The timing of Ondansetron Administration in Prevention of Postoperative Nausea and Vomiting
A comparative Study for Female Patients Undergoing Laparoscopic Cholecystectomy

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ABSTRACT:
BACKGROUND:
Postoperative nausea and vomiting (PONV) is a common distressing experience in patients following laparoscopic cholecystectomy.

OBJECTIVE:
This study was aimed at comparing the better timing of Ondansetron administration in prevention of PONV in female patients underwent elective laparoscopic cholecystectomy done under general anesthesia.

PATIENTS AND METHODS:
Fifty ASA physical status I and II female patients, aged 19 to 45 years, were enrolled in this prospective study to receive 4mg IV Ondansetron preoperatively (Group A), or 4 mg IV Ondansetron postoperatively (Group B), 25 patients each. A standardized general anesthetic technique was employed. Any episode of PONV was assessed at 8 hours postoperative period, every 2 hours, starting at time zone 0 (at post-anesthesia recovery unit), and ending at time zone 3 (hour 8 postoperatively). Complete response is defined as no PONV during 8 hours postoperative period. Incomplete response is defined as developing of postoperative nausea only during 8 hours postoperative period. Failure of prevention is defined as developing of PONV during 8 hours postoperative period.

RESULTS:
Complete response occurred in 60 and 64% in Groups A and B respectively. Incomplete response occurred in 12 and 4% in Groups A and B respectively. Failure of prevention occurred in 28 and 32% in Groups A and B respectively.

CONCLUSION:
There is no significant clinical difference between preoperative or postoperative Ondansetron administration of the same dosage in both groups in prevention of postoperative nausea and vomiting.

KEYWORDS: ondansetron, postoperative nausea and vomiting.

INTRODUCTION:
Laparoscopic cholecystectomy has become the treatment of choice for cholelithiasis due to its associated advantages of reduced morbidity and a shorter hospital stay\(^{(1,2)}\). The latter advantage has been negated by PONV, which is turning out to be the leading cause of unexpected re-admission after ambulatory surgery\(^3\). The reported incidence of PONV is 25% to 75% within the first 24 h after laparoscopic cholecystectomy when no prophylactic antiemetic is administered\(^{3,4,5,6,7,8}\). PONV is among the most unpleasant experiences associated with surgery and one of the most common reasons for poor patient satisfaction\(^{(9,10)}\).

Reduction of incidence of PONV, by utilizing Ondansetron, has been shown to improve patient satisfaction\(^{(11)}\). Nausea was defined as the subjectively unpleasant sensation associated with an awareness of the urge to vomit. Vomiting was defined as the forceful expulsion of gastric contents from the mouth\(^{(10)}\). Ondansetron (brand name: Zofran) is a highly selective 5-HT3 receptor antagonist; has onset of action of less than 30 minutes and its half life is approximately 4 hours. Exact duration unknown but it is prolonged compared to its half-life\(^{(12)}\).

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PATIENTS AND METHODS:
This study aimed to investigate comparative effectiveness between preoperative and postoperative Ondansetron administration in prophylaxis of PONV in female patients who underwent laparoscopic cholecystectomy under general anesthesia. After obtaining patient consent, fifty ASA physical status I-II female patients, aged between 19 and 45 years, underwent video-assisted elective laparoscopic cholecystectomy under general anesthesia, had been studied; from September 1, 2011 to May 24, 2012; at Baghdad Teaching Hospital, Medical City Complex, Baghdad, Iraq. Patients were randomly divided into two groups, group A and B, containing 25 patients each. Group A refers to patients received (4 mg) IV Ondansetron 15 minutes before induction, Group B refers to patients received (4 mg) IV ondansetron after extubation and PONV at this time is excluded. The patients were followed up for developing of PONV at 8 hours postoperative period, every 2 hours, starting at time zone 0 (at post-anesthesia recovery unit), and ending at time zone 3 (hour 8 postoperative period).

Exclusion Criteria
• Patients belonging to ASA grade III and IV.
• Pregnant or menstruating women.
• Patients with history of motion sickness.
• Menopause age.
• Patients have received antiemetic within 24 hours before surgery.
• Patients on chronic steroid therapy.
• Patients suffering from diabetes mellitus, hiatus hernia, gastrointestinal, renal or hepatic diseases.
• Patient who required conversion from laparoscopic technique to open approach.
• Patients with smoking habit.

Drugs have anti-emetic property (dexamethasone, metoclopramide, midazolam, and propofol); have been excluded.

Standardized anesthetic regimen was employed for all patients. Anesthesia was induced with 50 mcg fentanyl IV, 20 mg ketamine IV., and 5-7 mg/kg thiopentone sodium IV. Tracheal intubation was facilitated with 0.5 mg/kg Atracurium IV. Intubation time was less than 15 seconds. Anesthesia was maintained with 1 MAC Halothane and 100% Oxygen, using IPPV with MV setting of 6 – 7.2 L/Min. Intraoperative fluid administration was 600±100 ml/hr of 0.9% normal saline or 1/5 glucose saline. Reversal agent was 2.5 mg neostigmine IV, Atropine 0.6 mg was added to reduce Neostigmine side effects. The extubation was done once the patient became fully awake. Durations of CO2 insufflation, surgery and anesthesia had been recorded. CO2 insufflation pressure was recorded between 11 – 13 mm Hg. Patients received 100 mg IM Tramadol as postoperative analgesia, after admitting to surgical ward. Patients were monitored postoperatively every 2 hours during 8 hours. Both nausea and vomiting were assessed separately as present or absent. All observations were recorded by direct questioning (with only two possible answers of yes/no). Complete response is defined as no episode of PONV during 8 hours of postoperative period. Incomplete response is defined as developing of nausea only during 8 hours of postoperative period. Failure of prevention is defined as developing of PONV during 8 hours of postoperative period.

