Comparison of Efficacy of Granisetron, Ondansetron and Dexamethasone in Prevention of Postoperative Nausea and Vomiting

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Abstract
The incidence of post-operative nausea and vomiting (PONV) has been quoted to be as high as 30% and is an important cause of postoperative patient discomfort. We conducted a prospective randomized double-blind study in patients undergoing elective laparoscopic surgery. The aim was to compare the efficacy of ondansetron, granisetron and dexamethasone in the management of PONV, when administered at the end of surgery. We randomized 30 patients into each drug group. Patient characteristics, incidence of PONV within 24 hours, and incidence of side effects were compared among the three groups and statistical significance was assessed. We observed that patients in group granisetron had least incidence of early nausea (3.3%), delayed nausea (3.3%), early vomiting (3.3%) and delayed vomiting (3.3%). Patients in group ondansetron had higher incidence of early nausea (6.7%), delayed nausea (23.3%), delayed vomiting (23.3%) and similar incidence of early vomiting (3.3%). Patients in group dexamethasone had highest incidence of early nausea (33.3%), early vomiting (23.3%), but incidence of delayed nausea (3.3%) was similar to group granisetron, none had delayed vomiting. These differences were statistically significant. Overall most of the side effects were slightly more common in ondansetron group (40%), however the findings were not statistically significant. We conclude that Injection Granisetron 1mg is a better antiemetic when compared to Injection Ondansetron 4mg and Injection Dexamethasone 8mg in prevention of postoperative nausea and vomiting within the first 24 hours after surgery in patients undergoing laparoscopic surgery, when the drug is administered just before the reversal of neuromuscular blockade.

Keywords: 5HT3 receptor antagonists, Dexamethasone, Efficacy, PONV

INTRODUCTION
The incidence of post-operative nausea and vomiting has been quoted to be as high as 30%.[1] It is one of the most common causes of patient discomfort following anaesthesia and also of unexpected delay in discharge from hospital. With current emphasis on ambulatory anaesthesia, effective management of PONV is a desirable goal.

Post-operative nausea and vomiting (PONV) is multifactorial. Patient related factors include age, gender, non-smoking status, a history of motion sickness, and a previous history of post-operative nausea.[2] Intraoperative factors include general anaesthetics, particularly volatile anaesthetics,[3] nitrous oxide,[4] opioids used for pain relief.[5] In their systematic review, Apfel CC et al[6] identified these factors as independent predictors of PONV. Other intraoperative factors include type, site and duration of surgical procedure[2] with an increased predisposition in surgeries lasting greater than 3 hours.[7] Many surgical procedures have been hypothesized causally to PONV, however most were not independent predictors. An
increased incidence of PONV was noted in literature in early postoperative period after laparoscopic cholecystectomy\(^{[6]}\) with a significantly higher incidence when CO2 insufflation was greater than 12 litres.\(^{[9]}\) In laparoscopic cholecystectomy the emetogenic stimulus could arise from stretching and irritation of the peritoneum.\(^{[8]}\) Apfel CC et al\(^{[6]}\) identified cholecystectomy, laparoscopic procedures and gynaecologic surgeries as independent predictors of PONV but they also made a note the data on type of surgical procedures affecting PONV is controversial and biased. Post-operative factors include pain, movement, dizziness, hypotension, gastro paresis, and early oral intake.\(^{[7]}\)

The introduction of 5HT3 receptor antagonists for the management of PONV has been advantageous as they were not associated with the adverse effects of antiemetics which were in prior use such as ill effects on vital signs or laboratory tests, extra pyramidal reactions, interactions with anaesthetic medications, and sedation. Headache is the most common side effect of ondansetron. Side effects are fewer with granisetron. Adverse effects like QT prolongation, bradycardia may be seen with granisetron but they are rare.

