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PREVENTION OF POSTOPERATIVE NAUSEA AND VOMITING IN FEMALES FOLLOWING ABDOMINAL HYSTERECTOMY UNDER GENERAL ANAESTHESIA :A COMPARISON BETWEEN RAMOSETRON AND GRANISETRON.

Anaesthesiology

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ABSTRACT

Objectives: To study the efficacy of ramosetron in prevention of post operative nausea and vomiting in females following abdominal hysterectomy under general anaethesia and to compare it with that of granisetron.

Methods: In this randomized, double blind study, 80 female patients divided into two groups of 40 each received either 2 mg Granisetron or 0.3 mg Ramosetron i.v towards the completion of surgery.Incidence of postoperative nausea and vomiting and requirement of rescue antiemetic was compared between the two groups at various intervals. The standardized anesthetics included isoflurane and nitrous oxide in oxygen.

Observations: The difference in the incidence of nausea, vomiting and requirement of rescue antiemetic immediately after extubation, 0-6 hours and 6-12 hours after extubation was statistically insignificant ($p>0.005$), while as the difference in the incidence of nausea, vomiting and requirement of rescue antiemetic 12-18 hours and 18-24 hours after extubation was statistically significant ($p<0.005$). No clinically important adverse events due to the study drug were observed in any of the groups.

Conclusion: Ramosetron was more effective than Granisetron for prevention of post-operative nausea and vomiting during 12 - 24 hours after anesthesia for abdominal hysterectomy under general anaesthesia.

KEYWORDS

Introduction:

Postoperative nausea and vomiting (PONV) is defined as nausea or vomiting occuring within 24 hours after surgery. PONV affects between 20% to 30% of patients[1,2,3,4] and has been described as the "big little problem" because its presence suggests an unsatisfactory outcome to the surgeon, anesthetist and the patient[5] . PONV is thought to be multifactorial in origin involving individual, anesthetic and surgical risk factors[2,6,7,8] . The individual risk factors include age[9] female sex[10,11] non-smoker[11,12] history of PONV or motion sickness[9,11,12]. The anesthetic factors responsible for PONV include the use of volatile anesthetics within 0-2 hours[13], use of nitrous oxide[14], use of intraoperative and postoperative opioids[11,15,16,17,18] and high doses of neostigmine[9] . With increasing duration of surgery and anesthesia, the risk of PONV increases possibly because of greater accumulation of emetogenic anesthetic agents[2,9,19] . The surgical factors involved in PONV include the duration of surgery[9] and the type of surgical procedure irrespective of the anesthetic technique used[20] .

The frequency of PONV in patients undergoing gynaecological surgery has been reported to be between 50% and 75%[21,22,23,24] . In adults, greater incidences of PONV are found after "open" gastrointestinal surgery, major gynecological surgery, laparoscopic surgery, breast surgery, craniotomy, or eye and otorhinolaryngologic surgery[25,26,27].

PONV results in increased patient discomfort and dissatisfaction[8] and in increased costs related to length of hospital stay[28]. Persistent nausea and vomiting may result in dehydration, electrolyte imbalance and delayed discharge, particularly after outpatient surgery[29] . Persistent retching or vomiting can cause tension on suture lines, venous hypertension and increased bleeding under skin flaps and can expose the subject to an increased risk of pulmonary aspiration of vomitus if airway reflexes are depressed from the residual effects of anesthetic and analgesic drugs[30]. Various drugs used for preventing PONV include the anticholinergics (glycopyrollate, scopalamine), phenothiazines (promethazine, prochloperazine), antihistamines (hydroxyzine, diphenhydramine), butyrophenones (droperidol), benzamides (metoclopromide) and steroids (betamethasone, dexamethasone)[31]. Some of these antiemetics are associated with adverse effects such as restlessness, dry mouth, sedation, hypotension, extra pyramidal symptoms and dystonic effects[31]. The newer antiemetic group, 5-HT_3 receptor antagonists, is generally superior to the traditional antiemetic agents for preventing PONV[31,32,33]. Popularly used drugs nowadays for prevention of postoperative nausea and vomiting include Ondansetron and Granisetron[31,33,34]. However these drugs are also not without side effects[31,33,34]. Ramosetron is a newly developed 5-HT_3 receptor antagonist with a higher affinity and longer duration of action compared with other 5-HT_3 receptor antagonists[35]. Ramosetron was found to be more effective for preventing nausea and vomiting compared with Ondansetron for spinal surgery[36], chemotherapy[37] and total knee replacement surgery . Also, Ramosetron was found to be more effective than Granisetron in gynaecologic surgery[39].

