ROLE OF RAMOSETRON AND ONDANSETRON IN LUCS AND LOWER LIMB SURGERY UNDER SPINAL ANAESTHESIA

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ABSTRACT

BACKGROUND

Death or serious morbidity resulting directly from anaesthesia is now extremely rare. However, postoperative nausea and vomiting (PONV) is still very common. Therefore, every anaesthetist must be aware of the physiology of PONV and its consequences, causes, associated factors and management. Postoperative Nausea and Vomiting (PONV) after spinal anaesthesia for caesarean delivery and lower limb surgery (LLS) are distressing to both patients and surgeons. Spinal anaesthesia has been shown to be an easy, rapid and safe technique.

Objective- To determine the efficiency of ramosetron and ondansetron in terms of prevention of nausea and vomiting intraoperatively and postoperatively in LSCS & LLS patients under spinal anaesthesia.

MATERIALS AND METHODS

Study Design- Randomised, double-blind study.

In this randomised, double-blind study, 60 patients received either ondansetron (4 mg) or ramosetron (0.3 mg) intravenously 10 min. before the administration spinal anaesthesia. 60 patients of age group 20-30 years, ASA Grade I & ASA Grade II, body weight ranging from 45-65 kg were studied. All the patients were subjected to elective caesarean section or LLS under spinal anaesthesia. They were randomly allocated into two groups namely study group (30 patients received inj. ramosetron 0.3 mg IV) and control group (30 patients received inj. ondansetron 4 mg IV). Patients were observed intraoperatively, in the recovery room and in the ward up to 24 hours. For episodes of nausea and vomiting, Rescue antiemetic was given if the patients had PONV score 2 and was recorded. All the patients were observed for side-effects such as dizziness, headache, sedation or extrapyramidal reaction and accordingly up to 24 hours.

RESULTS

Incidence of nausea and vomiting in immediate postoperative period was 10% in study group compared to 20% in control group. Dizziness and headache were comparable in both the groups.

CONCLUSION

Ramosetron is quite effective to prevent nausea and vomiting in LSCS & LLS patients under spinal anaesthesia. It reduces the incidence of nausea and vomiting intraoperatively and in the immediate postoperative period.

KEYWORDS

Spinal Anaesthesia, Caesarean Section, Lower Limb Surgery, Ramosetron, Postoperative Nausea and Vomiting, Ondansetron.

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BACKGROUND

In lower segment caesarean section (LSCS) & Lower limb surgery (LLS), spinal anaesthesia has become increasingly popular in recent years and is now a commonly performed surgical procedure. Regional anaesthesia is performed in 80% of anaesthetised patients compared to 20% who received general anaesthesia.^[1,2] Consciousness allows the patients to enjoy the early immediate contact with the newborn child (bonding), the procedure may be associated with various important problems,^[3] like arterial hypotension, headache, insufficient anaesthesia and psychological distress.^[4] A common problem in caesarean section & LLS is intra and postoperative nausea and vomiting under regional

anaesthesia.^[5,6] 72% of patients are afraid of nausea and vomiting and 71% feel significant discomfort. Previous reports and our observations suggest both nausea and vomiting as frequent phenomenon, with the incidences up to 80%.^[7,8] The major risk factors for nausea and vomiting during or after spinal anaesthesia in caesarean section & lower limb surgeries is arterial hypotension due to blockade of the sympathetic nerve system.^[9] Critical anaesthesiological complications such as airway obstruction, aspiration pneumonitis, and wound dehiscence are rare and mainly related to postoperative nausea and vomiting in general surgical patients.^[10,11,12] Nausea and vomiting may be influenced by hormonal changes in pregnancy, which alter the sphincter tone of the oesophagus and the stomach and the activity of small bowel and oesophagus, as well as adverse effects of uterotonic drugs, intraoperative manipulation of the uterus and psychological distress aggravated by insufficient anaesthesia.^[13,14,15] Vomiting centre represents several nuclei in the brainstem (e.g. nucleus tractus solitarius, area postrema), which are responsible for the co-ordination of the efferent limb of the vomiting reflex. It receives input from the afferent limbs of the reflex and the area postrema. The area

