Antiemetic Prophylaxis with Ondansetron or Granisetron in Patients Undergoing Laparoscopic Cholecystectomy

Dr. Tarek M. Esmael MD, Dr. Noha M. Ibrahim MD, Dr. Ehab M Mokbel MD.
From Departments of General Surgery1 and anesthesia2, Faculty of Medicine Menia, Zagazig and Mansoura University.

Abstract

Objective: To evaluate and compare the antiemetic efficacy of granisetron, ondansetron and placebo for prevention of postoperative nausea and vomiting (PONV) in patient undergoing laparoscopic cholecystectomy (LC).

Patients and Methods: A total of 80 patients, ASA physical status I or II, undergoing laparoscopic surgery with a standardized general anesthetic technique were enrolled in this study at Minia University Hospital. Patients were randomly assigned to receive Ondansetron 4 mg plus saline, Granisetron 3 mg plus saline, or normal saline (NaCl 0.9%) as placebo. The requirement for rescue antiemetics, incidence of PONV, and the side effects were recorded over the 48 h study period. Nausea scores were assessed using verbal rating scale (VRS) in the postoperative period.

Results: Five patients required conversion to open cholecystectomy and therefore were eliminated from the study, and the remaining 75 patients were subdivided randomly into 3 groups: ondansetron group (Group O, n=27), granisetron group (Group G, n=28), and placebo group (Group P, n=20). There were no significant differences in demographic data between the studied groups. The incidence of PONV was 37%, 32%, and 65% in ondansetron, granisetron, and placebo group, respectively, during first 48 hours after anesthesia. There were no significant differences in the incidence of PONV and the use of rescue antiemetics between ondansetron and granisetron groups; however, in both groups these incidences were significantly lower than that in placebo group. There were no significant differences in the severity of postoperative vomiting between the three groups. In ondansetron and granisetron groups, nausea scores were significantly lower than that in placebo group up to 6 hours postoperatively.

Conclusion: Prophylactic antiemetics reduce the incidence of PONV in patients undergoing elective laparoscopic cholecystectomy. Ondansetron (4 mg) is as effective as granisetron (3 mg); however, ondansetron is preferred for routine antiemetic prophylaxis as it is less expensive.

Keywords: Laparoscopic cholecystectomy, nausea, vomiting, ondansetron, granisetron.

Introduction

Laparoscopic cholecystectomy (LC) is one of the most common surgical procedures [1]. Although serious adverse event are uncommon after LC, 40% to 75% of patients experience postoperative nausea or vomiting (PONV) [2-5]. PONV can detract from patients’ quality of life in hospital/treatment facility, as well as in the days immediately post discharge. In addition, PONV may increase perioperative costs, increase perioperative morbidity, increase post anesthesia care unit stay, prolong hospital stays, length of stay/delay discharge, delay the time that the patient can go back to work, and lead to readmissions [6]. Causes of PONV and post discharge nausea and vomiting (PDNV) are multifactorial and may include postoperative pain, the administration of opioid-containing medications, ambulation, and motion associated with traveling home by car [7]. No single drug therapy for PONV is completely effective. The control of postoperative nausea and vomiting (PONV) remains a difficult task. The optimal strategy to prevent PONV or to treat established symptoms is far from being obvious [8]. Ondansetron is a popular 5-HT3 serotonin receptor antagonist used for the management of PONV. Although there are ample clinical data demonstrating efficacy and low acquisition cost after the availability of its generic version, Ondansetron has a relatively short half-life (about 4 h) [9]. Granisetron is a more selective 5-HT3 receptor antagonist that is proven to be effective for the prophylaxis and treatment of PONV. It has been used for the management of PONV in doses of 0.35–3 mg [10, 11]. Despite its higher cost than ondansetron, granisetron may be more cost-effective if it provided greater antiemetic efficacy in the post discharge period [12]. This study was carried out to evaluate and compare the efficacy of preoperative intravenous administration of ondansetron (4 mg), granisetron (3 mg), or placebo (normal saline) in reducing the incidence and severity of PONV after laparoscopic cholecystectomy.

Patients and Methods

The study included 80 patients, 54 female and 26 male, aged between 20 and 65 years, ASA physical status I or II, undergoing general anaesthesia for elective laparoscopic cholecystectomy, from January 2009 to June 2012, after institutional approval from Minia University Hospital and the informed consent of all patients. Exclusion criteria included a history of allergy to any of the potential study medications, pregnancy, breastfeeding, active menstruation, vomiting or retching within 24 h before the operation, administration of antiemetic or psychoactive medication within 24 h before surgery, a history of severe (or unstable) cardiovascular, respiratory, metabolic, endocrine or neurologic disease, active...
alcohol or drug abuse, as well as impaired renal or hepatic function. Patients were sedated preoperatively with intravenous (IV) midazolam (1-2 mg) and fentanyl (50-100 μg). General anesthesia was induced with propofol (1.5-2.5 mg/kg) and vecuronium (0.1 mg/kg). Immediately after tracheal intubation, patients received 2-mL IV injection, either ondansetron 4 mg plus saline, granisetron 3 mg plus saline, or normal saline (NaCl 0.9%) as placebo.