Therefore the present study was conducted to study the efficacy of Ramosetron and its comparison with Granisetron in prevention of post operative nausea and vomiting following abdominal hysterectomy under general anesthesia.

Material & Methods:

After institutional ethical committee approval and written informed consent, the study was conducted in 80 female patients in two groups of 40 each of ASA physical status I and II ranging in the age group from 35 to 55 years scheduled for abdominal hysterectomy under general anaesthesia were selected . Patients with history of gastrointestinal disease, smoking, drug or alcohol abuse, previous post operative nausea and vomiting, antiemetic medication within 24 hours of surgery, abnormal kidney and liver function, menstruating women and pregnant or lactating women were excluded from the study.

Patients were randomly allocated to two groups of 40 each. Patients enrolled in the group-I (Granisetron) received 2 mg IV granisetron and those in the group-II (Ramosetron) received 0.3 mg IV ramosetron at the end of the surgery. The drugs were prepared by a single person in 5 ml syringes and in order to ensure a blind trial, the study medication was diluted in normal saline to make 4 ml of total volume of each drug .

Patients in group–I (Granisetron) received 2mg of granisetron diluted in 4ml of normal saline. Patients in group-II (Ramosetron) received 0.3mg of ramosetron diluted in 4ml of normal saline.

On the day before the surgery all the patients were clinically evaluated, assessed and investigated as per the proforma.

The study protocol was explained to the patient and written informed consent was taken from each participant. No pre-anesthetic medication was given.

Anesthesia was induced with 2mg/kg of propofol IV and 2 mcg/kg of fentanyl. Intubation of trachea was facilitated with atracurium 0.5 mg/kg. Anesthesia was maintained with 66% N2O and 0.5 % to 2% isoflurane in oxygen. Intra operative muscle relaxation was achieved with atracurium as required. Morphine 100mcg/kg was given IV before skin incision. Ventilation was mechanically controlled and adjusted to maintain ETCO2 at 30-40 mm Hg. Intraoperative monitoring included ECG, pulse oximetry, ETCO2, systolic, diastolic and mean blood pressure which was recorded at interval of every 5 minutes.

After completion of surgery neuro-muscular blockade was reversed with glycopyrrolate 10mcg/kg and neostigmine 40mcg/kg and patient was extubated when adequate spontaneous ventilation was established.

The postoperative nausea and vomiting (PONV) was defined as a subjective unpleasant sensation associated with an urge to vomit. The incidence of nausea and vomiting was recorded every 6- hours for a period of 24 hours by direct questioning to the patient or to her attendant by the same anaesthetist. No distinction was made between vomiting and retching (retching event was considered as vomiting event).Nausea and vomiting was evaluated on a three point scale as per the proforma 3. (none =0,nausea=1 and vomiting = 2).

Rescue antiemetic medication, if and when required, was given in the form of granisetron 2mg,repeated, if the patient experienced severe nausea or if there were more than 3 emetic episodes within a period of 15 minutes or if the patient had asked for it. The data obtained was statistically evaluated and analysed.

The data obtained was statistically evaluated and analysed using unpaired students t-test, chi-square test and Fisher's exact test.

Results:

The two groups were comparable with respect to age, weight, duration of anaethesia and duration of surgery. The average age of the patients in the granisetron group (I) was 46.60 ± 5.90 years and 44.85 ±7.37 years in ramosetron group (II). Average weight of the patients in granisetron group (I) was 71.50 ± 9.75 kgs against 68.55 ±8.69 kgs in ramosetron group (II). The mean duration of anaethesia in granisetron group (I) was 178.12 ± 46.95 minutes and 162.12 ± 25.66 minutes ramosetron group (II). Average surgical time in granisetron group (I) was 129.75 ± 44.08 minutes against 123.87 ± 26.80 minutes ramosetron group (II).

Table 1: Post Operative Nausea and Vomiting (PONV) score immediately after extubation.

PONV Score	Granisetron group		Ramosetron group		P value	Remark
	No.	%	No.	%		
Nausea	3	7.5	1	2.5	0.305	NS
Vomiting	1	2.5	0	0	0.996	NS
Rescue antiemetic required	0	0	0	0	-	-

NS = Not significant

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

PONV Score	Granisetron group		Ramosetron group		P value	Remark
	No.	%	No.	%		
Nausea	5	12.5	4	10	0.823	NS
Vomiting	1	2.5	1	2.5	1.000	NS
Rescue antiemetic required	0	0	0	0	-	-

NS = Not significant

Table 3: Post Operative Nausea and Vomiting (PONV) score 6-12 hours after extubation.