Dexamethasone is effective against PONV with no steroid-related complications after single bolus dose. Dexamethasone is effective when given just before induction of anaesthesia\(^{[10]}\) unlike 5HT3 receptor antagonists which are most effective when administered upon completion of surgery.\(^{[11]}\)

**Aims and objectives:** 1. To assess the efficacy of prophylactic antiemetic drug therapy with respect to early nausea, early vomiting, delayed nausea, delayed vomiting, requirement of rescue antiemetic 2. To assess the side effects related to prophylactic antiemetic drug therapy

**MATERIALS AND METHODS**

This is a prospective, randomised, double blind study conducted over a period of 2 years, among 90 patients undergoing elective laparoscopic surgery. Inclusion criteria: Patients with American Society of Anesthesiologists (ASA) physical status grades I and II, age between 18 – 55 yrs, weight between 40 – 75 kg and posted for elective laparoscopic surgeries were included in the study. Exclusion criteria: Patients with ASA physical status grade III, IV and V, past history of post-operative nausea and vomiting, history of motion sickness, on chronic steroid therapy, with peptic ulcer disease, diabetes mellitus, intestinal obstruction, hiatus hernia, neurological diseases, who received opioids, Non-Steroidal Anti Inflammatory Drugs (NSAIDs), steroids, antiemetics in the last 24 hours prior to surgery, pregnant and lactating women and those not willing to participate in the study were excluded. Institutional Ethics Committee approval was obtained. Written informed consent was taken from each patient participating in the study.

Patients were randomly divided in to 3 groups. Each group was allocated 30 patients: Group ‘G’ received Injection Granisetron 1mg\(^{[12]}\) IV, Group ‘O’ received Injection Ondansetron 4mg\(^{[13]}\) IV and Group ‘D’ received Injection Dexamethasone 8mg\(^{[14]}\) IV. Randomisation into one of the three groups was done by a computer- generated random number table and sealed opaque envelope technique before beginning of the study. The random drug was administered to the patient by the anaesthetist who was blinded to the nature of the drug and who made the observations.

Pre-operative evaluation was done a day before surgery and once determined fit for surgery, the patients were instructed to stay nil per oral after midnight, medicated with tablet Alprazolam 0.5mg orally on the night before surgery and tablet Ranitidine 150 mg on the night before surgery as well in the morning before surgery. In the operating room, patient monitoring was done with Electro cardiogram (ECG), Noninvasive blood pressure (NIBP), pulse oximetry (SpO₂), End tidal CO₂ (ETCO₂). Intravenous cannulation followed by Ringer’s lactate infusion and pre oxygenation for 3 min were done. Anaesthesia was induced with Injection Midazolam 0.05 mg/kg IV, injection Fentanyl 2 mcg/kg IV and injection Thiopentone 3.5 mg/kg IV. Neuromuscular blockade was achieved by Inj. Vecuronium 0.1 mg/kg IV. After 3 min. of assisted ventilation, tracheal intubation was done with an appropriate size endotracheal tube. General anaesthesia was maintained with Isoflurane 0.5 – 2%; Oxygen plus air in 50:50 ratio.

After completion of surgery, study medication was administered according to the groups. For the purpose of standardisation we have given all the three study drugs i.e. granisetron, ondansetron and dexamethasone at the end of the surgery before the reversal of neuromuscular blockade, to the respective...
patient according to the assigned group. Reversal of neuromuscular blockade was achieved with with Inj. Neostigmine 0.05 mg/kg and Inj. Glycopyrrolate 0.01 mg/kg IV. Patients were extubated after adequate reversal and recovery.

Symptoms of post-operative nausea and vomiting, pain, requirement of rescue antiemetic and side effects were recorded with in the first 24 hours after surgery at intervals of 0-2 hours (early), 2-24 hours (delayed).

Early Nausea and Early Vomiting [3]: Defined as nausea and vomiting occurring within 2 hours after surgery.

Delayed Nausea and Delayed Vomiting [3]: Defined as nausea and vomiting occurring from 2 - 24 hours after surgery.

Rescue antiemetic was provided with Inj. Ondansetron 4 mg IV in case of patient complaining of nausea or had vomiting and Inj. Paracetamol 1gm IV is given as rescue analgesic if patient complains of pain.

