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Antiemetic in Caesarean section under spinal anaesthesia: new option

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Abstract: ***Objective:*** *Postoperative nausea and vomiting (PONV) after spinal anaesthesia for caesarean delivery are distressing to patients, anaeathesist and surgeon. This study was designed to evaluate the efficacy and safety of granisetron and ramosetron (both potent 5HT$_3$ receptor antagonist) on the incidences of nausea and vomiting in caesarean delivery after spinal anaesthesia in India.*
Place & Duration of Study: *The study was done at Eden Hospital, Medical College, Kolkata 700073, India for six months (November, 2011 to April, 2012).*
Patients, Design & Methods of Study: *In this randomized, double-blind study, 120 parturients (60 in each group) received granisetron (2mg in 2 ml) or ramosetron (0.3 mg in 2 ml) intravenously immediately after clamping of the foetal umbilical cord. Nausea, vomiting and adverse events were then observed for 48 h after administration of spinal anaesthesia.*
Results: *A complete response (defined as no postoperative nausea and vomiting) during first 0-2 h postoperative after administration of spinal anaesthesia was achieved in 83.3 % of patients with granisetron and in 86% of patients with ramosetron. The corresponding incidence during 2 to 24 h was 85% and 88.3 %, while it was 70% and 91.6% at 24–48 h after anesthesia ($p < 0.05$). At 24–48 h after anesthesia, nausea and vomiting were less severe in patients who received ramosetron than in those who received granisetron (*$p < 0.05$*). Patients who received ramosetron were also more satisfied than those who received granisetron (*$p < 0.05$*). No difference in adverse events was observed in any of the groups.*
Conclusion: *Prophylactic therapy with ramosetron is more effective than prophylactic therapy with granisetron for the long-term prevention of PONV in caesarean section in India.*

I. Article Proper:

Introduction: Postoperative nausea and vomiting (PONV) after spinal anaesthesia in caesarean delivery are common occurrences[1] and reported incidences are quite high[1-2]. Furthermore, post-delivery PONV can complicate postoperative care in several ways - (i) aspiration of vomit, (ii) electrolyte disturbance and dehydration, (iii) delay of nutrition, fluid intake and oral drug therapy, and (iv) wound dehiscence. For PONV prevention, selective serotonin 5- hydroxytryptamine type 3 (5-HT$_3$) receptor antagonists are considered one of the first-line therapy because of their efficacy and fewer side-effects compared with other antiemetics[3]. Most research on the 5-HT$_3$ receptor antagonists has been on ondansetron, and its antiemetic efficacy has been well established in chemotherapy-induced emesis and the prevention and treatment of PONV. Granisetron is a selective 5- HT$_3$ receptor antagonist and has more potent and longer acting properties than ondansetron for the treatment of cisplatin–induced emesis[4]. Recently granisetron has been found to have a prophylactic antiemetic effect on PONV in patients undergoing surgery under general anaesthesia[5]. Ramosetron is another recently developed selective 5-HT$_3$ receptor antagonist. It exhibits significantly greater binding affinity for 5-HT$_3$ receptors with a slower dissociation rate from receptor binding, resulting in more potent and longer receptor antagonizing effects compared with older 5-HT$_3$ receptor antagonists[6,7]. Ramosetron and granisetron are similar with respect to prevention of emesis, nausea or drug-related adverse events in acute cisplatin-induced emesis, though ramosetron had a longer duration of action[8]. So far there is limited data on either granisetron or ramosetron in the Indian context[9], more so regarding their use for preventing PONV in caesarean delivery.

We hypothesized that ramosetron is more effective than granisetron for the long-term prevention of PONV[7,10]. To test this hypothesis, we designed this prospective, randomized, double-blinded trial to assess the efficacy and safety of granisetron and ramosetron for preventing PONV patients undergoing spinal anaesthesia for caesarean delivery.

Methods: After ethical committee approval from Institutional Ethics Committee, Medical College, Kolkata and written informed consent, 120 women (ASA 1 and 2) aged between 22 and 35 yrs undergoing elective caesarean delivery were included in this study. 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 hr. before surgery or having any contraindication to regional anesthesia were excluded from this study.