PONV Score	Granisetron group		Ramosetron group		P value	Remark
	No.	%	No.	%		
Nausea	6	15	4	10	0. 557	NS
Vomiting	3	7.5	2	5	0.975	NS
Rescue antiemetic required	1	2.5	0	0	0.996	NS

NS = Not significant

However a statiscally significant different was observed in PONV scores 12-18 hours after extubation between the two groups.

Incidence of nausea was 25% (10) in the Granisetron group and 7.5% (3) in the Ramosetron group. The difference in the incidence of nausea between the two groups was statistically significant with the p value of 0.034.

Incidence of vomiting was 25% (10) in the Granisetron group and 7.5% (3) in the Ramosetron group; the difference in the incidence of vomiting was statistically significant with a p-value of 0.034.

Incidence of requirement of rescue antiemetic was 15% (6) in the Granisetron group and 2.5% (1) in the Ramosetron group; the difference in the incidence of requirement of rescue antiemetic was statistically significant with a p-value of 0.048.

Table 4: Post Operative Nausea and Vomiting (PONV) score 12-18 hours after extubation.

PONV Score	Granisetron group		Ramosetron group		P value	Remark
	No.	%	No.	%		
Nausea	10	25	3	7.5	0. 034	S
Vomiting	10	25	3	7.5	0.034	S
Rescue antiemetic required	6	15	1	2.5	0. 048	S

S = Significant

After 18-24 hours of extubation a statistically significant difference was observed in PONV Scores between the two groups.

Incidence of nausea was 35% (14) in the Granisetron group and 5% (2) in the Ramosetron group. The difference in the incidence of nausea between the two groups was statistically highly significant with the p value of 0.001.

Incidence of vomiting was 32.5% (13) in the Granisetron group and 10% (4) in the Ramosetron group; the difference in the incidence of vomiting was statistically significant with a p-value of 0.014.

Incidence of requirement of rescue antiemetic was 20% (8) in the Granisetron group and 5% (2) in the Ramosetron group; the difference in the incidence of requirement of rescue antiemetic was statistically significant with a p-value of 0.043.

Table 5: Post Operative Nausea and Vomiting (PONV) score 18-24 hours after extubation.

PONV Score	Granisetron group		Ramosetron group		Remark	P value
	No.	%	No.	%		
Nausea	14	35	2	5	0. 001	HS
Vomiting	13	32.5	4	10	0.014	S
Rescue antiemetic required	8	20	2	5	0. 043	S

HS = Highly Significant; S = Significant

Discussion:

While multiple advances have been made in last several years in minimizing adverse outcomes after anesthesia, patients continue to rank nausea and vomiting as their most undesirable surgical outcome[10,40] and is one of the most unpleasant complications associated with anesthesia and surgery[11]. Generally, one-third of

patients undergoing surgery and anesthesia are known to suffer from postoperative nausea, vomiting, or both, and often rate PONV worse than postoperative pain[41]. After gynaecological surgery its incidence has been reported to be between 50% and 75%[21,22,23,24].

With the idea of safety and comfort in mind, it is expected that efforts would be made to reduce the chances of vomiting associated with anesthesia and surgery; therefore many nonspecific and therapeutic measures have been applied to prevent sickness during and after the operation[33].

Several 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 anesthesia strategy[33]. The problem is multifactorial in origin, including patient characteristics, nature of underlying disease, the type of surgery, as well as the anesthetic agents and postoperative care[33]. The main patient related factors are age, gender, history of motion sickness, previous nausea and vomiting and pregnancy. The incidence of PONV in females has been reported to be very high and is approximately two to three times more prevalent in adult women than in men, with greater severity of vomiting in women[33]. Women are more sensitive to all emetic stimuli. The mechanism of postoperative nausea and vomiting in them is then complicated by the prevailing hormone status[42]. Hence the incidence of emetic episodes is four times higher in the menstrual age group than post-menopausal[42], as the changing endocrine environment sensitizes the brainstem emetic mechanism to the action of other emetic stimuli[33].

Various drugs used for preventing PONV include the anticholinergics (glycopyrollate, scopalamine), phenothiazines (promethazine, prochloperazine), antihistamines (hydroxyzine, diphenhydramine), butyrophenones (droperidol), benzamides (metoclopromide) and steroids (betamethasone, dexamethasone)[31]. Some of these antiemetics are associated with adverse effects such as restlessness, dry mouth, sedation, hypotension, extra pyramidal symptoms and dystonic effects[31].

