They are ondansetron and granisetron selective 5-hydroxytryptamine 3 (5-HT3) receptor antagonists [6]. These receptors are located peripherally as cardiac chemoreceptors on the cardiac vagal afferent and centrally in the chemoreceptor trigger zone [7]. On the other hand, the Bezold–Jarisch reflex (BJR) is one of the mechanisms, which explain the occurrence of hypotension after spinal anesthesia through serotonin with decreased blood volume [7–10]. Stimulation of cardiac chemoreceptors in the heart by decreased venous return increases the parasympathetic activity, while it decreases the sympathetic activity resulting in vasodilatation and bradycardia [11].

Moreover, 5-HT3 receptors are present also in the spine and have antinociceptive effect, which can be antagonized by selective 5-HT3 receptor antagonist [12].

On the other hand, previous studies proved that the level of serotonin increased significantly in cerebrospinal fluid after intrathecal bupivacaine, and the sensory block of intrathecal lidocaine was antagonized by ondansetron [13,14].

The aim of this study was to compare the effects of the two serotonin receptor antagonists ondansetron and granisetron on the spinal induced hypotension, bradycardia, sensory, and motor block after intrathecal hyperbaric bupivacaine in parturients undergoing cesarean sections.

2. Patients and methods

After approval of the medical ethics committee and obtaining written consent from each patient, this comparative study was conducted in Zagazig University Surgical Hospitals. Sixty pregnant women, ASA I–II physical status, aged from 20 to 40 years scheduled for elective cesarean section were included in this prospective study. Women with contraindication for neuraxial block (like disturbed hemodynamics, coagulation defects, history of hypersensitivity to granisetron or local anesthetic agents, hypertensive disorders of pregnancy, cardiovascular insufficiency, on selective serotonin reuptake inhibitors or migraine medications) or patient refusal were excluded from the study. All patients were requested during the preanesthetic visit to be fasting 6–8 h preoperatively. Before the spinal block noninvasive blood pressure (BP), pulse rate and pulse oximetry (SPO2) readings were recorded, and a peripheral 18-gauge i.v. cannula was inserted. All patients received i.v. ranitidine (1 mg/kg) and preload with lactated Ringer's solution 20 mL/kg/h given over 30 min.

Patients were randomly divided into three equal groups containing twenty patients each. Group O received 4 mg ondansetron diluted in 10 ml of normal saline intravenously, group G received intravenous 1 mg granisetron diluted in 10 ml of normal saline, and group S received intravenous 10 ml normal saline injected over 1 min, 5 min before starting the subarachnoid block.

In the operating room, baseline values of noninvasive blood pressure (BP), electrocardiogram (ECG), and pulse oximetry (SPO2) were recorded. The 10 ml solution (ondansetron, granisetron, or saline) was given intravenously; then 5 min later, spinal anesthesia was done for the patient in the sitting position at the level of L3–4 or L4–5 by injection of 2 ml 0.5% hyperbaric bupivacaine (Marcaine®, AstraZeneca, Södertälje, Sweden) intrathecal through a 25-gauge Quincke needle after cerebrospinal fluid free flow without barbotage, and then, patients placed in the supine position with left lateral tilt by 15°. Intravenous lactated Ringer's solution was infused at 15 ml/kg/h till the end of surgery.

A resident anesthesiologist blinded to the study drug solutions measured and recorded the haemodynamics, presence of nausea, vomiting, shivering, or inadequate analgesia.

Mean Arterial Pressure (MAP), heart rate (HR), and oxygen saturation (SPO2) were recorded from the starting of spinal anesthesia at 2-min interval for 20 min then every 5 min till the end of operation.

Moreover, the upper sensory level was assessed using a short beveled 25-gauge needle by bilateral loss of pinprick at the midclavicular line every 2 min till the fixation of the sensory level at two consecutive times, and this is the maximum sensory level; then, the patients were evaluated every 15 min till sensory level regression to S1.

Also, motor block was assessed every 2 min by the modified Bromage scale till the complete motor block then every 15 min till complete motor recovery.

Modified Bromage scale [15]:

- 0 = able to move hip, knee, ankle, and toes.
- 1 = unable to move hip, able to move knee, ankle, and toes.
- 2 = unable to move hip and knee, able to move ankle and toes.
- 3 = unable to move hip, knee and ankle, able to move toes.

