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RESEARCH ARTICLE

COMPARATIVE EVALUATION OF EFFICACY OF ONDANSETRON, GRANISETRON AND RAMOSETRON FOR PREVENTION OF NAUSEA AND VOMITING IN PATIENTS UNDERGOING CAESAREAN SECTION

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Abstract

Background: Ramosetron is a new selective 5-hydroxytryptamine type 3 (5-HT_3) receptor antagonist that reportedly has more potent antiemetic effects compared with other 5-HT_3 receptor antagonists. The purpose of this study was to compare the efficacy of Ramosetron with Ondansetron and Granisetron for the prevention of nausea and vomiting in patients undergoing caesarean section.

Method: In this prospective, randomized, double blind study, we have compared Ondansetron, Granisetron and Ramosetron for prevention of nausea and vomiting in patients undergoing elective caesarean section. 150 patients were divided into three groups: Group O (Ondansetron 4 mg), Group G (Granisetron 3 mg) and Group R (Ramosetron 0.3 mg). Incidence and severity of nausea and vomiting, use of rescue antiemetic and side effects and complications were evaluated during and upto 24 hrs after surgery.

Result: Complete response was maximum in group R (96%) and similar in group O and G (94%) during intraoperative period. It was observed in 80% patients in group O and 86% and 94% patients in group G and R respectively in early post operative period (0-6 hrs). The corresponding incidence in late post operative period (6-24 hrs) was 66%, 80% and 90% in group O, G and R respectively. No serious adverse effects were observed in any group.

Conclusion: Ramosetron followed by Granisetron is comparably better than Ondansetron for prophylaxis of nausea and vomiting during and after caesarean section.

INTRODUCTION

Nausea and vomiting is commonly experienced, unpleasant and distressing symptoms in patients following surgery. The overall incidence of nausea and vomiting averages between 25 and 30% of patients during caesarean section but has been reported to be as high as 80% without any pharmacological intervention [1, 2]. Conditions associated include age, female gender, type of surgical procedure, pre-operative medications, type and duration of anesthetic agents, history of postoperative nausea and vomiting (PONV), smoking status, and degree of postoperative pain [3-5]. The occurrence of nausea and vomiting after surgical procedures can result in delayed post-anesthesia care unit (PACU) discharge, unanticipated hospital admissions (for outpatient procedures), and extended length of stay; all of which may impact patient satisfaction and increase health care costs. There are four main classes of drugs for treatment of nausea and vomiting, anticholinergic, antihistaminic, D2 antagonist and 5-HT_3 antagonist. The introduction of 5- HT_3 antagonist is a major advancement in the treatment of nausea and vomiting due to less adverse effect than traditionally used antiemetic [6]. Ramosetron exhibits significantly greater binding affinity for HT_3 receptors with a slower dissociation rate from receptor binding, resulting in more potent and longer receptor antagonizing effects compared with older 5HT_3 antagonists [7]. This study aims to evaluate and compare

the efficacy of Ondansetron, Granisetron and Ramosetron for prevention of nausea and vomiting in patients undergoing caesarean section.

METHOD

After approval from institutional ethical committee, this prospective, randomized, double blind study was conducted in the Department of Anesthesiology and Critical Care, Pt J. N. M. Medical College, Raipur (Chhattisgarh), India. 150 patients of ASA grade I-II, aged 18-40 yrs scheduled for elective caesarean section under subarachnoid block were enrolled in the study. Exclusion criteria were patients having history of PONV, motion sickness, allergic to study drugs, drug or alcohol abuse, significant renal, hepatic, cardiac and coagulation abnormalities, known contraindication to subarachnoid block, patients who received antiemetic drugs within 24 hrs prior to surgery and refusal to enroll in the study.