Results were tabulated and compared between the groups. Parameters that were compared between the groups were age, gender, weight, duration of anaesthesia, duration of surgery, duration of CO2 insufflation, incidence of early nausea, delayed nausea, early vomiting, delayed vomiting, requirement of rescue anti emetic, incidence of pain, side effects like fatigue, dizziness, headache, pruritus, flushing, cough, diarrhoea and heartburn

Statistical analysis

All data was tabulated in Microsoft office excel sheet and statistical analysis was with software SPSS version 22. Quantitative data like age, gender, weight, duration of anaesthesia, duration of surgery, duration of CO2 insufflation and number of patients requiring rescue anti emetic were compared using ANOVA. Qualitative data like incidence of nausea, vomiting, pain, side effects were compared using Chi-Square test. A p value of less than 0.05 is considered statistically significant. In ANOVA test if p value is less than 0.05, then post hoc-Bonferroni test was done to identify the two groups which has significant difference.

RESULTS

There were no statistically significant differences between the three groups with respect to patient characteristics such as age, male to female ratio, weight, ASA physical status. (table 1)

There was no statistically significant difference in the intraoperative factors in each group that could have influenced the occurrence of PONV, which were mean duration of anaesthesia, mean time of CO2insufflation, mean duration of surgery, and the type of laparoscopic surgery done. (table 2)

Patients assigned to group granisetron had least incidence of early nausea (3.3%), delayed nausea (3.3%), early vomiting (3.3%), delayed vomiting (3.3%). Patients assigned to group ondansetron had more incidence of early nausea (6.7%), delayed nausea (23.3%), delayed vomiting (23.3%) and similar incidence of early vomiting (3.3%). Patients assigned to group dexamethasone had highest incidence of early nausea (33.3%), early vomiting (23.3%), but incidence of delayed nausea (3.3%) was similar to that of group granisetron and none had delayed vomiting. These differences were statistically significant.

Patients in group dexamethasone required rescue antiemetic (23.3%) less often than group ondansetron (30%) but more often than group granisetron (6.7%). However, the difference in requirement of rescue antiemetic treatment among the three groups, was not statistically significant.

The overall incidence of nausea (early + delayed) in group G was 6.7% (2 (1+1) patients); in group O was 30% (9 (2+7) patients); and in group D was 36.7% (11(10+1) patients).

The overall incidence of vomiting (early + delayed) in group G was 6.7% (2 (1+1) patients); in group O was 26.7% (8 (1+7) patients); and in group D was 23.3% (7 (7+0) patients).

Pain was observed in 1 patient in group O and no patient complained of pain in groups D and G. There was no statistically significant difference between the groups with regard to pain.

Overall side effects were slightly more common among patients administered ondansetron (40%) than in the other 2 groups (26.7% in each group), except, flushing which was noted only in dexamethasone group; pruritus which affected 1 patient each in group granisetron and group ondansetron; and headache noted in equal numbers of patients in each group (2
each). However the differences were not statistically significant.

DISCUSSION

The exact cause of PONV in laparoscopic surgeries is not known completely, but among others, some known risk factors are long period of CO₂ insufflation, postoperative use of opioids, intra operative hypotension, manipulation of abdominal viscera and history of motion sickness. These latter were avoided in our study.

Pain has been repeatedly cited as a cause of PONV. In our study postoperative pain scores were comparable in all three groups. Rescue analgesic requirement was also not statistically different between the groups. Dexamethasone has potent anti-inflammatory effect, and it may be beneficial for postoperative pain.\(^\text{15}\) However in our study potent opioid (fentanyl) was administered as premedication. Therefore, the influence of dexamethasone on postoperative pain may have been masked. Apfel CC et al\(^\text{16}\) noted that the use of propofol for general anaesthesia reduces the risk of PONV by 19 percent. In our study we used thiopentone instead of propofol as induction agent, thus the confounding effect of the anti-emetic property of propofol was overcome.

In our study the incidence of early post-operative nausea and early postoperative vomiting was lower and nearly similar among patients who received granisetron (3.3% each) and ondansetron (6.7% and 3.3% respectively) and was much higher in those who received dexamethasone (33.3% and 23.3% respectively). The incidence of delayed post-operative nausea and delayed postoperative vomiting was lower and nearly similar among patients who received granisetron (3.3% each) and dexamethasone (3.3% and none respectively) and higher in those who received ondansetron (23.3% each), and these differences were statistically significant.

The requirement of rescue antiemetic was much higher in group O and group D patients compared to group G, however the difference was not statistically significant.