- 4 = unable to move hip, knee, ankle and toes.

Decrease in MAP more than 20% of the preoperative value was treated with i.v. 6 mg ephedrine.

Decrease in HR to less than 50 beat/min was treated with 0.5 mg atropine intravenous.

Shivering was treated with i.v. 25 mg tramadol.

Nausea and vomiting were treated with i.v. 10 mg metoclopromide.

Pain was treated with i.v. 50 μg fentanyl, but if persisted, it was considered failed spinal anesthesia, and patient anesthetized generally and excluded from the study.

2.1. Statistical analysis

Data were checked, entered and analyzed by using (SPSS version 19). Data were expressed as mean ± SD for quantitative variables, number and percentage for categorical variables Chi-squared (χ^2) or fisher exact test, ANOVA (F test) and LSD (when ANOVA was significant) for comparison in between groups. $P < 0.05$ was considered statistically significant.

3. Results

In the present study, there were no significant differences between the two groups as demographic data (age, weight, and height) and the procedure duration regards (Table 1).

There were nonsignificant differences among the groups as regard the basal MAP and HR (See Fig. 1) and (Table 2).

But as regards the decrease in MAP, there was significant difference between group O and both groups G and S at 5, 10, 15, 20, and 25 min. While there was insignificant differences between groups G and S, after 25 min, there was nonsignificant differences among the three groups (see Table 2 and Fig. 1).

There were no significant differences in HR among the three groups.

There was no significant difference of the time of fixation of sensory level among the three groups (See Table 3).

On the other hand, there were two significant segments regression in group G faster than both groups S and O (64 ± 20 vs 80 ± 24 min and 73 ± 27 min, respectively) (Table 3). Also, regression to T10, T12, and S1 was faster in group G than groups O and S, but no significant differences found between groups O and S (Table 3).

Also in (Table 3), there were no significant differences among the three groups in the time to maximum motor block, time to motor recovery by one level, and the time to complete motor recovery.

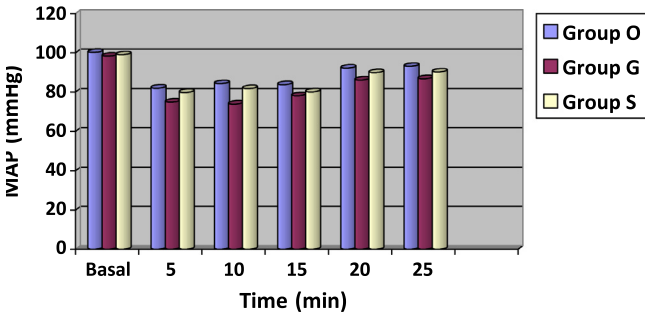

Figure 1 Changes in Mean Arterial Pressure (MAP) in the 3 groups.

Oxygen saturation did not change significantly in all groups.

There were no statistically significant differences in occurrence of shivering, pain, or bradycardia (Table 4). But 10% of patients in group S and 15% of patients in group G suffered from bradycardia and treated by atropine (0.5 mg can be repeated every 3–5 min if needed to a maximal total dose of 3 mg).

Although no patient in all groups suffered from vomiting, there was significant increase in the number of cases experienced nausea in group S more than groups G and O (40% vs 10% and 5%, respectively), but no significant differences found between groups G and O. Moreover, there was significant increase in the use of ephedrine in groups S and G more than group O (35% and 25% vs 5%, respectively) (Table 4).

There were two cases of failed spinal anesthesia anesthetized generally and excluded from the study.

4. Discussion

Spinal anesthesia is one of the regional techniques commonly used with cesarean section parturients to avoid most of risks which can happen with general anesthesia [2]. But that technique carries some risks also: the most common risk is hypotension due to almost complete sympathetic block as the level of block must be to T4 for adequate coverage plus the effect of gravid uterus on the venous return [2,16,17].

Several studies were done in a trial to prevent undesired cardiovascular effects of spinal anesthesia like hypotension, which is considered one of the most risky effects [2]. But in this study, comparison done between two strong antiemetic medications which are ondansetron and granisetron as regard their effects on blood pressure changes, sensory, and motor block of spinal anesthesia given to C.S. parturients as both medications have the same mechanism of action.

