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ORIGINAL ARTICLE

Randomized, Placebo-Controlled Trial of Granisetron for Control of Nausea and Vomiting During Cesarean Delivery Under Spinal Anesthesia

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Abstract

Objective(s) The objective of this study was to evaluate the efficacy and safety of granisetron ($5HT_3$ receptor antagonist) on the incidence of nausea and vomiting in cesarean deliveries under spinal anesthesia.

Method(s) In the randomized, double-blind study, 80 parturients received granisetron 40 μg/kg or placebo ($n = 40$ each) intravenously, immediately after clamping of the fetal umbilical cord. Nausea, vomiting, and adverse events were then observed for 24 h after administration of spinal anesthesia.

Results A complete response (defined as no postoperative nausea and vomiting) during 0–4 h after administration of spinal anesthesia was achieved in 80 % of patients with granisetron and in 45 % of patients with placebo. The corresponding incidences during (4–24 h) were 82.5 and 55 % (P value <0.05). No difference in adverse events was observed in any of the groups.

Conclusion(s) Prophylactic use of granisetron is effective for preventing emetic episodes during spinal anesthesia for cesarean delivery.

Keywords Nausea and vomiting · Spinal anesthesia · Granisetron · Cesarean section

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Introduction

Nausea and vomiting in cesarean delivery under spinal anesthesia are a common problem [1] and have been reported in more than 66 % cases [1, 2]. Postoperative nausea and vomiting (PONV) can be unpleasant and disturbing to the patient and make surgery difficult. Furthermore, this can complicate postoperative care in several ways—(i) aspiration of vomitus, (ii) electrolyte disturbance and dehydration, (iii) delay of nutrition, fluid intake, and oral drug therapy, and (iv) wound dehiscence.

Among the antiemetics used currently, 5-hydroxytryptamine type 3 ($5\text{-}HT_3$) antagonists such as ondansetron and granisetron are increasing in popularity. Granisetron is a selective $5\text{-}HT_3$ receptor antagonist and has more potent and longer-acting properties than ondansetron for the treatment of cisplatin-induced emesis [3]. Recently, granisetron has been found to have a prophylactic antiemetic effect on PONV in patients undergoing surgery under general anesthesia [4]. So far, there is a scarcity of data for

other 5-HT_3 antagonist (granisetron, dolosetrone, and tropisetron) in the Indian context, and limited data on the granisetron in association with spinal anesthesia for preventing PONV in cesarean delivery. We conducted this prospective, randomized, double-blind, placebo-controlled study to evaluate the efficacy of granisetron for preventing PONV in patients undergoing cesarean delivery under spinal anesthesia.

Methods

The study was conducted during the period of January 2007 to January 2008 after the ethical committee's approval and written informed consent. A total of 80 women (ASA 1 and 2) aged 22–35 years undergoing elective cesarean delivery were recruited for the study. All women were explained the procedure and were randomly allocated into two groups (Group G and Group P) using a random number table. The women were matched for age and BMI. Women who had a history of motion sickness, previous history of emesis in post-delivery period, history of acid peptic diseases, body weight >85 kg, and those who had received antiemetic meditation 24 h before surgery, any chronic medical or surgical disorders complicating the pregnancy, and conditions contraindicating regional anesthesia were excluded from this study.

Group G received intravenously Granisetron 40 μg/kg and Group P received placebo (0.9 % saline). Study agents were administered intravenously immediately after clamping of the umbilical cord. Study medications were prepared by personnel not involved in this study in individual 5 ml syringes to ensure blinding to the anesthetists. Patients and investigators who collected post-delivery data were blinded to the study drug administered.

As preanesthetic medication, all parturients received 0.3 M sodium citrate (30 ml) orally before procedure. Each of the parturient received intravenous hydration with 20 ml/kg of lactated Ringer's solution before induction of spinal anesthesia. Pulse rate, blood pressure, SpO_2 of each parturient, and fetal heart rate were recorded before spinal anesthesia.

Under overall aseptic precaution, spinal anesthesia was administered in the right lateral decubitus position through $L_{3–4}$ intervertebral space using 25 gauge lumbar puncture needle with 0.5 % hyperbaric bupivacaine 2 ml (10 mg). Women were then placed supine with a wedge under right hip for 15° left uterine displacement. Oxygen 3 l/min was administered via face mask. Patients were monitored during procedure by continuous ECG, NIBP, and pulse oximetry. The decrease in systolic blood pressure >20 % of baseline values and/or less than 80 mmHg immediately after spinal injection was treated with additional intravenous fluids and/or ephedrine 5–10 mg intravenously, as indicated. After due confirmation of spinal block by loss of sensation to cold and pinprick at $T_{4–5}$ level, surgery was started. Syntocinon (10 Units) was administered through intravenous infusion at the time of umbilical cord clamping. Lower section Cesarean section was performed in all the cases with low transverse skin incision, and uterus was repaired in two layers with no 1.0 vicryl suture. Visceral and parietal peritoneum was not repaired. Rectus sheath and skin were repaired as usual. Patients in each group were allowed to receive pethidine 0.5 mg/kg intravenously if required for pain relief after delivery of the baby due to uterus exteriorization and/or peritoneum manipulation.

