Original Article

Indian Journal of Anaesthesia and Analgesia
Volume 4 Number 1, January - March 2017
DOI: http://dx.doi.org/10.21088/ijaa.2349.8471.4117.21

Study of Effect of Ramosetron and Granisetron in Prevention of Post Operative Nausea and Vomiting Following Laproscopic Cholecystectomy

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Abstract

Background: Post operative nausea and vomiting following laparoscopic cholecystectomy is a common complication. This study was designed to analyze and compare efficacy and adverse effect of ramosetron and granisetron in prevention of post operative nausea and vomiting following laparoscopic cholecystectomy.

Method: 100 patients of American Society of Anesthesiologists class I-II, aged 25 to 55 years scheduled for laproscopic cholecystectomy were included in study. Patients with history of smoking, drug or alcohol abuse, known allergy to granisetron or ramosetron, impaired kidney or liver function, motion sickness and history of previous post-operative nausea and vomiting, or those who received antiemetics within 24 hours before scheduled surgery, menstruating, pregnant or lactating women, or those on whom laparoscopic cholecystectomy was converted into open cholecystectomy were excluded from the study. 100 patients were divided into 2 groups of group A and Group B of 50 patients each. Group A patients received 2 mg of granisetron diluted to make 4ml in normal saline and group B patients received 0.3 mg of ramosetron diluted to make 4ml in normal saline given at the end of surgery

Results: No significant statistical difference seen immediately after extubation and 0 to 6 hrs and 6 to 12 hrs. but statistically significant result was observed 12 to 18 and 18 to 24 after surgery.

Conclusion: Ramosetron provides prolonged relief from post operative nausea vomiting as compared to granisetron in laproscopic cholecystectomy .

Keywords: Granisetron; Ramosetron; Laproscopic Cholecystectomy; Nausea Vomiting.

Introduction

Postoperative nausea and vomiting (PONV) is one of the most common complaints following anaesthesia and serious complications of clinical concern in the postoperative period and is often associated with increased morbidity of postoperative bleeding, wound dehiscence, fluid and electrolyte imbalance, delayed hospital discharge, and decreased satisfaction in surgical patients [1]. The main patient related factors are age, gender, history of motion sickness, previous nausea and vomiting, pregnancy , surgery within 1-7 days of menstrual cycle ,patients not smoking [2-6]. Laparoscopic cholecystectomy, a popular alternative to open cholecystectomy is associated with excessive episodes of nausea and vomiting in the postoperative period [7].

A variety of drugs are being used include include anticholinergics, phenothiazines, antihistamines, butyrophenones, benzamides and steroids. Some of these antiemetics are associated with adverse effects such as restlessness, dry mouth, sedation, hypotension, extrapyramidal symptoms and dystonic effects [8]. An ideal antiemetic should have quicker onset and longer duration of action and no or minimal undesired effects. The newer 5-HT3 receptor antagonists, is generally superior to the traditional antiemetic[2,4,8]. Therefore the present study was conducted to study the efficacy of a newer 5-HT3 receptor antagonists, ramosetron and its comparison with granisetron in prevention of postoperative nausea and vomiting following

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Received on 24.12.2016
Accepted on 29.12.2016

laparoscopic cholecystectomy. Granisetron is indicated in prevention of nausea and vomiting associated with surgery and anesthesia (i.e., PONV), and that associated with treatment of cancer by chemotherapy [4,7,8,9]. The dose in adults and children is i.v. 40 mcg/kg [2,4,8,9]. Adverse effects include decreased gastrointestinal motility, headache, diarrhoea, somnolence, dizziness.and dyspepsia [4,9].

Ramosetron, a newer antiemetic with adult dose of 0.3 mg intravenously once a day has high bioavailability and elimination half life of 9 hours. It makes it more potent with a longer duration of action than older 5-HT3 receptor antagonists [1]. Paediatric dose has been found to be 6 mcg/kg in 4-10 years of age[1]. Adverse side effects include headache, dizziness, diarrhoea, constipation, drowsiness, sedation, muscle pain[10].