All women were explained the procedure and were randomly allocated, using a random number table, to receive intravenously one of three treatment regimens: Group G (no. = 60) received granisetron 2 ml (2 mg), while Group R (no. = 60) received ramosetron (0.3mg) in 2 ml. 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 covered and coded syringes to ensure blinding to the anesthetists. Patients and investigators who collected post delivery data were blinded to the study drug administered. Each parturient were pre-loaded with 15 ml/Kg of lactated Ringer's solution before induction of spinal anaesthesia. Pulse rate, blood pressure, SpO_2 of each parturient and foetal heart rate were recorded before spinal anaesthesia. Under all aseptic precaution, lumbar puncture was performed in sitting position through L_{3-4} inter-vertebral space using 25 gauge Whitacre type lumber puncture needle and 0.5% hyperbaric bupivacaine 2 ml (10 mg) was injected. Women were then placed supine with a wedge under right hip for 15º left uterine displacement. Oxygen 3 lit/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 mm Hg immediately after spinal injection was treated with additional intravenous fluids and/or ephedrine 5-10 mg intravenously, as indicated. Following conformation of spinal block by loss of sensation to cold and pinprick to T_{4-5} level, surgery was started. Syntocinon 10 units were administered through intravenous infusion at the time of umbilical cord clamping. 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.

Nausea was defined as a subjectively unpleasant sensation associated with awareness of the urge to vomit; *retching* was defined as the laboured, spasmodic rhythmic contraction of the respiratory muscles without the expulsion of gastric contents. *Vomiting* was defined as the forceful expulsion of gastric contents from mouth[11]. 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. All episodes of PONV (nausea, retching, and vomiting) were recorded by direct questioning by trained nurses blinded to the study group or by spontaneous complaint by the patients during three periods within the first 48 h after anesthesia: 0–2 h in the post-anesthetic care unit, 2–24 h in the postpartum ward and 24-48 h in the general ward. 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. Patient satisfaction regarding their satisfaction to be free of nausea and vomiting were performed on a linear numerical scale ranging from 0 (complete dissatisfaction) to 10 (complete satisfaction) at the completion of the study.

Sample size was predetermined using a power analysis to achieve an 80% chance (β = 0.2) of detecting a 40% reduction in PONV from a basal incidence of 70% (from 70% to 42%) with an assumed significance level of α = 0.05.[12] A calculated minimum sample size was 49 patients in each group. A larger number of patients were included to allow for possible incomplete data collection or patient dropout. Statistical analysis was performed using SPSS for Windows (version 14, SPSS Inc., Chicago, IL, USA). A one-way analysis of variance was used to compare the continuous variables among the groups. If a significant difference was noted, a Bonferroni multiple comparison test was used to determine intergroup differences. Categorical variables were analyzed using the χ^2 test or Fisher's exact test, as appropriate. A *p*-value of <0.05 was considered statistically significant. Data are presented as mean (SD), numbers, ranges or percentages.

II. Results

Patient profile and information on the surgery and operative management were summarized in **Table I** and **Table II**. The treatment groups were comparable with regard to patient demographics and operative management. The incidence of a complete response (no PONV, no rescue) 0–2 h after anesthesia was 83.3% with granisetron and 86.6% with ramosetron; the corresponding incidence 2–24 h after anesthesia was 85% and 88.3%; while the corresponding incidence 24–48 h after anesthesia was 70% and 91.6% respectively. Thus, a complete response 24–48 h after anesthesia was more frequent in patients who had received ramosetron than in those who had received granisetron ($p < 0.05$). At 24–48 h after anesthesia, incidences of nausea and vomiting were lesser in patients who received ramosetron than in those who received granisetron ($p < 0.05$). Patients who received ramosetron were also more satisfied than those who received granisetron ($p < 0.05$) (**Table III**).

Observed adverse events were headache, 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 IV & Fig I**.

III. Discussion

Nausea and vomiting during regional anaesthesia for caesarean section is relatively high[1] without prophylactic antimetic[2]. The aetiology of emetic symptoms following regional anaesthesia for caesarean delivery is complex and depends on a variety of factors including maternal demographics, operative procedure, the occurrence of postoperative pain, use of perioperative opioids, and anaesthetic techniques[11], peritoneal traction[12] and exteriorisation of uterus[13]. Maternal hypotension[13] after induction of spinal anaesthesia is related to an increased incidence of intraoperative, post-delivery emetic episodes. This hypotension may trigger the vomiting centre to induce emesis due to hypoxia[13,14]. In this study 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. Also the hypotension following spinal anaesthesia and requirement of ephedrine were more or less similar in both groups. In addition, patients in each group consumed similar amounts of pethidine as analgesic in the postoperative period. In our study as the treatment groups were similar with regard to maternal characteristics and operative management, we inferred that the differences in the incidence of PONV among the groups can be attributed to the study drug.

The exact mechanism of granisetron and ramosetron in the prevention of PONV is unknown, but these drugs may act by potently blocking 5-HT_3 receptors sites at area postrema and the nucleus tractus solitarius[14]. The dose of granisetron 2mg (approximately 40 µg/Kg) used in this study was based on the report published by Fujii et al[15], as well as a previous study done in the Indian context[16]. The dose of ramosetron in our study (300 µg) was based on previous studies[17].