Intraoperative and postoperative emetic episodes (nausea, retching, and vomiting) were recorded by direct questioning or by spontaneous complaint by the patients at any time by the attending anesthesiologist blinded to which type of treatment the patients had received.

Nausea was defined as a subjectively unpleasant sensation associated with awareness of the urge to vomit. *Retching* was defined as the labored, spasmodic, and rhythmic contraction of the respiratory muscles without the expulsion of gastric contents. *Vomiting* was defined as the forceful expulsion of gastric contents from mouth [6].

If two or more episodes of emesis occurred in each observation period, another rescue antiemetic (ondansetron 4 mg) was given intravenously. We made no distinction between vomiting and retching. At the end of each observation period, the patients evaluated the severity of nausea with a linear numerical scale ranging from 0 (no nausea) to 10 (severe nausea). The details of adverse effects were recorded during study period by the attending anesthesiologist. Postoperative analgesia was provided with pethidine 1.5 mg/kg administered intramuscularly.

Statistical Analysis

Statistical differences between two groups in discrete and continuous variables were tested using χ^2 and Student's t test, respectively. A P value of <0.05 was considered significant. All values were expressed as mean ± SD range or number %.

Results

Patient profile and information on the surgery and operative management are summarized in Tables 1 and 2. The treatment groups were comparable with regard to patient demographics and operative management.

In the initial 4 h after administration of spinal anesthesia, a complete response (i.e., no PONV) occurred in 32

Table 1 Maternal demographics

	Group G Granisetron ($n = 40$)	Group P Placebo ($n = 40$)
Age (years)	25 ± 3.5	25 ± 2.1
Weight (kg)	56 ± 7.2	57 ± 8
Primigravida	28	29
Multigravida	12	11
ASA grade		
1	31	30
2	9	10
Baseline systolic blood pressure (mmHg)	124.5 ± 8.1	124.5 ± 6.1

No significant difference

Table 2 Operation details

	Group G Granisetron ($n = 40$)	Group P Placebo ($n = 40$)
Duration of surgery (min)	48.2 ± 8	46.7 ± 6
Uterus exteriorized (n)	36	35
Duration of uterus exteriorized (min)	18 ± 5.4	18 ± 6.1
Total ephedrine (mg)	6.5 (0–10)	6.5 (0–10)
No. of patients receiving intraoperative pethidine (n)	18	16
Intraoperative pethidine consumption (mg)	27 ± 4.1 (25–40)	27 ± 3 (25–40)
Postoperative pethidine consumption (mg)	231.5 (202–360)	232.5 (207–360

(80 %) of patients who had received granisetron and in 18 (45 %) of patients who had received placebo. The corresponding incidences for next 20 h was 33 (82.5 %) of patients in granisetron group and 22 (55 %) of patients in placebo group. Thus, a complete response during the first 24 h after administration of spinal anesthesia was significantly more common in patients who had received granisetron than placebo ($P < 0.01$) shown in Table 3.

The overall cumulative incidences (0–24 h) of PONV were 10 (25 %) with granisetron and in 25 (62.5 %) with placebo.

Observed adverse events were headache, dry mouth/lip, dizziness, constipation, and myalgia which were not clinically serious. No difference in the incidence of adverse effects was observed between the groups as shown in Table 4.

Table 3 Response in the 2 groups during initial 4 h (0–4 h) and the next 20 h (4–24 h) after administration of spinal anesthesia

	Group G Granisetron ($n = 40$)	Group P Placebo ($n = 40$)	P
0–4 h after spinal anesthesia			
Complete response (no PONV)	32 (80 %)	18 (45 %)	<0.01
Nausea	5 (15.5 %)	14 (37.5 %)	
Vomiting	3 (7.5 %)	7 (17.5 %)	
Severity of nausea	0 (0–7)	0 (0–9)	
4–24 h after spinal anesthesia			
Complete response (no PONV)	33 (82.5 %)	22 (55 %)	<0.01
Nausea	4 (10 %)	11 (27.5 %)	
Vomiting	3 (7.5 %)	7 (17.5 %)	
Severity of nausea	0 (0–7)	0 (0–9)	
Overall cumulative incidences of PONV (0–24) h	10 (25 %)	25 (62.5 %)	<0.001

Table 4 Adverse effects

	Group G Granisetron ($n = 40$)	Group P Placebo ($n = 40$)
0–4 h after spinal anesthesia		
Headache	8 (20 %)	7 (17.5 %)
Dizziness	5 (15.5 %)	3 (7.5 %)
Constipation	2 (5 %)	2 (5 %)
Myalgia	1 (2.5 %)	1 (2.5 %)
4–24 h after spinal anesthesia		
Headache	7 (17.5 %)	7 (17.5 %)
Dizziness	3 (7.5 %)	3 (7.5 %)
Constipation	2 (5 %)	2 (5 %)
Myalgia	0	0

Discussion

Nausea and vomiting during regional anesthesia for cesarean section is relatively high [1] without prophylactic antiemetic [2]. The etiology of emetic symptoms in these cases is complex.