The newer antiemetic group, 5-HT_3 receptor antagonists, is generally superior to the traditional antiemetic agents for preventing PONV[31,32,33]. These antiemetics do not have the adverse effects of the traditional antiemetics. Headache and dizziness are the main side effects of 5-HT_3 antagonists in the dosage used for PONV[31,32,33]. Selective serotonin $5HT_3$ receptor antagonists are considered as first line in the prevention of PONV, due to their proven efficacy and favourable side effect profile[35,37,43].

In our study, we found that there was **no statistically significant** difference in the PONV scores in the two groups immediately after extubation and upto 12 hours post operatively meaning thereby that Ramosetron is as effective as Granisetron in preventing PONV in female patients undergoing abdominal hysterectomy under general anesthesia.

Our results are in accordance with the results obtained by Yoshita Fuji, Yuhji Saitoh, Hiroyoshi Tanaka, Hidenori Toyooka, who in their study "Ramosetron versus Granisetron for prevention of postoperative nausea and vomiting after laparoscopic cholecystectomy" found no statistically significant difference in the PONV scores in the two groups immediately after extubation and upto 12 hours after extubation[44].

Our results are in accordance with the results obtained by Yoshita Fuji, Hiroyoshi Tanaka, who in their study "comparison of Granisetron and Ramosetron for the prevention of nausea and vomiting after thyroidectomy" observed no statiscally significant difference in the PONV scores immediately after extubation[131] and upto 12 hours after extubation[45].

However in our study we found that there was a statistically significant difference 12-18 hours and 18-24 hours after extubation.

Our results are also in accordance with the results obtained by Feng Yi Feng, Pin Zhang, You Jian He, Yu Hong Li, Mei Zhen Zhou, Gang Cheng, Minoru Yamamoto, who in their study " Comparison of the selective serotonin-3 antagonists Ramosetron and Granisetron in treating acute chemotherapy - induced emesis, nausea, and anorexia: a single-blind, randomized, crossover study" observed that, 18-24 hours after administration of chemotherapy, patients given Ramosetron had significantly better scores for nausea than the patients given Granisetron[46].

Our results are also in accordance with the results obtained by Yoshita Fuji, Yuhji Saitoh, Hiroyoshi Tanaka, Hidenori Toyooka, who in their study "Ramosetron versus Granisetron for prevention of postoperative nausea and vomiting after laparoscopic cholecystectomy (1999)" found statistically significant difference in the PONV scores in the two groups 24-48 hours hours after anesthesia[44].

We observed that Ramosetron is more potent than Granisetron and the need for rescue antiemetics in the Ramosetron group was less than that in the Granisetron group. Ramosetron has better inhibitory activities than those of formerly available antagonists such as ondansetron, granisetron, and tropisetron[35]. Ramosetron is more potent and has longer-lasting antiemetic effects than older agents because of a slower rate of dissociation from the target receptor and higher binding affinity[35]

Ramosetron is a newly developed 5-HT3 receptor antagonist with a more potent and longer antagonizing effect compared with older 5-HT3 receptor antagonists[47]. The elimination half life of Ramosetron (9 hours) is longer than that of Granisetron (4.9 hours)[35].Because of these pharmacological properties, Ramosetron is clinically reported to be more potent with a longer duration of action than older 5-HT3 receptor antagonists[35,47]. Ramosetron has also been known to be equivalent to Granisetron in the overall antiemetic effect and even superior to Granisetron in the no-vomiting (emesis free) rate for patients receiving chemotherapy[48].

We also observed that Ramosetron has a longer antiemetic duration than Granisetron and was associated with longer emesis free periods in the study group than in the Granisetron group.

Ramosetron has been found to be 58 times more potent than Granisetron and its antiemetic effect lasts 10.7 times longer than that of Granisetron in ferrets treated with cisplatin[46]. It has been also seen that Ramosetron has high pharmacological bioavailability[49]. The high bioavailability of Ramosetron results in antagonism at maximum number of 5-HT3 receptors which explains its better efficacy and superiority over Granisetron in prevention of PONV[48]. Ramosetron has been seen to have a higher affinity for 5HT3 receptors than Granisetron with a significantly higher efficacy 6-48 hours after treatment[48].

Besides, in our study only female patients were studied, thereby eliminating the bias of gender.

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