We could not find any report to compare the efficacy of granisetron and ramosetron for preventing PONV in caesarean section. Our results demonstrate that the antiemetic efficacy of ramosetron is similar to that of granisetron for preventing PONV during the first 24 hours (0–24 hours) after anesthesia and that ramosetron is more effective than granisetron for increasing a complete response (no PONV, no rescue) within the next 24 hours (24–48 hours). This is similar to a study done to compare these drugs in abdominal procedures[18]. This suggests that ramosetron has a more potent antiemetic effect that lasts up to 24 hours longer than granisetron. The exact reason for the difference in effectiveness between granisetron and ramosetron is not known but may be related to the elimination half-life (granisetron 3.1 ± 1.2 hours versus ramosetron 5.8 ± 1.2 hours) and/or more potent affinities of 5-HT_3 receptor antagonists[19].

Our study could be criticized because we use opioid analgesia (pethidine) perioperatively, a recognized cause of PONV[20]. But there is an association between pain and PONV[10,21], and treating pain with opioids may relieve PONV.[21,22] Both granisetron and ramosetron are much more expensive than other available antiemetics in our set up. However, we should also consider the outcome of the patients and overall cost of care if emesis was to occur, as single doses of both granisetron and ramosetron are effective for 24 hr or more.

In conclusion, prophylactic therapy with granisetron and ramosetron were both effective and comparable for prevention of post delivery emesis in the first 24 h, but ramosetron is a better prophylactic for PONV after 24 hr, leading to overall better patient satisfaction.

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Table I: Maternal Demographics

	Granisetron (n = 60)	Ramosetron (n= 60)
Age (years)	25.7 ± 3.5	26 ± 4.1
Weight (Kg)	56.8 ± 7.2	57.1 ± 7.7
Multipara (no.)	22	22
ASAGrade 1	51	49
ASAGrade 2	9	11
Baseline systolic blood pressure (mm of Hg)	124.6 ± 8.1	127.5 ± 7.7

[No significant difference]

Table II: Operative Management

	Granisetron (n = 60)	Ramosetron (n= 60)
Duration of Surgery (min)	48.2 ± 8.1	49.1 ± 7.6
Uterus exteriorised (no.)	56	55
Duration of uterus exteriorized (min)	18.1 ± 5.4	18.5 ± 6.7
Total ephedrine (mg)	6.5 (0-10)	7 (0-10)
No. of patients receiving intraoperative pethidine	18	17
Intraoperative pethidine consumption (mg)	27 ± 4.1 (25 - 50)	26.9 ± 4.1 (25 - 50)
Postoperative pethidine consumption (mg)	230.5 (180 - 360)	228.9 (180 - 360)

Figures in ( ) indicate ranges [No significant difference]

Table III: Number (%) of patients having complete response (i.e. no PONV), nausea, vomiting during initial 2 h (0-2 h) and the next 46 h (4-24 h and 24-48 h) after administration of spinal anaesthesia

	Granisetron (n= 60)	Ramosetron (n= 60)	P value
0-2 h after spinal anaesthesia			
Complete response (no PONV)	50 (83.3)	52 (86.6)	0.7
Nausea	5 (8.3)	4 (6.6)	0.7
Vomiting	5 (8.3)	4 (6.6)	0.6
2-24 hrs after spinal anaesthesia			
Complete response (no PONV)	51 (85)	53 (88.3)	0.5
Nausea	5 (8.3)	4 (6.6)	0.7

Vomiting	4 (6.6)	3 (5)	0.7
24 -48 hrs after spinal anaesthesia			
Complete response (no PONV)	42 (70)	55 (91.6)	0.004*
Nausea	10 (16.6)	3 (5)	0.04*
Vomiting	8 (13.3)	2 (3.3)	0.02*
Overall Satisfaction	27 (45)	45 (75)	0.031*

***p<0.05**

Table IV : Adverse effects

	Granisetron(n= 60)	Ramosetron (n= 60)
0-4 h after spinal anaesthesia		
Headache	8 (13.3 %)	7 (11.6 %)
Dizziness	5 (8.3 %)	3 (5 %)
Constipation	2 (3.3 %)	2 (3.3 %)
Myalgia	1 (1.6 %)	1 (1.6 %)
4-24 hrs after spinal anaesthesia		
Headache	7 (11.6 %)	8 (13.3 %)
Dizziness	3 (5%)	3 (5%)
Constipation	2 (3.3 %)	2 (3.3 %)
Myalgia	0	0
24 -48 hrs after spinal anaesthesia		
Headache	6 (10 %)	5 (8.3 %)
Dizziness	3 (5 %)	3 (5 %)
Constipation	4 (6.6 %)	4 (6.6 %)
Myalgia	0	0

Fig: I.