Reduction in spinal-induced hypotension with ondansetron in parturients undergoing caesarean section: A double-blind randomised, placebo-controlled study

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ABSTRACT

Background: Subarachnoid block is the preferred method of anaesthesia for caesarean section, but is associated with hypotension and bradycardia, which may be deleterious to both parturient and baby. Animal studies suggest that in the presence of decreased blood volume, 5-HT may be an important factor inducing the Bezold Jarisch reflex via 5-HT3 receptors located in intracardiac vagal nerve endings. In this study, we evaluated the effect of ondansetron, as a 5-HT3 receptor antagonist, on the haemodynamic response following subarachnoid block in parturients undergoing elective caesarean section.

Methods: Fifty-two parturients scheduled for elective caesarean section were randomly allocated into two groups. Before induction of spinal anaesthesia Group O (n = 26) received intravenous ondansetron 4 mg; Group S (n = 26) received normal saline. Blood pressure, heart rate and vasopressor requirements were assessed.

Results: Decreases in mean arterial pressure were significantly lower in Group O than Group S from 14 min until 35 min. Patients in Group O required significantly less vasopressor (P = 0.009) and had significantly lower incidences of nausea and vomiting (P = 0.049).

Conclusion: Ondansetron 4 mg, given intravenously 5 min before subarachnoid block reduced hypotension and vasopressor use in parturients undergoing elective caesarean section.

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Keywords: Ondansetron; Spinal anaesthesia; 5-HT; Caesarean section

Introduction

The most popular form of anaesthesia for caesarean section, spinal anaesthesia, is frequently associated with hypotension and bradycardia. Hypotension results primarily from decreased vascular resistance, while bradycardia is secondary to a relative parasympathetic dominance, increased baroreceptor activity, or induction of the Bezold Jarisch Reflex (BJR).1 The incidence of hypotension and bradycardia has been reported to be 33% and 13%, respectively, in non-obstetric patients.1,2 In obstetric, non-labouring patients, the incidence of hypotension has been estimated to be as high as 50–60%; this is less common after the onset of labour.3

Owczuk et al. observed that intravenous ondansetron attenuated spinal-induced hypotension.4 Animal studies suggest that 5-HT (serotonin) may be an important factor associated inducing the BJR in the setting of decreased blood volume5–8; this effect can be blocked at the 5-HT3 receptor.9 We hypothesized that spinal-induced hypotension and bradycardia could be minimized with the use of intravenous ondansetron, a 5-HT3 receptor antagonist, in non-labouring obstetric patients undergoing caesarean section.

Methods

This study was conducted at the Department of Anaesthesiology, Institute of Post Graduate Medical Education and Research, Kolkata, India between September and December 2008. Institutional ethical committee approval and informed written consent were obtained from all patients. Participants were evaluated one day before surgery by an anaesthesiologist. Obstetric patients who were ASA physical status I, between 20 and 40 years of age, and undergoing an elective, lower segment caesarean section (CS) were included. Patients with contraindications to subarachnoid block (patient refusal, unstable hemodynamics, coagulation abnormality), history of hypersensitivity to ondansetron...
or local anaesthetic agents, hypertensive disorders of pregnancy, cardiovascular insufficiency, receiving selective serotonin reuptake inhibitors or migraine medications were excluded.

Patients were randomly allocated into two groups using a computer generated randomisation chart to receive either intravenous (i.v.) ondansetron 4 mg diluted in 10 mL of normal saline (Group O) or normal saline 10 mL (Group S) over 1 min, 5 min before spinal anaesthesia.

In the pre-anaesthesia room, non-invasive blood pressure (BP) and pulse rate were recorded and a peripheral 18-gauge i.v. cannula was inserted. All patients received i.v. ranitidine (1 mg/kg) and metoclopramide (0.4 mg/kg) and prehydration with lactated Ringer’s solution 20 mL/kg/h given over 30 min. In the operating room baseline values of pulse oximetry (SpO2), non-invasive BP and electrocardiogram (ECG) were recorded. The spinal technique was performed with the patient in the sitting position at L3-4 or L4-5. The study solution was administered intravenously and 5 min later, 0.5% hyperbaric bupivacaine 2 mL was administered after confirmation of cerebrospinal fluid through a 25- or 26-gauge Quincke spinal needle. Patients were immediately placed in the supine position with 15° left tilt. A second anaesthesiologist, blinded to the study solution, measured haemodynamic parameters and recorded the presence of nausea, vomiting, rigor, discomfort or inadequate analgesia.

Heart rate (HR), systolic (SBP), diastolic (DBP) and mean arterial pressure (MAP), and oxygen saturation (SpO2) were recorded at time of spinal drug administration and at 2-min intervals up to 20 min, followed by 5-min intervals until the end of surgery. Upper sensory levels were assessed at 5-min intervals. SBP <90 mmHg or DBP <60 mmHg were treated with i.v. phenylephrine 0.3 mg. Rigors and pain were treated with i.v. tramadol 25 mg and fentanyl 50 µg, respectively. Nausea and vomiting were treated with i.v. promethazine 12.5 mg. When phenylephrine or atropine were necessary, only values obtained before these medications were analysed. Pain that persisted after a single dose of fentanyl was considered a failed spinal anaesthetic, converted to general anaesthesia, and the patient excluded from the study.

**Statistical analysis**

For sample size calculations, we estimated that 23 subjects would be required per group in order to detect a 6 mmHg difference in MAP between groups with 80% power and 5% probability of type I error. This calculation was based on a 7 mmHg difference observed by Owczuk et al. in non-pregnant patients. Data was summarized by descriptive statistics. Numerical variables normally distributed were compared between groups by Student’s independent samples t test. Categorical variables were compared between groups by Fisher’s exact probability test. Repeated measures ANOVA was employed for intra-group comparison of numerical variables, followed by Dunnet’s test (with baseline value as the control value) for post hoc testing. All analyses were 2-tailed. P < 0.05 was considered statistically significant.