Similar to our findings, granisetron was found superior to ondansetron for preventing PONV in late postoperative period up to 24 hours in a study by Chaudhari SA et al\(^\text{17}\) and similarly effective in the early postoperative period. Oksuz H et al\(^\text{18}\) and Chidambaram A et al\(^\text{19}\) found granisetron significantly more effective than ondansetron in control of PONV.

In literature, the better efficacy of granisetron is attributed to a longer half-life of granisetron (8 to 9 hours) compared to ondansetron (3 hours) and higher specificity of granisetron.\(^\text{20}\) Also the elimination half-life of granisetron is 2.5 times that of ondansetron which translates to a lower dose frequency.\(^\text{21}\)

On the contrary Saha S et al\(^\text{22}\) found that granisetron was only minimally better than ondansetron in patients undergoing laparoscopic cholecystectomy; the authors made observations at regular time intervals in the postoperative period and found no statistically significant differences in incidence of PONV in granisetron and ondansetron group except for observations in the post-operative period of 5-8 hours for vomiting. In a study by Bestas A et al\(^\text{23}\) in adults undergoing laparoscopic cholecystectomy, during 24 hours postoperative period relief from PONV was found to be superior from granisetron and ondansetron than placebo, however there was no difference between granisetron and ondansetron. Similarly they both were found to have similar efficacy with respect to PONV in a study by White PF et al.\(^\text{24}\) Chen CC et al.\(^\text{25}\) Feroci F et al.\(^\text{26}\) Bilgin TE et al.\(^\text{27}\) and Bianchin A et al.\(^\text{14}\) have found that dexamethasone 8-10 mg prevents PONV.

In laparoscopic surgery, dexamethasone was found to be an effective alternative to ondansetron in a meta-analysis by Wang XX et al.\(^\text{28}\) and a study by D’souza N et al.\(^\text{29}\) However in these studies dexamethasone was given before surgery or induction of anaesthesia, which might have given sufficient time to achieve peak action for the prevention of PONV. In a study by Apfel CC\(^\text{16}\) there were no significant difference in efficacy of ondansetron 4mg and dexamethasone 4mg and dexamethasone was administered within 20 minutes of induction of anaesthesia. In our study, however, dexamethasone was given at the end of surgery which would have taken time to achieve peak action leading to early nausea and vomiting. In addition, in our study, we noted that the incidence of delayed nausea was lower and no cases of delayed vomiting were noted with dexamethasone.

In a study by Hessami MA et al.\(^\text{30}\) in patients undergoing laparoscopic cholecystectomy,
dexamethasone 8 mg was found equally efficacious to granisetron 3 mg, when given before induction of anaesthesia. In our study, for the purpose of standardisation we have given all the three study drugs i.e. granisetron, ondansetron and dexamethasone at the end of the surgery. Also the dose of granisetron employed was 1 mg in our study.

In our study, we found that drug related side effects were slightly more common in ondansetron group compared to others, however the differences were not statistically significant. Chidambaram A et al. noted fewer side effects with granisetron compared to ondansetron in a study undertaken in patients undergoing laparoscopic surgery.

**CONCLUSION**

We conclude that Injection Granisetron 1 mg is a better antiemetic when compared to Injection Ondansetron 4 mg and Injection Dexamethasone 8 mg in prevention of postoperative nausea and vomiting with in the first 24 hours after surgery in patients undergoing laparoscopic surgery, when the drug is administered just before the reversal of neuromuscular blockade. The greater efficacy and fewer side effects of granisetron may be explained by the fact that granisetron has a longer plasma half-life and is a more selective 5-HT3 receptor antagonist than ondansetron.