The effects of spinal anesthesia on women on their labor period are different from those observed in non-obstetric patients. The distribution of the anesthetic drug in cerebrospinal fluid (CSF) is less predictable in the former group, not only because of increased spinal canal pressure, but also as a consequence of the changes in CSF acid–base balance and protein content [1].

PONV depends on factors like maternal demographics [5], operative procedure, perioperative hypotension, postoperative pain, use of perioperative opioids, anesthetic

techniques [5], peritoneal traction, and exteriorization of uterus [6]. Maternal hypotension after induction of spinal anesthesia may trigger the vomiting center to induce emesis due to hypoxia [7].

During cesarean section, like other abdominal surgeries, the physical disruption and manipulation of abdominal viscera may cause the release of humoral substances including 5-HT, which may stimulate 5-HT3 receptors on the afferent vagus nerves [7], triggering the emetic reflex especially in awake patients.

Four major neuro-transmitter systems appear to play important roles in mediating the emetic response, viz. dopaminergic, histaminic (H1), cholinergic, muscarinic, and 5HT3.

The drugs for PONV management are thus generally antihistaminic, phenothiazine derivatives, anticholinergics, and dopamine receptor antagonists with unwanted side effects like sedation, dysphoria, extrapyramidal symptoms, dry mouth, restlessness, and tachycardia and have interactions with other anesthetic medications. Recently introduced 5HT3 receptor antagonists are devoid of such side effects and highly effective in prevention and treatment of PONV.

Current 5HT3 receptor antagonists include ondansetron, granisetron, dolasetron, and tropisetron. Ondansetron and granisetron are now available in India.

Gigillo et al. [8] in their study to prevent nausea and vomiting following cancer chemotherapy concluded that both ondansetron and granisetron have similar antiemetic efficacy but dose of granisetron is much less than ondansetron. 2 mg of granisetron IV is equivalent to 8–16 mg of ondansetron IV. Moreover ondansetron has a shorter half-life of 3 h, whereas granisetron has a half-life of 8–9 h, for which it is more effective in preventing nausea and vomiting. Granisetron is also a more selective 5HT3 receptor antagonist than ondansetron. An IV dose as low as 0.04 mg/kg is effective in preventing chemotherapy induced vomiting. A similar dose has been described as effective to prevent PONV. As the elimination half-life of granisetron is 9 h, which is 2.5 times longer than that of ondansetron, it requires less frequent dosing [9]. Granisetron was recently being used to prevent PONV after daycare gynecological procedures.

Granisetron has been shown to be more effective than droperidol [10]. Droperidol and metoclopramide are effective for the prevention of intraoperative, post-delivery emesis, but are ineffective for the reduction of the incidence of postoperative emesis unlike Granisetron which prevents both.

We have therefore studied the effects of granisetron in nausea and vomiting in cesarean deliveries under spinal anesthesia.

Our study groups were matched in their demographic and per operative characteristics. Pre-loading, left uterine displacement, supplementation of oxygen, and administration of incremental doses of ephedrine were performed for the prevention and early treatment of their hypotension. In our study, hypotension following spinal anesthesia and requirement of ephedrine were more or less similar in both groups.

Pethidine was used to control perioperative pain, patients in each group consumed similar amounts of pethidine.

Therefore, the differences in the incidence of PONV among the groups can be attributed to the study drug.

The dose of granisetron 40 μg/kg used in this study was based on the report published by Fujii et al. [11].

Our study could be criticized because we use opioid analgesia preoperatively, a recognized cause of PONV [10]. However there is an association between pain and PONV [5, 12], and treating pain with opioids may relieve PONV [12].

Similar to Fujii et al. [10], our results demonstrated that granisetron was effective for prevention of nausea and vomiting during and after spinal anesthesia for cesarean section when compared with placebo ($P < 0.01$). Granisetron is much more expensive than other available antiemetic in our setup. However, choice of antiemetic should not be limited to these costs but should also consider the outcome of the patients and overall cost of care if emesis was to occur.

In conclusion, prophylactic therapy with granisetron is effective for the prevention of PONV during the initial 24 h in particular, after administration of spinal anesthesia in elective cesarean delivery.

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