Table 1 Demographic data and procedure duration.

	Age (yr)	Height (cm)	Weight (kg)	Procedure duration (min)
Group O (n = 20)	32 ± 5	167 ± 5	79 ± 10	63 ± 7
Group G (n = 20)	30 ± 5	165 ± 5	75 ± 11	63 ± 9
Group S (n = 20)	31 ± 7	167 ± 6	74 ± 13	60 ± 8
P value	0.56	0.45	0.43	0.47

Data represented by mean ± SD.
No significant differences between the 3 groups.
Group O = Ondansetron.
Group G = Granisetron.
Group S = Saline.

Table 2 Changes in Mean Arterial Pressure (MAP) in the 3 groups.

	BP (mmHg) Basal	BP (mmHg) 5 min	BP (mmHg) 10 min	BP (mmHg) 15 min	BP (mmHg) 20 min	BP (mmHg) 25 min
Group O (n = 20)	100 ± 10	82 ± 12	84 ± 4	84 ± 4	92 ± 6	93 ± 5
Group G (n = 20)	98 ± 10	75 ± 8*	74 ± 9*	78 ± 3*	86 ± 6*	87 ± 6*
Group S (n = 20)	99 ± 8	80 ± 12*	82 ± 6*	80 ± 5*	90 ± 9*	90 ± 8*
P value	0.8	0.03	0.02	0.001	0.002	0.013

Data represented by mean ± SD and numbers.
Group O = Ondansetron.
Group G = Granisetron.
Group S = Saline.
* Compared with group O ($P < 0.05$).

Table 3 Spinal block timing course.

	Group O	Group G	Group S	P value
Time to upper sensory level block (min)	12.1 ± 2.3	11.2 ± 2.9	11.9 ± 3.8	0.6
Time to two segment regression (min)	72.8 ± 17.1*	64.3 ± 20.2	79.8 ± 23.5*	0.05
Time to sensory regression to T10 (min)	102.9 ± 25.0*	98.2 ± 21.1	115.7 ± 20.1*	0.037
Time to sensory regression to T12 (min)	126.2 ± 26.3*	107.8 ± 18.6	124.8 ± 15.6*	0.007
Time to sensory regression to S1 (min)	181 ± 31.9*	159.8 ± 21.4	179.5 ± 24.6*	0.005
Time to modefied Bromage scale = 4 (min)	10.1 ± 1.9	10.9 ± 2.0	9.8 ± 1.8	0.2
Time to modefied Bromage scale = 3 (min)	113.4 ± 21.9	109.3 ± 27.2	119.0 ± 15.1	0.5
Time to modefied Bromage scale = 0 (min)	168.2 ± 28.4	159.5 ± 33.8	170.2 ± 25.4	0.32

Data represented by mean ± SD.
Group O = Ondansetron.
Group G = Granisetron.
Group S = Saline.
* Significant compared with group G ($P < 0.05$).

Table 4 Incidence of side effects of the spinal anesthesia in the 3 groups.

	Shivering N (%)	Pain N (%)	Nausea N (%)	Bradycardia N (%)	Ephedrine use N (%)
Group O (n = 20)	2 (10.0)	2 (10.0)	1 (5.0*)	0 (0.0)	1 (5.0*)
Group G (n = 20)	2 (10.0)	3 (15.0)	2 (10.0*)	3 (15.0)	5 (25.0)
Group S (n = 20)	5 (25.0)	3 (15.0)	8 (40.0)	2 (10.0)	7 (35.0)
P value	0.3	0.86	0.008	0.21	0.05

Data represented as number and percentage.
Group O = Ondansetron.
Group G = Granisetron.
Group S = Saline.
* Significant compared with S ($P < 0.05$).

Subarachnoid block leads to decrease in the systemic vascular resistance and so pooling of blood and hypotension. BJR triggered by heart mechanoreceptors results in the systemic response to hyper and hypovolemia [18–20]. So, serotonin-induced BJR participates in the systemic response to spinal anesthesia by vasodilatation, hypotension, and bradycardia [10,21].