**Results**

Fifty-six patients were recruited: 26 in each group. No significant differences were observed in patient demographics between the two groups (Table 1). Decreases in HR (Fig. 1) were more common in Group S, but differences were statistically significant only twice: at 24 min [Group O: 93.9 ± 16.5 vs. Group S: 82.9 ± 14.1 beats/min, P = 0.031] and at 45 min [Group O: 94.3 ± 16.2 vs. Group S: 83.1 ± 7.5 beats/min, P = 0.02]. Significant decreases in MAP were observed in both groups. Differences were observed at 5 min [Group O 88 ±11.7 vs. Group S 82.2 ±10.5 mmHg, P = 0.038] and 6 min [Group O 87.5 ±11.3 vs. Group S 80.4 ±10.8 mmHg, P = 0.025]. Those in Group S had a significantly lower MAP between 14 and 35 min (Fig. 2).

The number of anaesthetized segments above S1 increased until 15 min in Group O, and 20 min in Group S (Fig. 3). Statistically significant differences between the numbers of segments blocked were observed only at 10 min (P = 0.01).

There were no significant changes in oxygen saturation in either group. The use of phenylephrine (P = 0.009) and development of nausea (P = 0.049) were significantly more common in Group S. There were no significant differences in the presence of rigors or the use of atropine and fentanyl. Three patients in Group O and five in Group S developed chest discomfort for which they received fentanyl. No patient experienced vomiting, underwent conversion to general anaesthesia or was excluded due to inadequate spinal anaesthesia.

<table>
<thead>
<tr>
<th>Table 1 Demographic details and side effects</th>
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<tbody>
<tr>
<td>Group O</td>
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<tr>
<td>(n = 26)</td>
</tr>
<tr>
<td>Age (years)</td>
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<tr>
<td>Weight (kg)</td>
</tr>
<tr>
<td>Discomfort/pain</td>
</tr>
<tr>
<td>Vasopressor use</td>
</tr>
<tr>
<td>Bradycardia</td>
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<tr>
<td>Rigor</td>
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<td>Nausea</td>
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Data are mean (SD) or number.
Fig. 1  Comparison of mean heart rate. *Significant decrease in heart rate in Group S at 24 and 45 min.

Fig. 2  Comparison of mean arterial blood pressure changes.

Fig. 3  Comparison of sensory level blockade.
Discussion

This study revealed that decreases in SBP and MAP were reduced with the use of i.v. ondansetron 4 mg given 5 min before spinal anaesthesia in parturients undergoing elective caesarean section. The use of phenylephrine and the incidence of nausea were also significantly reduced with ondansetron. Although significant differences in heart rate were observed between the groups on two occasions, the frequency of bradycardia was too small to achieve statistical significance and no patient in either group required atropine.

Sympathetic blockade from spinal anaesthesia decreases systemic vascular resistance and induces peripheral pooling of blood leading to hypotension. Mechanoreceptors in the heart wall that trigger the BJR, participate in systemic responses to hypervolaemia. In response to hypovolaemia, stimulation of cardiac sensory receptors in the left ventricle induces the BJR and results in reflex bradycardia, vasodilation and hypotension. Chemoreceptors are activated in response to decreased blood volume by serotonin, which is released from activated thrombocytes. Activation of 5-HT3 receptors, which are G protein coupled, ligand-gated fast-ion channels, results in increased efferent vagal nerve activity, frequently producing bradycardia. However, bradycardia occurs less frequently than hypotension following spinal anaesthesia, ranging from 2.1–4.9% vs. 36.8–52%, respectively. Thus, spinal anaesthesia causes vasodilatation, hypotension, and bradycardia by sympathetic blockade, the BJR and stimulation of 5-HT3 receptors in vagal nerve endings. Although we were unable to find reports of direct effects of 5-HT3 antagonist administration on cardiac output, we believe our results indicate that ondansetron prevented the serotonin-induced BJR, suppressed venodilatation, augmented venous return to the heart and resulted in lesser reductions in SBP and MAP. Blockade of the 5-HT3 receptor antagonizes the BJR induced by serotonin.

White et al. observed that i.v. administration of the 5-HT3 antagonist granisetron 50 μg/kg was efficacious in suppressing bradycardia and hypotension associated with the BJR in a rabbit model. Clinically, Tsikouris, et al. observed that granisetron/mg diminished heart rate fluctuations and decreased SBP changes during head-up tilt table tests, which are likely related to the BJR. Martinek concluded that i.v. ondansetron 4 mg with atropine 0.6 mg could revert asystole during spinal anaesthesia. Finally, Owczuk et al. in a mixed group of patients aged 20–70 years, found that ondansetron 8 mg decreased the incidence of bradycardia and hypotension after spinal anaesthesia.

Limitations in this study include not evaluating different doses of ondansetron. Ondansetron is used primarily for prophylaxis or treatment of postoperative nausea and vomiting (PONV) in intravenous doses of 4 mg and 8 mg. Doses as low as 0.05 mg/kg have been used to effectively decrease PONV; however, we selected the standard dose of ondansetron 4 mg used in our institution. In addition, we cannot comment on the effect of ondansetron on the incidence of bradycardia, due to its infrequent occurrence. Moreover, although we had hoped to report on DBP effects, which reflect arterial wall tone, it did not vary substantially. Larger groups are needed to evaluate the potential effect of ondansetron on bradycardia and DBP alterations.

We conclude that i.v. ondansetron 4 mg given before spinal anaesthesia can attenuate decreases in blood pressure following spinal anaesthesia in parturients undergoing elective caesarean section.

References