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postrema is located at the caudal end of the floor of the fourth ventricle known as Chemoreceptor Trigger Zone (CTZ). Evidence from ablation studies by Borison and Wang in the 1950s and the fact that the blood-brain barrier is defective in this area suggest that the area postrema is responsible for detecting toxins circulating in the blood and cerebrospinal fluid. This function is the nearby nucleus tractus solitarius where dopamine and opioid receptors are abundant.^[16]

Afferent limb of vomiting reflex from mechano- and chemoreceptors in the gastrointestinal tract is relayed via vagus nerve to the nucleus tractus solitarius in the brainstem. Abnormal gastric or intestinal distention, increased smooth muscle contraction and abnormal or toxic gastrointestinal contents can trigger the vomiting reflex. Peripheral 5-HT₃ receptors are intimately involved. Radiation, chemotherapy and other toxins release 5-HT from chromaffin cells in the gut, which stimulates vagal afferents –a process inhibited by the 5-HT₃ antagonist antiemetics. Afferent inputs also come from the vestibular system and the higher centres. Miscellaneous inputs come from nasopharyngeal tube, stimulation of the auricular branch of vagus and also pain pathways from the viscera reside in the splanchnic nerves and visceral pains. [Vide-Table-1, Vomiting reflex].

Nausea is not an inevitable consequence of vomiting but it is often a troublesome symptom after surgery and anaesthesia. However, a consistent finding is that antiemetic therapy is often very effective in reducing the incidence of vomiting or retching, but less so far nausea.

The potential adverse effects of PONV causes aspiration of stomach contents which increases the anaesthetic mortality and morbidity.

Oral administration of drugs (e.g. analgesics, antihypertensives), fluids and nutrients delay discharge from day care surgery and may disrupt neck, abdominal and eye sutures by PONV. A previous history of PONV, motion sickness, children and female gender are the major risk factors. Surgical factors associated with an increased risk of PONV are Gynaecological, ENT, Gastrointestinal, Head and Neck and squint surgery, duration of surgery and postoperative antibiotics. Perioperative use of opioids (oral, IM, epidural, spinal) is associated with an increased incidence of PONV and many anaesthetic techniques aim to avoid opioids for this reason. PONV may indicate postoperative hypotension, hypoxaemia, early fluid intake or mobilisation, psychological factors play an important role and may respond to appropriate non-pharmacological management. Dexamethasone and cannabinoids (e.g. nabilone, dronabinol) are effective against chemotherapy-induced emesis. Metoclopramide acts at the dopamine receptors in the stomach, upper intestine and CTZ. It enhances gastric emptying, intestinal transit and lower oesophageal sphincter pressure. The side effects of metoclopramide are extrapyramidal reactions, facial muscle spasm, trismus, oculogyric crises, opisthotonus hypotension, sinus tachycardia, supraventricular tachycardia.

Ondansetron was the first specific potent 5HT₃ receptor antagonist available for PONV. Oral bioavailability is 60% and elimination half-life is 4h. Granisetron, tropisetron and dolasetron have similar pharmacological properties. Major advantages of 5HT₃ receptor antagonists are wide therapeutic index, no extrapyramidal side-effects, no excessive sedation and no prolongation of recovery from anaesthesia.^[17]

Many drugs are used for management of PONV but few of them have side effects like sedation, dryness of mouth, restlessness and tachycardia. 5HT₃ receptors antagonists are devoid of such side-effects. Ondansetron, granisetron and newer drug such as ramosetron and palonosetron are commonly used drugs to prevent PONV.^[18]

Objectives

To determine the efficiency of ramosetron and ondansetron in terms of prevention of nausea and vomiting intraoperatively and postoperatively in LSCS & LLS patients under spinal anaesthesia in terms of prevention of nausea and vomiting intraoperatively and postoperatively.

