PREVENTION OF POST-OPERATIVE NAUSEA AND VOMITING IN FEMALES FOLLOWING THYROIDECTOMY: A COMPARISON BETWEEN RAMOSETRON AND GRANISETRON

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ABSTRACT
This study was designed to see the efficacy of ramosetron in prevention of postoperative nausea and vomiting in females following thyroidectomy under general anaesthesia and to compare it with that of granisetron. 100 female patients of physical status ASA I and II, aged 25-55 years scheduled for elective thyroidectomy under general anaesthesia were recruited. Patients with a history of smoking, drug or alcohol abuse, peptic ulcer disease, patients who had received antiemetics within 24 hours before surgery, menstruating, pregnant or lactating women and patients with history of motion sickness were excluded from study. Patients were divided into two equal groups of 50 each. Patients in group A (granisetron group) received 2mg of granisetron diluted in saline to make a total volume of 4ml and patients in group B (ramosetron group) received 0.3mg of ramosetron diluted in saline to make a total volume of 4ml towards the end of surgery. There was no significant difference in postoperative nausea and vomiting (PONV) scores between the two groups immediately after extubation and up to 12 hours postoperatively, however a statistically significant difference was observed in PONV scores 12-18 hours and 18-24 hours postoperatively between the two groups. Ramosetron is a better antiemetic and is superior to granisetron in providing prolonged relief from postoperative nausea and vomiting following thyroidectomy in females.

KEYWORDS: Ramosetron, Granisetron, Postoperative, Nausea Vomiting, Thyroidectomy, Females.

INTRODUCTION
Thyroidectomy is one of the commonest surgical procedures performed worldwide, but it has been reported to be associated with excessive episodes of nausea and vomiting in the
postoperative period. Postoperative nausea and vomiting (PONV) after thyroidectomy and other head and neck surgeries is especially common with some studies reporting an incidence of 60-76%[1].

Overall incidence of PONV after surgery and anaesthesia has been reported to be 20-30%[2,3], whereas particularly after thyroidectomy, the incidence increases to 60-84%[4]. Postoperative nausea and vomiting (PONV) remains an unpleasant and persistent clinical problem in the surgical patients after anesthesia[5]. Persistent vomiting may lead to disturbances in the electrolytes, dehydration, minor incisional pain to more severe hematomas which is of particular concern to thyroid surgery as it can lead to airway obstruction[6,1], delayed wound healing, wound dehiscence and bleeding, aspiration of vomitus, esophageal rupture, raised intracranial pressure and bilateral pneumothorax. Furthermore, discharge from post-anesthetic care unit (PACU) may be delayed and hospital stay prolonged, thereby increasing the overall medical cost[5,7,8].

The main patient-related factors are age, gender, history of motion sickness, previous nausea and vomiting, pregnancy[5,9], surgery within 1-7 days of menstrual cycle[7,10] and patients not smoking[5,7,8]. Women are more sensitive to all emetic stimuli. The mechanism of postoperative nausea and vomiting in them is complicated by the prevailing hormonal status[7]. Hence the incidence of emetic episodes (PONV) is 2-3 times more prevalent in women than men[7] and four times higher during menses[7], four times higher in the menstrual age group than post menopausal, as the changing environment sensitizes the brainstem to the action of other emetic stimuli[5,7,8,9].