After preanesthetic examination, patients were explained about the procedure and informed written consent was obtained. All the parturients were randomly allocated into one of the three treatment groups: Group O (Ondansetron 4 mg), Group G (Granisetron 3 mg) and Group R (Ramosetron 0.3 mg) of 50 each by card sampling method. Every parturient included in the study were allowed to choose a card in the preoperative period. A randomization list was generated and syringes containing each drug were prepared and administered by the person not involved in the study. Patients and investigators who collected the data were blinded to the study drug administered. After shifting patient on operation table multipara monitor was connected and all the parameters (Pulse, BP, ECG, SpO_2, RR, and $EtCO_2$) were recorded. Pre-hydration was done with IV Ringer lactate 10-15ml/kg body weight immediately before administration of subarachnoid block. Under all aseptic precautions lumber puncture was performed with 25/26 gauge Quincke's needle in the L_3-L_4 or L_4-L_5 space in left lateral decubitus position using midline technique. After confirming free flow of CSF, 0.5% hyperbaric Bupivacaine 2 ml (10 mg) was injected and patients were immediately turned to supine position. A wedge of 15^0 was placed under the right hip. Supplemental oxygen (2 l/min) was administered via nasal prongs to all the parturient. After due confirmation of subarachnoid block by loss of sensation to cold and pinprick at T_4-T_5 level, surgery was started. After delivery of baby and clamping of umbilical cord IV oxytocin 10 unit was administered. Study drug was administered intravenously according to the group assigned [8-10]. Maternal hypotension after SAB was treated by increasing the rate of IV fluid administration and/or by injecting ephedrine 5-10 mg IV. Diclofenac 75mg IM was given 2 hrs after completion of surgery and further advised as twice a day dose or on request from patient for postoperative analgesia. Vital parameters were recorded at every 5 min intervals up to 20 min, thereafter every 10 min intervals till the end of procedure and hourly for the first 3 hrs, at 12 hrs and at 24 hrs postoperatively.

Nausea was defined as a subjective unpleasant sensation associated with urge to vomit. Vomiting was defined as forceful expulsion of gastric contents from the mouth. Complete response was defined as no emetic symptoms and no need for another rescue antiemetic. The intensity of nausea and vomiting was assessed in intraoperative, early postoperative (end of surgery upto 6 hrs) and late postoperative (6 hrs - 24 hrs) period by **Nausea and Vomiting Score** (0 - complete response, 1 - nausea only, 2 - nausea & vomiting) [11]. The intensity of nausea episode was assessed using a 100 mm **Visual Analogue Scale (VAS)** (0 = No nausea, 100 = Severe nausea) [12]. Rescue antiemetic IV metoclopromide 10 mg was given if vomiting occurred once or nausea of VAS score >40 or at the patient request. The degree of overall satisfaction with management of nausea and vomiting was assessed and asked by patient at the end of observation period (24 hrs) by **Patient Satisfaction Score** (Grade 0 = Poor, Grade 1 = Adequate, Grade 2 = Good, Grade 3 = Excellent) [12]. Adverse effects of study drug like headache, constipation, dizziness and any other symptoms (flushing, diarrhoea, hypotension, ECG changes, extrapyramidal and allergic reactions) were recorded. Apgar score was not recorded in our study because study drug was administered after clamping of umbilical cord [8-10].

The collected data were tabulated and analyzed by various statistical techniques like percentage, mean and standard deviation. Significance of difference between mean of the groups was found by paired t- test.

RESULT

The patients characteristic, indication and duration of surgery was not statistically significant amongst all groups (Table-1). There was no significant difference in the measured mean arterial pressure, systolic and diastolic blood pressure, heart rate, respiratory rate and $EtCO_2$ amongst all groups. No significant fall in BP was observed after spinal anesthesia in all groups.

Table 1: Demographic Profile

Variables	Range	Group O (Mean±SD)	Group G (Mean±SD)	Group R (Mean±SD)	p Value		
					O-G	O-R	G-R
Age (yrs)	18-40	23.92±3.34	26.46±3.58	23.88±2.21	>0.05	>0.05	>0.05
Weight (kg)	45-65	54.84±8.23	50.16±5.12	49.12±16.35	>0.05	>0.05	>0.05
Duration of surgery (min)	45-65	50.1±7.52	48±6.30	50.1±7.52	>0.05	>0.05	>0.05