Materials and Methods

This prospective randomized double blind study was conducted in the Department of Anaesthesiology at Indira Gandhi Institute of Medical Sciences, Patna, Bihar from September 2014 to July 2015. 100 patients divided in two groups of 50 each of ASA grade I and II, aged between 25 and 55 years who gave written informed consent years were included in the study. Sample size has been estimated based on an alpha error of 0.05 and a power of 80%. Patients with history of smoking, drug or alcohol abuse, known allergy to granisetron or ramosetron, impaired kidney or liver function, motion sickness and history of previous post-operative nausea and vomiting, or those who received antiemetics within 24 hours before scheduled surgery, menstruating, pregnant or lactating women, or those on whom laparoscopic cholecystectomy was converted into open cholecystectomy were excluded from the study. After approval by institutional ethical committee 100 patients were randomised using computer generated sequence into two groups of 50 each Group A: were to receive 2 mg of granisetron ; Group B: Patients were to receive 0.3 mg of ramosetron . Blinding was done by closed envelop technique On the day before the surgery all the patients were clinically evaluated, assessed and investigated .The study protocol was explained and written informed consent was taken from each participant. All patients received oral pantoprazole 40mg as pre anesthetic medication at 6AM on the day of surgery. In operation theatre after securing intravenous line, standard monitoring including ECG, NIBP and pulse oximetry were attached and base line parameters recorded. General anesthesia was induced with intravenous fentanyl 2mcg/kg, propofol 2 mg /kg followed by atracurium 0.5 mg/kg to facilitate insertion of endotracheal tube of appropriate size. A nasogastric tube was inserted and suction applied to empty stomach of air and other contents. Anaesthesia was maintained with isoflurane in a mixture of oxygen and nitrous oxide. Intra operative muscle relaxation was achieved with atracurium as required. Ventilation was mechanically controlled and adjusted to maintain $ETCO_2$ at 30-40 mm Hg with an Anaesthetic/Respiratory analyzer (Drager Fabius GS). During surgery patients were positioned in the reverse trendlenburg position with the right side of the table elevated. The abdomen was insufflated with carbon dioxide to an abdominal pressure of 10 to 14 mm Hg. Intraoperative monitoring including ECG, pulse oximetry, $ETCO_2$, systolic, diastolic and mean blood pressure were recorded after every 5 minutes**.** Boluses of injection fentanyl 1mcg/kg intravenously were given if the heart rate and blood pressure increased more than 30% of the preoperative baseline. Injection paracetamol 15mg/kg and diclofenac sodium aqueous 75 mg was given via intravenous infusion unless contraindicated and was given during maintenance also. Duration of anaesthesia, surgery and carbon dioxide insufflations was recorded as per the proforma .Drug was prepared by a trained nurse in 5 ml syringe diluted to 4 ml with normal saline, and given towards the end of the procedure. Patients enrolled in the granisetron group received 2 mg IV of granisetron and those in the ramosetron group received 0.3 mg IV of ramosetron towards the completion of the surgical procedure. After completion of surgery, neuromuscular blockade was reversed with neostigmine 0.04 mg/kg and glycopyrolate 0.01mg/kg. Before extubation of trachea, the nasogastric tube was again suctioned and then removed. When adequate spontaneous ventilation was established, muscle relaxation reversed and patient was following commands, tracheal extubation was done. The incidence of nausea and vomiting was recorded immediately after extubation and every 6 hours for a period of 24 hours by direct questioning to the patient or to his attendant by the same anesthetist. Nausea and vomiting were evaluated on a three point scale as per the proforma 0 =none; 1 =nausea; 2=vomiting Adverse effects, if any, were recorded in all patients. Student t test (unpaired two tailed) has been used to find the significance of age, weight and duration of anesthesia, surgery and CO_2insufflation between two groups. Chi square/ Fischer exact test has been used to find the significance

of incidence of nausea and vomiting between the two groups of patients. A p-value <0.05 was considered significant. Clinical Trials Registry India (CTRI) registration number is CTRI/2015/09/009815.

Results

There was no statistically significant difference (p > 0.05) among the groups in respect of age, weight, duration of anesthesia, surgery and duration of CO_2 insufflation (Table 1).

Immediately after extubation, 0-6 hours and 6-12 hours the difference of incidence of nausea was statistically insignificant but at 12-18 hours and 18-24 hours it was statistically insignificant (p value > 0.05) [Table 2a,b,c,d,e].

The most common side effects of the drugs in the two groups observed in our study were headache (12%in granisetron group and 10% in ramosetron group), and dizziness (6% in granisetron group and 4% in ramosetron group which was not statistical significant between the two groups.

Table 1: Demographic profile of patients

	Demographic Profile	Granise Tron	Ramose Tron	P value
1	Age (yrs)	40.14±8.42	39.76±8.64	0.8262
2	Weight (kg)	53.20±8.76	52.84±7.58	0.8269
3	Duration of Anesthesia (minutes)	46.48±7.14	46.36±4.15	0.8856
4	Duration of Surgery	34.54±3.66	34.02±2.80	0.4268
5	Duration of CO_2 Insufflation (minutes)	28.10±3.16 minutes	27.18±2.24 minutes	0.0962

Table 2: Post operative nausea and vomiting score at a) immediately after extubation, b) 0-6hours, c) 6-12 hours, d) 12-18hours, e) 18-24 hours.