Various drugs used for preventing PONV include the anticholinergics (glycopyrollate, scopolamine), phenothiazines (promethazine, prochlorperazine), antihistamines (hydroxyzine, diphenhydramine), butyrophenones (droperidol), benzamides (metochlorpromamide) and steroids (betamethasone, dexamethasone). Some of these antiemetics are associated with adverse effects such as restlessness, dry mouth, sedation, hypotension, extrapyramidal symptoms and dystonic effects[11]. Three major groups of drugs, among the traditional antiemetics, that remain in use for PONV are the benzamides, butyrophenones and steroids. The newer antiemetic group of drugs, 5-HT3 receptor antagonists, is generally superior to the traditional antiemetic agents for preventing PONV. These antiemetics do not have the adverse effects of the traditional antiemetics. Headache and dizziness are the main side effects of 5-HT3 antagonists in the dosage used for PONV[5,7,11].
Popularly used drugs nowadays for prevention of postoperative nausea and vomiting include Ondansetron and Granisetron. However these drugs are also not without side effects. The unwanted effects of Ondansetron are headache, dizziness, musculoskeletal pain, drowsiness, sedation, shivers, malaise, fatigue, injection site reaction, urinary retention, chest pain, hypotension, fever, pruritus, paraesthesia, raised liver enzymes, slight QT-prolongation and reduced heart rate\textsuperscript{7,11,12}. The adverse effects of Granisetron include decreased gastrointestinal motility resulting in mild transient constipation (thus patients with subacute intestinal obstruction should be monitored)\textsuperscript{7,12}, headache, diarrhoea, somnolence, dizziness, dyspepsia, transient increase in hepatic transaminases\textsuperscript{7}. Granisetron lacks dysphoric, sedative and extrapyramidal side effects. No safety profile is available for its use in neonates and pregnant women and therefore may be avoided in them\textsuperscript{11,13}.

An ideal antiemetic used for prevention of postoperative nausea and vomiting should have quicker onset and longer duration of action and should have least undesired side effects. Therefore to have the above-mentioned properties and to overcome the side effects of previously used drugs for post-operative nausea and vomiting, a need was felt to try a new drug with a better clinical profile and less side effects.

Ramosetron, a newer antiemetic drug is a 5-HT\textsubscript{3} blocker. It has been shown by various investigators that Ramosetron has a longer duration of action\textsuperscript{5,13,14,15,16,17,18} and least unwanted side effects as compared to the previously used antiemetics for prevention of postoperative nausea and vomiting.

Therefore the present study was conducted to study the efficacy of Ramosetron and to compare it with Granisetron in prevention of post operative nausea and vomiting following thyroidectomy in female patients.

**MATERIAL & METHODS**

After institutional ethical committee approval and written informed consent, this study was conducted on 100 female patients of ASA physical status I & II in the age group of 25-55 years scheduled for elective thyroidectomy under general anaesthesia. Patients with a history of smoking, history of drug or alcohol abuse, history of peptic ulcer disease, patients with impaired kidney or liver function, patients who had received anti-emetics within 24 hours before scheduled surgery, menstruating, pregnant or lactating women and patients who had history of motion sickness were excluded from study.

Patients were randomly allocated to two groups of 50 patients each. 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. The
drugs were prepared by a single person in 5ml syringes and all study medication was diluted
in normal saline to make 4ml of total medication in order to ensure blinding.
Group A: Patients received 2 mg of Granisetron diluted to make 4ml in normal saline.
Group B: Patients received 0.3 mg of Ramosetron diluted to make 4ml in normal saline.

On the day before the surgery all the patients were clinically evaluated, assessed and
investigated as per the protocol. 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 100 mcg/kg of morphine. Intubation
of trachea was facilitated with atracurium 0.5 mg/kg. Anesthesia was maintained with 66%
N₂O and 0.6 % isoflurane in oxygen. Intra operative muscle relaxation was achieved with
atracurium as required. Ventilation was mechanically controlled and adjusted to maintain an
end-tidal CO₂ (ETCO₂) at 30-40 mm Hg.

During surgery patients were positioned with extended neck and slight head down position
as per the convenience of surgeon. Intraoperative monitoring included ECG, pulse
oximetry, ETCO₂, systolic, diastolic and mean blood pressure, which was recorded every 5
minutes. Ketorolac 0.5 mg /kg i/m was given towards end of surgery. Duration of anesthesia
and surgery was recorded in every patient.

After completion of surgery, patient was repositioned and neuromuscular blockade was
reversed with neostigmine 0.04 mg/kg and glycopyrolate and patients were extubated when
adequate spontaneous ventilation was established.

The post-operative nausea and vomiting (PONV) was defined as a subjective
unpleasant sensation associated with an urge to vomit (Retching and Vomiting was grouped
together).

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 anesthetist. 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.