Table 2: Nausea and Vomiting Score

Score	Intraoperative			Early postoperative			Late postoperative		
	Group O n(%)	Group G n(%)	Group R n(%)	Group O n(%)	Group G n(%)	Group R n(%)	Group O n(%)	Group G n(%)	Group O n(%)
0	47 (94)	47 (94)	48 (96)	40 (80)	43 (86)	47 (94)	33 (66)	40 (80)	45 (90)
1	3 (6)	3 (6)	2 (4)	7 (14)	5 (10)	3 (6)	12 (24)	8 (16)	5 (10)
2	0 (0)	0 (0)	0 (0)	3 (6)	2 (4)	0 (0)	5 (10)	2 (4)	0 (0)

Table 3: Rescue antiemetic

Intraoperative			Early postoperative			Late postoperative		
O n (%)	G n (%)	R n (%)	O n (%)	G n (%)	R n (%)	O n (%)	G n (%)	R n s(%)
0 (0)	0 (0)	0 (0)	5 (10)	2 (4)	0 (0)	10 (20)	2 (4)	0 (0)

Table 4: VAS Score

Group O	Group G	Group R	p Value		
			O-G	O-R	G-R
Early Postoperative (0-6 hr)					
16.8±13.59	10.6±12..34	8.5±11.21	**<0.05**	**<0.001**	**<0.001**
Late Postoperative (6-24 hr)					
26.9±23.79	12.8±23.31	4.9±9.31	**<0.05**	**<0.001**	**<0.001**

Table 5: Adverse Effects

Adverse effects	Group O n (%)	Group G n (%)	Group R n (%)
Headache	5 (10)	5 (10)	3 (6)
Constipation	2 (4)	1 (2)	2 (4)
Dizziness	2 (4)	2 (4)	2 (4)
Others	0 (0)	0 (0)	0 (0)

Table 6: Patient Satisfaction Score

Score	Group O n (%)	Group G n (%)	Group R n (%)
Excellent	6 (12)	10 (20)	13 (26)
Good	21 (42)	20 (40)	25 (50)
Neutral	18 (36)	15 (30)	10 (20)
Dissatisfied	5 (10)	5 (10)	2 (4)

DISCUSSION

Nausea and vomiting during regional anesthesia for caesarean section is very high without prophylactic antiemetic [9]. The etiology of emetic symptoms is complex. During caesarean section, the physical disruption and manipulation of abdominal viscera may cause the release of humoral substances including 5-HT_3, which may stimulate 5-HT_3 receptors on the afferent vagus nerves triggering the emetic reflex especially in awake patients [13]. Sympathetic block secondary to regional anaesthesia results in nausea and vomiting induced by gastrointestinal hyperactivity due to relative overactivity of the vagus.There is no control group in our study as Aspinall and Goodman (1995) have suggested that placebo controlled study may be unethical if active drugs are available because PONV are common and distressing symptoms against which there is effective treatment [14].

In our study during intraoperative period complete response was maximum in group R (96%) and similar in group O (94%) and G (94%). Incidence of nausea in group O and G was 6% while it was 4% in group R. None of patients of any group had vomiting during intraoperative period. No statistically significant difference were found between O vs G, O vs R and G vs R ($p>0.05$). Similar studies done previously by Fujji et al, Garcia-Miguel FJ et al and Pan PH et al for granisetron and ondansetron found same results as they also found complete response in maximum patients during intraoperative period and none of their patient required antiemetic [8-10].

Our study suggests that antiemetic efficacy between ondansetron and ramosetron is statistically significant in early postoperative period (0-6 hr). However, there were no significant difference between group O vs G and group R vs G during first 6hrs postoperatively. A similar study was undertaken by Fujji et al for prevention of PONV after laparoscopic cholecystectomy and complete response was 85% with granisetron and 93% with ramosetron ($p>0.05$) [12]. Their results were comparable to our study. In another study done by Fujji et al complete response was 87% and 90% with granisetron and ramosetron respectively [15]. Yamac et al also observed similar incidence of nausea and vomiting with ondansetron (10% and 10%) and Granisetron (5% and 10%) [16]. Lee J W et al and Kim S I et al also found higher incidence of nausea and vomiting in patients receiving ondansetron and ramosetron during 0-2hr postoperatively [7,17]. Higher incidence of PONV in their study could be attributed to use of general anesthesia and study in highly susceptible women (non-smoker, those receiving opioid based patient controlled analgesia. Dipasari Bhattacharya et al also observed higher incidence of vomiting with ondansetron (20%) and granisetron (7%) which could be attributed to laparoscopic surgery [18].