Ondansetron is one of the medications studied before by Sahoo et al. [22] and proved that it attenuated spinal induced hypotension if given intravenously in C.S. patients before spinal anesthesia, and our results coincided with their findings. On the other hand, Tsikouris et al. [23] in their study on granisetron found that it decreased heart rate and BP changes occurred during the head-up tilt table test due to BJR and that study encouraged the authors of the present study to compare between it and ondansetron as regard their hemodynamic effects on C.S. parturients under spinal anesthesia. But, it was found that granisetron had no effects on the hemodynamic variables, and this is in agreement with Mowafi et al. [12].

Animal studies clarified that serotonin has antinociceptive effect at the spinal cord level by inhibiting the excitatory transmitters and increasing the inhibitory transmitters [24,25]. Consequently, serotonin antagonists decreasing the nociceptive threshold as proved by Giordano and Dyche [26].

When the effects of ondansetron and granisetron on sensory regression and motor block of subarachnoid anesthesia were studied, it was found that IV ondansetron did not affect sensory or motor block of intrathecal bupivacaine the same as Samra et al. proved in their study [27] but against the results of Fassoulaki et al. [14], who found that systemic ondansetron enhance the sensory block regression after intrathecal lidocaine.

Conversely, in this study, we found that IV granisetron prior to intrathecal bupivacaine resulted in faster sensory regression but no effect on the motor block .That results agreed with Mowafi et al. [12] who studied the effects of IV granisetron on the sensory and motor blockade produced by intrathecal bupivacaine and with Fassoulaki et al. [14] who studied the effects of IV ondansetron on the spinal anesthesia with lidocaine.

These differences between the effects of ondansetron and granisetron although both of them from the same category and the same mechanism of action may be due to the action of ondansetron on mixed receptors and the high selectivity of granisetron on 5-HT3 receptors but minimal affinity of it for other 5-HT receptors, adrenergic, histaminic, dopaminergic, or opioid receptors [6,28].

5. Conclusion

It is concluded that in parturient females undergoing elective cesarean section, intravenous 4 mg ondansetron before subarachnoid block significantly decreased both the hypotension and the doses of vasopressor used, while intravenous 1 mg granisetron prior to subarachnoid block induced faster sensory recovery compared to both the ondansetron and saline groups, with no significant differences between the later two groups.

Limitations in this study included not comparing different doses of both medications and not comparing ondansetron with commonly used vasopressors to evaluate which is beneficial for patients especially because of the higher cost of serotonin receptors antagonists. Other studies recommended to evaluate whether the spinal bupivacaine dose must be adjusted in patients treated with granisetron due to the possibility of its reversal of perioperative analgesia.

References

[1] Cyna AM, Andrew M, Emmett RS, Middleton P, Simmons SW. Techniques for preventing hypotension during spinal anaesthesia for caesarean section (review). Cochrane database of systematic reviews. JohnWiley & Sons, Ltd.; 2006 [issue 4].

[2] Glosten B. Anesthesia for obstetrics. In: Miller RD, editor. Anesthesia. Philadelphia: Churchill Livingstone; 2000.

[3] Ben David B, Miller G, Gavriel R, Gurevitch A. Low-dose bupivacaine–fentanyl spinal anesthesia for caesarean delivery. Reg Anesth Pain Med 2000;25:235–9.

[4] Choi DH, Ahn HJ, Kim MH. Bupivacaine-sparing effect of fentanyl in spinal anesthesia for caesarean delivery. Reg Anesth Pain Med 2000;25:240–5.

[5] Mebazaa MS, Ouerghi S, Meftah RB, et al. Reduction of bupivacaine dose in spinal anaesthesia for caesarean section may improve maternal satisfaction by reducing incidence of low blood pressure episodes. MEJ Anesth 2010;20(5):673–8.

[6] Van Wijngaarden I, Tulp MT, Soudijn W. The concept of selectivity in 5-HT receptor research. Eur J Pharmacol 1990;138:301–12.

[7] Martinek RM. Witnessed asystole during spinal anesthesia treated with atropine and ondansetron: a case report. Can J Anesth 2004;51(3):226–30.

[8] Veelken R, Hilgers KF, Leonard M, et al. A highly selective cardiorenal serotonergic 5-HT3-mediated reflex in rats. Am J Physiol 1993;264:1871–7.