Table 2a: Post operative nausea and vomiting score immediately after extubation

	Granisetron		Ramosetron		Pvalue	Remarks
PONV score	No	%	No	%		
Nausea	5	10	4	8	1.000	Not Significant
Vomiting	2	4	1	2	1.000	Not Significant
Rescue antiemetic required	2	4	1	2	1.000	Not Significant

Table 2b: Post Operative Nausea and Vomiting (Pony) score 0-6 hours after extubation

	Granisetron		Ramosetron		Pvalue	Remarks
PONV score	No	%	No	%		
Nausea	8	16	6	12	0.7742	Not Significant
Vomiting	4	8	2	4	0.6777	Not Significant
Rescue antiemetic required	1	2	2	2	1.000	Not Significant

Table 2c: Post operative Nausea and Vomiting (PONV) score 6-12 hours after extubation

	Granisetron		Ramosetron		P value	Remarks
PONV score	No	%	No	%		
Nausea	10	20	6	12	0.4139	Not Significant
Vomiting	4	8	2	4	0.6777	Not Significant
Rescue antiemetic required	3	6	1	2	1.6173	Not Significant

Table 2d: Post operative Nausea and Vomiting (PONV) score 12-18 hours after

	Granisetron		Ramosetron		P value	Remarks
PONV score	No	%	No	%		
Nausea	16	32	6	12	0.0283	Significant
Vomiting	10	20	2	4	0.0277	Significant
Rescue antiemetic required	8	16	1	2	0.0309	Significant

Table 2e: Post operative Nausea and Vomiting (PONV) score 18-24 hours after extubation

PONV score	Granisetron		Ramosetron		P value	Remarks
	No	%	No	%		
Nausea	18	32	8	16	0.0390	Significant
Vomiting	14	28	33	6	0.0064	Significant
Rescue antiemetic required	8	16	1	2	0.0309	Significant

Discussion

Despite the latest advances in anesthesia and the introduction of new class of antiemetics, almost one third of patients undergoing surgery suffer from postoperative nausea, vomiting, or both, and often rate PONV as worse than postoperative pain [6]. PONV is commonly experienced after general anesthesia in laparoscopic surgery , and its incidence ranges between 60% to 72%[11]. Its etiology after laparoscopic cholecystectomy is not known but probably associated with effect of intraperitoneal carbon dioxide insufflation on residual stretching and irritation of the peritoneum [12]. Although always self limiting and nonfatal PONV can cause significant morbidity,[13] Efforts are being made to reduce the chances of vomiting associated with anaesthesia and surgery. Many studies have been conducted to know the mechanism and causes of postoperative nausea and vomiting and to find out the safe and satisfactory antiemetic or emesis free anaesthesia. Multiple factors like patient related, surgery related, anesthesia related risk factors like use of volatile anesthetics,N2O, postoperative opioids, postoperative pain, and intraoperative hypovolemia have been found [14]. In our study we have standardized the factors that may play a role in the development or attenuation of PONV and also standardized the anesthetic technique for all the patients. There was no statistical difference between the two groups with respect to their demographic profile such as age, weight, height, sex, duration of anesthesia and surgery, We can therefore presume that the difference in effects between the two groups can be attributed to the drugs administered. PONV is classified as early, occurring up to 2 to 6 hours after surgery, or late, occurring up to 24-48 hours after surgery.The causative factors for early and late PONV may be different with use of volatile anesthetics being a main cause for early PONV [15].We have, therefore, chosen 6 h interval for our study design.

We found no statistically significant difference in the PONV scores in the two groups immediately after extubation, 0 to 6 hrs and 6 to 12 hrs hence proving that upto 12 hrs ramosetron is as effective as granisetron for preventing PONV which are similar as found by I Bhat et al and Waqar-ul-nisa et al [10,11].

We found a statistically significant difference in the PONV scores between the two groups 12-18 and 18 to 24 hours after extubation hrs which is same as results found by Bhat et al and Waqar-ul-nisa et al but differ from Newstar et al . who observed that the differences in the PONV scores were statistically insignificant during early (0-2 hrs) as well as 2 to 24 hrs [12].

The persistent response of ramosetron lasting over the period of 48 hrs after surgery may be a reflection of its more prolonged elimination half life of ramosetron (9 hours) and granisetron (4.9 hours) [16,17]. Ramosetron is 58 times more potent than granisetron, and its antiemetic effect lasts 10.7 times longer than that of granisetron in patients treated with cisplatin[18]. Ramosetron has a longer half life than that reported for granisetron (5.8 h for ramosetron and 3.1 – 3.2 h for granisetron)[13]. Because of these pharmacological properties, ramosetron is reported to be more potent with a longer duration of action than older 5-HT3 receptor antagonists [19,20]. The more potency and longer duration of action of ramosetron could be the reasons that gave us favorable results for ramosetron over granisetron .

The side effects of the drugs noticed during the study were headache (12% in granisetron group and 10% in ramosetron group) and dizziness (6% in granisetron group and 4% ramosetron group) were of mild nature and self limiting. The side effects observed in our study were similar to most of other studies [12]. The side effects were of mild nature and self-limiting. The differences of adverse effects in the two groups were found to be notsignificant ($P > 0.05$). There were certain limitations in this study i.e. the bias of gender was not eliminated from the study. Further, it may also be extrapolated to a larger sample size to overcome the possibility of beta error if any. However, our study suggested that Ramosetron is superior to granisetron in providing prolonged relief from postoperative nausea and vomiting .

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