In late postoperative period (6-24 hr) we found ramosetron better in preventing nausea and vomiting than ondansetron and granisetron. Incidence of complete response was 66%, 80% and 90% with group O, G and R respectively. 24% patients had nausea and 10% patients had nausea and vomiting in group O, 16% of patients had nausea and 4% had vomiting in group G while only 10% patients had nausea and none of them had vomiting in group R during 6-24 hrs postoperatively. Fujji et al found similar incidence of complete response, nausea and vomiting which were 85%, 8% and 7% with granisetron while 90%, 5%and 5% with ramosetron respectively during 3-24 hr period [15]. In another study Fujji et al found similar incidence of complete response (85%), nausea (10%) and vomiting (5%) with granisetron [8]. Yamac Erhan et al also observed same incidence of nausea & vomiting with ondansetron (0% and 5%) and granisetron (10% and 0%) during 6-24hr postoperatively [16]. Kim SI et al and Lee JW et al found higher incidence of nausea & vomiting with ondansetron and ramosetron in late postoperative period also due to preponderance of patient undergoing laproscopic surgery and opioid based postoperative analgesia [7,17]. The reported efficacy of ramosetron is similar to that of granisetron in the cisplatin induced emesis. However, ramosetron appear to have a longer duration of action during the 24 hr after cisplatin chemotherapy [19, 20]. In addition, it has been reported that ramosetron was comparable with granisetron to prevent PONV 0-2 hr after surgery but ramosetron was more effective than granisetron for preventing PONV 24-48 hr after surgery [12, 15].

Although efficacy of ramosetron has been shown similar to granisetron for prevention of nausea and vomiting, but it is superior to ondansetron and granisetron for reducing the requirement of rescue antiemetics. In group O 10% and 20% patients required rescue antiemetic in early and late postoperative period. 8% of patients of

group G & none of the patient in group R required rescue antiemetic in postoperative period up to 24 hr. In study of Fujji et al [15] none of patient required rescue antiemetic in group G & R while Yamac et al [16] found 10% patient required antiemetic in granisetron and Kim et al [7] found 15% patient required antiemetic with ramosetron because there were higher incidence of PONV in their study due to laparoscopic surgery. Bordner et al found higher incidence of requirement of rescue antiemetic (43%) with ondansetron due to patients undergoing laparoscopic surgery [21].

In our study mean VAS was statistically significant between group O vs G and highly significant between group O vs R and G vs R. Fujii Y et al also observed similar results (mean VAS <10) with granisetron and ramosetron. Kim SI et al showed higher mean VAS score with ondansetron and ramosetron in the patients undergoing laparoscopic surgery.

The most frequently reported adverse events of 5-HT_3 receptor antagonists are dizziness and headache. Similar results were observed by Kim SI et al, Pan PH et al, Lee JW et al, and McKenzie R et al [7, 10, 17, 20]. Adverse effects observed in our study were similar in all three groups. No significant difference was found amongst all groups in patient satisfaction score which is comparable to Fujji et al & Kim et al [12, 7]. Only 10% patients of group O and G and 4% patients of group R were not satisfied because they had experienced headache and/or vomiting in postoperative period.

CONCLUSION

Ramosetron and granisetron appreciably and remarkably reduced nausea and vomiting during and after surgery. Ondansetron reduced nausea and vomiting upto 6 hrs but as its half life is short ($t_{1/2}$-3.5 hrs), it was not that effective in late postoperative period.

To conclude Ramosetron followed by granisetron are comparably better than ondansetron for prophylaxis of nausea and vomiting during and after caesarean section. Ramosetron and granisetron are highly effective upto 24hrs with single dose, and are devoid of many side effects associated with traditional antiemetics.

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