Anesthesia was maintained with nitrous oxide 66% and isoflurane 1%-3% (inspired concentration) in oxygen. Ventilation was controlled mechanically and was adjusted to keep endtidal CO2 between 30 mmHg and 35 mmHg throughout surgery. A nasogastric tube was inserted and suction applied to empty the stomach of air and other contents. Before extubation of the trachea, the nasogastric tube was again suctioned and then removed. Muscle relaxants were used as needed. At the end of surgery, reversal of muscle relaxation was achieved with 0.02 mg/kg atropine IV and 0.04 mg/kg neostigmine IV, and then the trachea was extubated. If patients experienced nausea and/or vomiting, rescue antiemetic treatment (metoclopramide 10 mg IV) was administered.

Postoperative pain was initially treated with boluses of fentanyl, 25 μg IV. The essential steps of the operative technique included: induction of pneumoperitoneum; placement of a laparoscope through the infraumbilical port; inspection of the abdomen, reverse Trendelenburg position; additional trocars in the epigastrium, right midclavicular line, and right anterior axillary line; grasping and elevation of the fundus of the gallbladder; dissection of any adhesions to the omentum, colon, and duodenum; incision of the peritoneum over the infundibulum; detection of the cystic duct and cystic artery close to the gallbladder; doubly clip and division of the cystic artery and cystic duct; dissection of the gallbladder from the liver with electrocautery; checking hemostasis; removal of the gallbladder; placement of a closed suction drain; removal of trocars; and closure of large trocar sites.

All adverse events and rescue medications administered during the 48-h study period were recorded. Subjective experience of nausea and pain at rest was scored using verbal rating scale (VRS) from 0 to 10, with (0) representing no nausea or pain and (10) representing nausea or pain as bad as it can possibly be.

Data are presented as mean values ± standard deviation (SD), or numbers (n), and percentages (%). Normally distributed continuous data were analyzed using Student’s t-test. Continuous data not normally distributed (e.g., pain scores) were analyzed by a Mann-Whitney U-test. Categorical data were analyzed using the Chi-square (χ2) test or Fisher’s exact test where appropriate. A P-value of <0.05 was considered statistically significant.

Results

Out of 80 patients, 5 patients (3 female and 2 male) required conversion to open cholecystectomy and therefore were eliminated from the study; thus, 75 patients completed the protocol and are included in the statistical analysis. The studied patients were subdivided randomly into 3 groups: one group included 27 patients (19 female and 8 male) received Ondansetron (group O), another groups included 28 patients (22 female and 6 male) received Granisetron (Group G), and the third group included 20 patients (14 female and 6 male) received normal saline as placebo (Group P). There were no significant differences in age, gender, weight, height, history of PONV and history of motion sickness between the studied groups (Table 1).

During the first 48 hours after anaesthesia, the incidence of PONV was 37% in ondansetron group, 32% in granisetron group, and 65% in placebo group. The percentage of rescue antiemetic requirements was 44.4% in ondansetron group, 39.2% in granisetron group, and 75% in placebo group. There were no significant differences in the percentage of patients experienced PONV and rescue antiemetics between ondansetron and granisetron groups, however, there was a significant reduction in percentage of patients experienced PONV and the need for rescue antiemetics in both treatment groups when compared to placebo group (P-value <0.05) (Table 2). There were no significant differences in the severity of postoperative vomiting between the three groups (Table 3).

The comparison of nausea scores through first postoperative 48 hours using verbal rating scale (VRS), showed no significant difference between Ondansetron and Granisetron groups, however, both groups showed a significant reduction of nausea scores up to 6 hours postoperatively when compared to placebo group (P-value <0.05) (Fig. 1).