0=none
1=nausea
2=vomiting.
Rescue antiemetic medication, if required, was given in the form of Granisetron 2mg, repeated, if the patient experienced severe nausea, if there were more than 3 emetic episodes within a period of 15 minutes or if the patient asked for it.

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

RESULTS

The two groups were comparable with respect to age, weight, duration of anaesthesia and duration of surgery. The average age of the patients in granisetron group was 38.44 years and 38.50 years in ramosetron group. Average weight of the patients in granisetron group was 63.0 kgs against 63.74 kgs in ramosetron group. The mean duration of anaesthesia in granisetron group was 60.8 minutes and 62.40 minutes in ramosetron group. Average surgical time in granisetron group was 55.28 minutes against 56.42 minutes in ramosetron group.

There was no statistically significant difference in PONV scores immediately after extubation and upto 12 hours postoperatively.

Table 1 : Showing PONV scores immediately after extubation.

<table>
<thead>
<tr>
<th>PONV Score</th>
<th>Granisetron group</th>
<th>Ramosetron group</th>
<th>P value</th>
<th>Remark</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Nausea</td>
<td>4</td>
<td>8</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Rescue antiemetic required</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

NS = Not significant, PONV = Post-operative nausea & vomiting.

Table 2 : Showing PONV scores 0-6 hours after extubation.

<table>
<thead>
<tr>
<th>PONV Score</th>
<th>Granisetron group</th>
<th>Ramosetron group</th>
<th>P value</th>
<th>Remark</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Nausea</td>
<td>9</td>
<td>18</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5</td>
<td>10</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Rescue antiemetic required</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

NS = Not significant.
Table 3: Showing PONV scores 6-12 hours after extubation.

<table>
<thead>
<tr>
<th>PONV Score</th>
<th>Granisetron group</th>
<th>Ramosetron group</th>
<th>P value</th>
<th>Remark</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Nausea</td>
<td>11</td>
<td>22</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6</td>
<td>12</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Rescue antiemetic required</td>
<td>5</td>
<td>10</td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>

NS = Not significant.

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

The incidence of nausea was 30% in granisetron group and only 12% in ramosetron group. The difference was statistically significant. 18% of patients in granisetron group had vomiting whereas only 2% of patients in ramosetron had episodes of vomiting. The difference was statistically significant. The incidence of rescue antiemetic needed was 20% in granisetron group and only 2% in ramosetron group with a statistically significant difference between the two groups.

Table 4: Showing PONV scores 12-18 hours after extubation.

<table>
<thead>
<tr>
<th>PONV Score</th>
<th>Granisetron group</th>
<th>Ramosetron group</th>
<th>P value</th>
<th>Remark</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Nausea</td>
<td>15</td>
<td>30</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>Vomiting</td>
<td>9</td>
<td>18</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Rescue antiemetic required</td>
<td>10</td>
<td>20</td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>

S = Significant.

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

The incidence of nausea was 34% in granisetron group and only 10% in ramosetron group. The difference was highly significant. Episodes of vomiting occurred in 20% of patients in granisetron group and only 4% in ramosetron group with a statistically significant difference. 24% of patients in granisetron group required rescue antiemetic whereas only 6% of patients required rescue antiemetic in ramosetron group. The difference was statistically significant.
Table 5: Showing PONV scores 18-24 hours after extubation.

<table>
<thead>
<tr>
<th>PONV Score</th>
<th>Granisetron group</th>
<th>Ramosetron group</th>
<th>P value</th>
<th>Remark</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Nausea</td>
<td>17</td>
<td>34</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10</td>
<td>20</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Rescue antiemetic required</td>
<td>12</td>
<td>24</td>
<td>3</td>
<td>6</td>
</tr>
</tbody>
</table>

HS = Highly Significant.

DISCUSSION

Despite the latest advances in anesthesia and the introduction of new class of antiemetics, postoperative nausea and vomiting (PONV) is still one of the most common complaints of patients in the post-operative period. One and a half century is over since the first anesthesia was administered and despite the remarkable advances in this specialty and the development of newer anesthetics the incidence of postoperative nausea and vomiting has been unacceptably high. Generally, one-third of patients undergoing surgery and anaesthesia are known to suffer from postoperative nausea, vomiting, or both, and often rate PONV as worse than postoperative pain[8]. After thyroidectomy its incidence has been reported to be as high as 60-84%[3]. Thyroidectomies performed under general anaesthesia are associated with high incidence of PONV, justifying the use of prophylactic antiemetics in patients undergoing this intervention[19].