MATERIALS AND METHODS

In this randomised, double-blind study, 60 patients received either ondansetron (4 mg) or ramosetron (0.3 mg) intravenously 10 min. before the administration of spinal anaesthesia. The study was done at Murshidabad Medical College & Hospital & B. S. Medical College, Bankura, West Bengal during the period of July 2016 to June 2017. From the existing research, it was noted that around half of the patients who underwent spinal anaesthesia developed nausea and/or vomiting. Assuming the 50% reduction in nausea/vomiting by giving ramosetron over ondansetron, 95% confidence level, the final sample size per group using the following formula was 27, which was rounded off to 30. $n = Z_{\alpha/2}^2 [P_1(1-P_1) + P_2(1-P_2)] / (P_1 - P_2)^2$; where Z_{α} for 95% confidence level is 1.96, $P_1=0.5$ and $P_2=0.25$.

So, 60 patients of age group 20-30 years, ASA Grade I & ASA Grade II, body weight ranging from 45-65 kg were studied. All the patients were subjected to elective caesarean section & LLS under spinal anaesthesia. Block randomisation method with a block of four was used to allocate patients into two groups namely study group (30 patients received inj. ramosetron 0.3 mg IV) and control group (30 patients received inj. ondansetron 4 mg IV) by the investigators and coded accordingly. The codes were neither disclosed to the concerned Anaesthetist and the team, nor to the patient. Patients with H/O diabetes mellitus, allergic to local anaesthetic, with hepatic disorders and taking antiemetic medication were excluded in our study. After pre-anaesthetic evaluation and investigation, the patient was explained about the procedure. Informed consent was taken. Baseline vital parameters were recorded.

There were no significant differences between two groups regarding patients' characteristics (age, body weight, height and previous history of motion sickness and PONV), type of anaesthesia and preoperative starvation. All the patients were preloaded with RL 10 mL/kg to prevent intraoperative hypotension followed by nausea and vomiting. All patients were premedicated with midazolam 3.75 mg orally 1 hour before transfer to the operating theatre. Spinal anaesthesia was induced in sitting position between L3/L4 with 0.5% hyperbaric bupivacaine with 25/26G spinal needle. Dosage depended on the body height. Body height 150 cm resulted in 1.8 mL bupivacaine 0.5%, every 5-cm additional height resulted in an additional 0.2 mL bupivacaine dosage.

Patients were observed intraoperatively, in the recovery room and the ward up to 24 hours for episodes of nausea and vomiting or retching which were evaluated on 3-point PONV score (0- no nausea & vomiting, 1- episode of nausea, 2-

retching and vomiting) for next 24 hrs. Rescue antiemetic was given for the patients with PONV score 2 and was recorded. All the patients were observed for side-effects such as dizziness, headache, sedation or extrapyramidal reaction and treated accordingly up to 24 hours.

Data were analysed using unpaired "t" test, chi square and chi square for trend test using MS excel and Epi Info 3.4 software and p value<0.05 was Considered Statistically Significant. Data was presented as mean $\pm$ standard deviation and percentage.

RESULTS

There were 60 patients who underwent randomisation into two groups. 30 patients (Study group) received ramosetron and another 30 patients (Control group) received ondansetron. The demographic data with respect to age, sex, height and weight were comparable in both groups (Table 2). There was no statistically significant difference in respect to duration of surgery and duration anaesthesia in both the groups. When PONV score was 2, rescue antiemetic was given (i.e. 6.66% in study group). Incidence of side effects (headache, constipation and dizziness) was comparable in both the groups (Table 5).

Figure 1. Shows the Vomiting Reflex

Study Group		Control Group	P Value
Age (Years)	24.22 $\pm$ 2.56	24.66 $\pm$ 2.62	P>0.05 NS
Height (Cm)	154.36 $\pm$ 8.86	157.42 $\pm$ 9.56	P>0.05 NS
Weight (Kg)	65.2 $\pm$ 4.8	64.2 $\pm$ 4.6	P>0.05 NS
Duration of Surgery (min.)	40.26 $\pm$ 6.6	41.43 $\pm$ 6.8	P>0.05 NS

NS-Not Significant.