**REFERENCES**


29. D’souza N, Swami M, Bhagwat S. Comparative study of dexamethasone and ondansetron for prophylaxis of postoperative


TABLES

Table 1: Patient characteristics

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean age (yrs)</th>
<th>M:F</th>
<th>Mean Weight (kg)</th>
<th>ASA Physical status</th>
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<tbody>
<tr>
<td>Granisetron (n=30)</td>
<td>39.9667</td>
<td>9:21</td>
<td>56.2000</td>
<td>ASA I: 22, ASA II: 8</td>
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<tr>
<td>Ondansetron (n=30)</td>
<td>42.8333</td>
<td>16:14</td>
<td>58.7000</td>
<td>ASA I: 22, ASA II: 8</td>
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<td>Dexamethasone (n=30)</td>
<td>38.9333</td>
<td>11:19</td>
<td>56.1667</td>
<td>ASA I: 24, ASA II: 6</td>
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P value 0.276 0.164 0.127 0.786

Table 2: Operative factors

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean duration of anaesthesia (min*)</th>
<th>Mean duration of CO2 insufflation (min*)</th>
<th>Mean duration of surgery (min*)</th>
<th>Type of Surgery</th>
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</thead>
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<tr>
<td>Granisetron (n=30)</td>
<td>134.8333</td>
<td>118.00</td>
<td>125</td>
<td>Laparoscopic cholecystectomy</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Laparoscopic deroofing of hydatid cyst</td>
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</table>

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<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Granisetron n=30</th>
<th>Ondansetron n=30</th>
<th>Dexamethasone n=30</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients with symptoms (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early nausea</td>
<td>1(3.3%)</td>
<td>2(6.7%)</td>
<td>10(33.3%)</td>
<td>0.0014</td>
</tr>
<tr>
<td>Early vomiting</td>
<td>1(3.3%)</td>
<td>1(3.3%)</td>
<td>7(23.3%)</td>
<td>0.0117</td>
</tr>
<tr>
<td>Delayed nausea</td>
<td>1(3.3%)</td>
<td>7(23.3%)</td>
<td>1(3.3%)</td>
<td>0.0117</td>
</tr>
<tr>
<td>Delayed vomiting</td>
<td>1(3.3%)</td>
<td>7(23.3%)</td>
<td>0</td>
<td>0.0027</td>
</tr>
<tr>
<td>Rescue antiemetic requirement</td>
<td>2(6.7%)</td>
<td>9(30%)</td>
<td>7(23.3%)</td>
<td>0.0666</td>
</tr>
<tr>
<td>Pain /requirement of rescue analgesia</td>
<td>0</td>
<td>1(3.3%)</td>
<td>0</td>
<td>0.3638</td>
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</table>

* min, minutes

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<thead>
<tr>
<th>Ondansetron (n=30)</th>
<th>132.8333</th>
<th>116.83</th>
<th>117.33</th>
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<tr>
<td>Dexamethasone (n=30)</td>
<td>137.1667</td>
<td>119.33</td>
<td>123.5</td>
<td>29</td>
<td>1</td>
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<tr>
<td>P value</td>
<td>0.897</td>
<td>0.964</td>
<td>0.795</td>
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### Table 4: Side effects

<table>
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<tr>
<th>Side effects</th>
<th>Granisetron (n=30)</th>
<th>Ondansetron (n=30)</th>
<th>Dexamethasone (n=30)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>1(3.3%)</td>
<td>2(6.7%)</td>
<td>1(3.3%)</td>
<td>0.7698</td>
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<tr>
<td>Diarrhoea</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1.0000</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1(3.3%)</td>
<td>2(6.7%)</td>
<td>1(3.3%)</td>
<td>0.7698</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0</td>
<td>2(6.7%)</td>
<td>1(3.3%)</td>
<td>0.3554</td>
</tr>
<tr>
<td>Flushing</td>
<td>0</td>
<td>0</td>
<td>2(6.7%)</td>
<td>0.1293</td>
</tr>
<tr>
<td>Headache</td>
<td>2(6.7%)</td>
<td>2(6.7%)</td>
<td>2(6.7%)</td>
<td>1.0000</td>
</tr>
<tr>
<td>Heartburn</td>
<td>3(30%)</td>
<td>3(30%)</td>
<td>1(3.3%)</td>
<td>0.5381</td>
</tr>
<tr>
<td>Pruritus</td>
<td>1(3.3%)</td>
<td>1(3.3%)</td>
<td>0</td>
<td>0.5997</td>
</tr>
<tr>
<td>Total</td>
<td>8(26.7%)</td>
<td>12(40%)</td>
<td>8(26.7%)</td>
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