[9] Velken R, Swain LL, Di Bona GF. Epidural serotonin receptors in circulatory control in conscious Sprague-Dawley rats. Am J Physiol 1990;258:468–72.

[10] Yamano M, Ito H, Kamato T, Miyata K. Characteristics of inhibitory effects of serotonin (5-HT) 3 receptor antagonist, YMO60 and YM114 (KAE 393), on von Bazold Jarisch reflex induced by 2 methyl 5 HT, veratridine and electrical stimulation of vagus nerves in anaesthetized rats. Jpn J Pharmacol 1995;69:351–6.

[11] Kinsella SM, Tuckey JP. Perioperative bradycardia and asystole: relationship to vasovagal syncope and the Bezold–Jarisch reflex. Brit J Anaeth 2001;86(6):859–68.

[12] Mowafi HA, Arab SA, Ismail SA, et al. The effects of intravenous granisetron on the sensory and motor blockade produced by intrathecal bupivacaine. Anesth Analg 2008;106:1322–5.

[13] Naesh O, Hindberg I, Christiansen C. Subarachnoid bupivacaine increases human cerebrospinal fluid concentration of serotonin. Reg Anesth 1996;21:446–50.

[14] Fassoulaki A, Melemeni A, Zotou M, Sarantopoulos C. Systemic ondansetron antagonizes the sensory block produced by intrathecal lidocaine. Anesth Analg 2005;100:1817–21.

[15] Martin-Salvaj G, Van Gessel E, Forster A, Schweizer A, Iselin-Chaves I, Gamulin Z. Influence of duration of lateral decubitus on the spread of hyperbaric tetracaine during spinal anesthesia: a prospective time-response study. Anesth Analg 1994;79:1107–12.

[16] Russell IF. Levels of anaesthesia and intraoperative pain at caesarean section under regional block. Int J Obstet Anesth 1995;4:71.

[17] Rocke DA, Rout CC. Volume preloading, spinal hypotension and caesarean section. Brit J Anaesth 1995;75(3):257–9.

[18] Mark AL. The Bezold–Jarisch reflex revisited: clinical implications of inhibitory reflexes originating in the heart. J Am Coll Cardiol 1983;1:90–102.

[19] Aviado DM, Guevara Aviado D. The Bezold–Jarisch reflex: a historical perspective of cardiopulmonary reflexes. Ann NY Acad Sci 2001;940:48–58.

[20] Campagna JA, Cartner C. Clinical relevance of Bezold Jarisch reflex. Anesthesiology 2003;98:1250–60.

[21] Yamano M, Kamato T, Nishida A, et al. Serotonin (5-HT)3-receptor antagonism of 4,5,6,7-tetrahydrobenzimidazole derivatives against 5-HT-induced bradycardia in anesthetized rats. Jpn J Pharmacol 1994;65:241–8.

[22] Sahoo T, Goswami A, Hazra A, et al. Reduction in spinal-induced hypotension with ondansetron in parturients undergoing caesarean section: a double-blind randomised, placebo-controlled study. Int J Obstet Anesth 2012;21:24–8.

[23] Tsikouris JP, Kluger J, Chow MS, White CM. Usefulness of intravenous granisetron for prevention of neurally mediated hypotension upon head upright tilt testing. Am J Cardiol 2000;85:1262–4.

[24] Xu W, Qiu XC, Han JS. Serotonin receptor subtypes in spinal antinociception in the rat. J Pharmacol Exp Ther 1994;269:1182–9.

[25] Yoshimura M, Furue H. Mechanisms for the antinociceptive actions of the descending noradrenergic and serotonergic systems in the spinal cord. J Pharmacol Sci 2006;101:107–17.

[26] Giordano J, Dyche J. Differential analgesic action of serotonin 5-HT3 receptor antagonists in three pain tests. Neuropharmacology 1989;28:431–4.
[27] Samra T, Bala I, Chopra K, et al. Effect of intravenous ondansetron on sensory and motor block after spinal anaesthesia with hyperbaric bupivacaine. Anaesth Intens Care 2011;39:65–8.
[28] Aapro M. Granisetron: an update on its clinical use in the management of nausea and vomiting. Oncologist 2004;9: 673–86.