The exact mechanism underlying higher incidence of PONV related to thyroidectomy is not clearly understood, but some clinical studies have held that vagal stimulation during surgical manipulation[20,21,22] may be responsible and that a chemical stimulus released during surgery may activate chemoreceptor trigger zone[23]. Some investigators[20] have been doubtful about the role of changes in the levels of thyroid hormones in production of nausea and vomiting as these patients were evaluated as euthyroid preoperatively.

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.

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. 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. 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\textsuperscript{[7]}. 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. Hence the incidence of emetic episodes are four times higher in the menstrual age group than post-menopausal\textsuperscript{[24]}, as the changing endocrine environment sensitizes the brainstem emetic mechanism to the action of other emetic stimuli\textsuperscript{[7]}.

There are numerous antiemetic drugs available having different mechanisms of action and target sites with varying potency and pharmacokinetic profiles. Routinely employed drug classes are prokinetics, dopaminergic antagonists, 5HT3 antagonists, butyrophenones, anticholinergic, henothiazines, antihistaminics, benzamides and steroids. Most of the antiemetics are known to cause drowsiness, dysphoria, hallucinations, dry mouth and extrapyramidal side effects\textsuperscript{[11,25]}.

Though hazards associated with a single dose of an anti-emetic are small, as compared to the hazards and inconvenience of vomiting yet efforts are always on to develop drugs which can be used safely as antiemetics without having untoward side effects, especially on the cardiovascular and respiratory system. As a result of this continuous search for better antiemetics, 5HT3 receptor antagonists were introduced with an idea of good margin of safety.

In our study, we found no statistically significant difference in PONV scores in two groups immediately after extubation and up to 12 hours postoperatively, meaning thereby that Ramosetron is as effective as Granisetron in preventing PONV in female patients undergoing thyroidectomy.

Precise mechanism of Granisetron for prevention of PONV remains unclear, but it has been suggested that Granisetron acts as a 5-HT3 receptor antagonist. Similar mechanism has been suggested for Ramosetron.

Our results are in accordance with the results obtained by Yoshita Fuji, Yuhji Saitoh, Hiroyoshi Tanaka, Hidenori Toyooka, who in their study found no statistically significant difference in the PONV scores in the two groups immediately after extubation and up to 12 hours postoperatively\textsuperscript{[9]}.
However a statistically significant difference was observed in postoperative nausea and vomiting scores in our study 12-18 hours and 18-24 hours after extubation.

Our results are in accordance with the results obtained by Yoshita Fuji, Yuhji Saitoh, Hiroyoshi Tanaka, Hidenori Toyooka, who in their study concluded that Ramosetron is more effective than Granisetron for prevention of postoperative nausea and vomiting during 0-48 hours after anaesthesia for laparoscopic cholecystectomy\[9\].

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 observed that, 18-24 hours after administration of chemotherapy, patients given Ramosetron had significantly better scores for nausea than the patients given Granisetron\[16\].

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 is a newly developed 5-HT3 receptor antagonist with a more potent and longer antagonizing effect compared with older 5-HT3 receptor antagonists\[2\]. The elimination half life of Ramosetron (9 hours) is longer than that of Granisetron (4.9 hours)\[26\]. 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\[2,26\]. 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\[27\].

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\[16\]. The more potency and longer duration of action of Ramosetron could be the reasons that gave us favorable results for Ramosetron over Granisetron in prevention of PONV.

It has been also seen that Ramosetron has high pharmacological bioavailability\[28\]. 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. Ramosetron has been seen to have a higher affinity for 5HT3 receptors than Granisetron with a significantly higher efficacy 6-48 hours after treatment\[27\]. Besides, as we studied only female patients, the bias of gender was eliminated in our study.
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