Table 2. Demographic Profile

Study Group			Control Group	
No. of Patients (n=30)		%	No. of Patients (n=30)	%
Nausea Immediately	3	10%	6	20%
0-3 hrs.	2	6.66%	3	10%
3-6 hrs.	0	0%	2	6.66%
6-12 hrs.	0	0%	0%	0%
12-24 hrs.	1	3.3%	2	6.66%
Total	6	19.96%	13	42.32%

Table 3. Distribution of Patients Experiencing Nausea in First 24 Hours

PONV Score Study Group			Control Group	
	No (n=30)	(%)	NO (n=30)	(%)
0 (No nausea & vomiting)	22	(73.34%)	14	(46.67%)
1 (Episode of vomiting)	6	(20%)	11	(36.67%)
2 (Episode of retching, vomiting)	2	(6.66%)	5	(16.67%)
Total	30	(100%)	30	(100%)

Table 4. PONV Score

Chi square for trend= 4.105; p = 0.0427

Study Group			Control Group	
Complications				
No (n=30)		(%)	NO(n=30)	(%)
Dizziness	11	(36.66%)	9	(30%)
Headache	6	(20%)	5	(16.66%)
Satisfaction				
Satisfied	24	(80%)	18	(60%)
Unsatisfied	6	(20%)	12	(40%)
Table 5. Side Effects and Patient Satisfaction				

Table 5. Side Effects and Patient Satisfaction

Chi sq = 2.86; p = 0.09

In the early postoperative period (immediately), the incidence of nausea was 20% in the control group and was 10% in study group. Within 0-3 hrs., the incidence of nausea was 10% in control group and 6.66% in study group. Within 12-24 hrs., the incidence of nausea was 6.66% in control group and 3.3% in study group.

PONV score 0 (no nausea & vomiting) was observed in 53.34% in control group and 73.34% in study group. PONV score 2 (Episode of retching, vomiting) was 13.33% in control group and 6.66% in study group. Dizziness was 30% in control group and 36.66% in study group. Patient's satisfaction was 80% in study group and 60% in control group.

DISCUSSION

The study was conducted on the background that an optimal perioperative patient comfort is of outstanding interest and nausea & vomiting with average incidence of 30% is rated as one of the most undesirable events in the context of surgery and anaesthesia.^[19,20,21] Therefore, every attempt should be made, especially in context of birth, to avoid this complication, which is an unpleasant adverse effect, but also may cause severe complications such as wound dehiscence, dehydration, aspiration or pneumothorax.^[10,11] There were no definite studies performed regarding comparison of ramosetron and ondansetron in LSCS & LLS patients under spinal anaesthesia.

In our study, we have observed number of patients who had episodes of nausea and vomiting in LSCS & LLS patients under spinal anaesthesia. Ramosetron, recently developed selective 5HT₃ receptor antagonist. It shows significantly greater affinity for 5HT₃ receptors, resulting in more potent, longer receptor antagonising effects compared to older 5HT₃ antagonist.^[22,23]

Ramosetron is more potent and has longer duration of action than granisetron in prevention of emesis after Cisplatin therapy and prevention of PONV.^[24]

Choi and Colleagues reported that ramosetron IV was better than ondansetron IV in reducing the severity of nausea, incidence of vomiting and the rescue antiemetics at 6-24 hrs. after operation in patients who have undergone spinal surgery.^[25]

PONV score was 0 in 73.4% patients in study group (Ramosetron group) as compared to 53.4% patients in control group (Ondansetron group) in our study.

It suggests that ramosetron is quite effective in controlling nausea and vomiting in both intraoperative and postoperative period.

Fujii et al reported that ramosetron is effective in preventing PONV after major gynaecological surgery.^[26]

In our study, ramosetron 0.3 mg was effective in reducing the incidence of PONV (26.66% in study group versus 46.66% in control group).

Kim et al performed similar study in gynaecological surgery and they have observed similar results as well.^[27]

The most frequently reported adverse events of 5HT₃ receptor antagonists are dizziness and headache.^[28] Adverse events observed in our study were similar in both the study and control groups.

CONCLUSION

On the basis of the present study, it can be concluded that inj. ramosetron 0.3 mg IV is much more effective for prevention of postoperative nausea and vomiting in LSCS and LLS patients under spinal anaesthesia. Ramosetron seems to be a useful alternative and relatively a safe drug for effective antiemetic prophylaxis. It also reduces the PONV score and incidence of nausea in both the groups.

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