Table 1. Patient demographics.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group O (n = 27)</th>
<th>Group G (n = 28)</th>
<th>P-value</th>
<th>Group P (n = 20)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>44±13</td>
<td>42±14</td>
<td>0.58</td>
<td>45±16</td>
<td>0.59</td>
</tr>
<tr>
<td>Female/Male</td>
<td>19/8</td>
<td>22/6</td>
<td>0.48</td>
<td>14/6</td>
<td>0.69</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>79.6±25.1</td>
<td>78.2±21.3</td>
<td>0.82</td>
<td>77.2±23.1</td>
<td>0.77</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>163.2±20.7</td>
<td>161.6±18.4</td>
<td>0.76</td>
<td>164.6±22.3</td>
<td>0.67</td>
</tr>
<tr>
<td>History of PONV</td>
<td>3(11.1%)</td>
<td>4(14.2%)</td>
<td>0.72</td>
<td>2(10%)</td>
<td>0.74</td>
</tr>
<tr>
<td>History of motion sickness</td>
<td>6(22.2%)</td>
<td>5(17.8%)</td>
<td>0.68</td>
<td>5(20%)</td>
<td>0.64</td>
</tr>
<tr>
<td>History of smoking</td>
<td>6(22.2%)</td>
<td>6(21.4%)</td>
<td>0.94</td>
<td>5(20%)</td>
<td>0.77</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>66±16</td>
<td>64±17</td>
<td>0.65</td>
<td>63±14</td>
<td>0.63</td>
</tr>
</tbody>
</table>

2. Treatment groups compared to placebo group.
Table 2. Number and percentage of patients experienced postoperative nausea and vomiting (PONV) and rescue antiemetics during the first 48 hours after anaesthesia.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group O (n = 27)</th>
<th>Group G (n = 28)</th>
<th>P-value</th>
<th>Group P (n = 20)</th>
<th>P-value *</th>
</tr>
</thead>
<tbody>
<tr>
<td>PONV</td>
<td>10 (37%)</td>
<td>9 (32%)</td>
<td>0.70</td>
<td>13 (65%)</td>
<td>0.01*</td>
</tr>
<tr>
<td>Rescue antiemetics</td>
<td>12 (44.4%)</td>
<td>11 (39.2%)</td>
<td>0.69</td>
<td>15 (75%)</td>
<td>0.01*</td>
</tr>
</tbody>
</table>

*: Treatment groups compared to placebo group. *: significant difference.

Table 3. Severity of postoperative nausea and vomiting.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group O (n = 27)</th>
<th>Group G (n = 28)</th>
<th>P-value</th>
<th>Group P (n = 20)</th>
<th>P-value *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Once</td>
<td>4 (14.8%)</td>
<td>3 (10.7%)</td>
<td>0.64</td>
<td>6 (30%)</td>
<td>0.08</td>
</tr>
<tr>
<td>Twice or more</td>
<td>6 (22.2%)</td>
<td>6 (21.4%)</td>
<td>0.94</td>
<td>7 (35%)</td>
<td>0.22</td>
</tr>
</tbody>
</table>

*: Treatment groups compared to placebo group.

Discussion

Postoperative nausea and vomiting (PONV) can occur after local, regional, or general anesthesia and is associated with a variety of postsurgical complications that can adversely affect patient recovery and discharge [13]. The laparoscopic approach causes less morbidity and mortality than open cholecystectomy. It also offers a shorter duration of surgery and less intense pain [14, 15]. However, LC patients often experience postoperative nausea and vomiting (PONV) during the first 24 h after surgery [5]. In the present study, the baseline incidence of PONV (65%) in the placebo group is consistent with the incidence reported in previous studies for patients who underwent laparoscopic cholecystectomy. In literature, the reported incidence of PONV after LC varies from 50 to 70% [2, 16]. The etiology of PONV after LC is multifactorial. In the present study, many of these factors were standardized and there were no differences in these factors among the studied groups. Factors affecting PONV after LC are patient characteristics, surgical procedure, anesthetic technique, and postoperative care [17]. The incidence of PONV for female patients is three times that for males due to increased gonadotropin, estrogen, and plasma progesterone levels during their menstrual cycles [19]. Patients with a history of motion sickness or previous PONV are at increased risk for the development of emetic symptoms due to a low threshold for vomiting [17]. Cigarette smoking confers protection against PONV due to the presence of an antiemetic substance in tobacco smoke [19]. Surgical factors include operations (LC) with intraperitoneal insufflation of carbon dioxide (CO2), which has an effect on residual stretching and irritation of the peritoneum [20] and duration of surgery [21]. Each 30-min increase in duration of surgery increases the risk for PONV by 60% so that a baseline risk of 10% is increased by 16% after 30-min [21]. Anesthesia-related factors include the choice of preanesthetic medication and anesthetic agent (nitrous oxide [N2O], propofol). Hartung [22] found an increased rate of PONV with the use of N2O. In contrast, Taylor et al. [23] demonstrated that the use of N2O had no clinical effect on surgical condition during LC and did not increase the
incidence of PONV. Patients with propofol anesthesia have a lower incidence of PONV after LC than those with thiopentone/halothane anesthesia [24].

In the present study, the incidence of PONV, requirements of rescue antiemetic, and postoperative nausea scores significantly reduced when ondansetron (4 mg, IV) and granisetron (3 mg, IV) were compared to placebo. Ondansetron and granisetron are serotonin (5-HT3) receptor antagonists which considered as a highly effective drugs in the prevention of PONV after LC [2, 25-27]. Their actions involve both central and peripheral mechanisms in the control of nausea and vomiting. Centrally, they bind competitively and selectively to serotonin receptors in the CTZ of the CNS. In addition to their central effects, they also block receptors in the gastrointestinal tract, which prevents the action of serotonin and inhibits emetic symptoms [28]

Similar to our findings, ondansetron 4 mg administered IV immediately before induction of anesthesia reduces the incidence of PONV after LC [29-31], and is more effective than droperidol 1.25 mg or metoclopramide 10 mg [32]. A study by Naguib et al. [29] compared the antiemetic activity of the prophylactic administration of ondansetron (4 mg), tropisetron, granisetron, metoclopramide, and placebo. Ondansetron was found to be most effective and significantly better than metoclopramide and placebo. A study by Liberman et al. [31] showed that intravenous injection of 4 mg ondansetron was effective in reducing nausea and vomiting after ambulatory laparoscopic cholecystectomy. Another study demonstrated that ondansetron was able to reduce the incidence of nausea and vomiting between 1 and 4 h after an operation. However, there was no difference in the incidence of vomiting during the early recovery period (0–1 h) and 4 to 24 h after operation [32]. More recent study by Grover e al., [27] concluded that oral disintegration of an ondansetron 8-mg or ondansetron 4 mg administered IV are effective in preventing PONV after LC.

In contrast to the reported efficacy of ondansetron in preventing PONV after LC, a study by Koivuranta et al. [33], reported that 4 mg ondansetron failed to prevent PONV compared to placebo. More than 40% of patients experienced nausea and emesis, the rate of which was not reduced with the use of ondansetron. Also, a study by So et al., [34] found no difference in episodes of vomiting and usage of antiemetics between the ondansetron and control groups. Both groups were equally satisfied with the procedures. Therefore, those authors concluded that routine use of ondansetron does not reduce the incidence of postoperative nausea and vomiting after laparoscopic cholecystectomy.

In the present study, granisetron was as effective as ondansetron in prevention of PONV after LC. Granisetron is a highly selective and potent 5-HT3 receptor antagonist [35]. It acts specifically at 5-HT3 receptors on the vagal afferent nerves of the gut. Granisetron produces irreversible block of the 5-HT3 receptors and it may account for the long duration of this drug [36]. There is a controversy about the efficacy of granisetron in preventing PONV after LC. A study by White et al., [12] showed that the incidences of PDNV, requirements for rescue antiemetics, and quality of recovery did not differ between the ondansetron and granisetron. The antiemetic drug acquisition costs to achieve comparable patient satisfaction with ondansetron and granisetron were US $25.65 and $47.05, respectively. Therefore, ondansetron (4 mg IV) was more cost-effective than granisetron for routine antiemetic prophylaxis as part of a multimodal regimen in patients undergoing either outpatient or inpatient laparoscopic surgery. A study by Fuji et al., [37] concluded that granisetron is more effective than droperidol and placebo for reducing the incidence and severity of PONV after laparoscopic cholecystectomy. Another study by those authors [38] suggested that granisetron is a better anti-emetic than droperidol or metoclopramide for the prevention of post-operative nausea and vomiting after laparoscopic cholecystectomy when compared with a placebo. A study by Okus et al., [39] revealed that granisetron, when given prophylactically, resulted in a significantly lower incidence of PONV than metoclopramide and ondansetron, whereas metoclopramide was ineffective. Thus, those authors concluded that granisetron may be an effective treatment in the prophylaxis of PONV. Moreover, other studies found that prophylactic therapy with granisetron in combination with droperidol [40, 41], or dexamethasone [42-44] is more effective than granisetron alone for the prevention of PONV after LC.

In conclusion, for patients scheduled to undergo LC who are at high risk for PONV, the prophylactic use of antiemetics should be considered. Preoperative antiemetic prophylaxis with 5-HT3 receptor antagonists reduces incidence of PONV, requirements of rescue antiemetics and postoperative nausea scores after LC. There were no significant differences between granisetron (3 mg, iv) and ondansetron (4 mg, iv) with respect to their efficacy for preventing PONV. Garnisetron is more expensive than ondansetron, thus, regarding the cost-effectiveness of routine antiemetic prophylaxis, ondansetron is preferred.

References
4- Fuji Y. The utility of antiemetics in the prevention and treatment of postoperative nausea and vomiting in patients scheduled for laparoscopic