RESULTS:
A total of 50 patients were enrolled in the study. Twenty-five patients (group A) received 4 mg IV ondansetron preoperatively, whereas 25 patients (group B) received 4 mg IV ondansetron postoperatively. There was 1 patient which was converted to open cholecystectomy, had been excluded from group A. two patients in (group A) had bile spillage during operation and they recovered uneventfully. There were no other perioperative complications. There were no significant differences (P>0.05) between the groups in the Age, Duration of anesthesia, Duration of surgery or Duration of CO2 insufflation; as it is shown in (Table. 1). The incidences of postoperative nausea and vomiting, after 8 hours, are summarized in Table.2. Complete response occurred in 60 and 64% in Groups A and B respectively. Incomplete response occurred in 12 and 4% in Groups A and B respectively. Failure of prevention occurred in 28 and 32% in Groups A and B respectively. All these variables show no clinical significance in both groups.

DISCUSSION:
This is the 1st study compared the incidence of PONV in patients received ondansetron preoperatively or postoperatively, in relation to laparoscopic cholecystectomy. In addition it the 1st study explored the role of female gender and productive age in the incidence of PONV. Risk factors that have been reported to be associated with the incidence of PONV include prolonged CO2 insufflation(11), use of halogenated anesthetics and Fentanyl(10,13), and non-smoking status(3, 14). PONV after laparoscopic cholecystectomy are more likely to affect female patient within productive age(15). In this study,
beside high incidence of PONV associated with laparoscopic cholecystectomy, risk factors included are female gender, at productive age, non smoker, had been anesthetized using halogenated anesthetics and Fentanyl, and had received postoperative analgesia with emetic property (Tramadol). CO2 insufflation time in group A and B was shorter than time taken for CO2 insufflation in other studies\(^{(3,4, 6, 11, 16, 17)}\). Patient with motion sickness had been not included in the study to find out nausea and vomiting related to perioperative causes. Patients with previous experience of PONV also were excluded, to explore precise effect of laparoscopic cholecystectomy on PONV incidence. The incidence of PONV does not depend on the BMI value, the lack of influence by BMI has been reported recently by previous studies\(^{(13,15)}\); Therefore we did not involve BMI in our study as a risk factor.

Liberman et al\(^{(3)}\), showed that IV injection of 4 mg ondansetron was effective in reducing nausea and vomiting after ambulatory laparoscopic cholecystectomy. The selection of drug dosage was based on previous studies\(^{(18,19,20)}\). All patients involved in this study received a standard protocol for anesthesia; hence, the results were not affected by variations in the anesthetic medications. During first 6 hours postoperatively, Erhan et al\(^{(21)}\), found that the incidence of complete response was 70%, incomplete response was 25%, and failure of prevention was 5% in the group (n=20) that received 4 mg IV ondansetron preoperatively. Erhan et al, results was based on mixed gender group with mean age was 50.3± 14.6; comparing to group A (of our study) which consists of females only and with mean age of 34.35 ± 7.50, there are obvious demographic differences which make incidence of failure of prevention different.

So et al\(^{(22)}\), had been investigated the effect of 4 mg IV Ondansetron that had been administered at the end of surgery to group (n=36) of patients, they found that incidence of failure of prevention and incomplete response were 5% and 2.7% respectively, during first 2 hours after surgery. Their study differs from our study in anesthetic technique; they used 67% nitrous oxide and Intravenous morphine (0.1–0.2 mg/kg) in addition to agents we used in our study anesthetic technique. In addition, pethidine is administered as postoperative analgesia. Nitrous oxide, morphine and pethidine have well-established emetic property.

A placebo group was not included in this study for ethical reasons (i.e., so that all patients were relieved of the distressing PONV experience). Biswas et al\(^{(23)}\) have reported Ondansetron were effective in preventing early PONV (0-4 hours). Rajeeva et al\(^{(24)}\) have demonstrated that, the duration of action of Ondansetron is less than 8 hours. Similar to other 5-HT3 antagonists, Ondansetron has got a serum half-life of 4–9 hrs\(^{(4, 18, 25)}\).

Ondansetron is relatively expensive comparing to other antiemetics, Ondansetron 8 mg IV ampoule cost in Iraqi market is about 20, 000 ID.

### Table 1: Patient characteristics and surgical-anesthetic factors; number, mean ± SD.

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
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<tbody>
<tr>
<td>Number</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>Age (years)</td>
<td>34.35±7.5</td>
<td>34.8±7.2</td>
</tr>
<tr>
<td>Duration of anesthesia (minute)</td>
<td>61.1±5.09</td>
<td>62.73±4.8</td>
</tr>
<tr>
<td>Duration of surgery (minute)</td>
<td>48.35±6.29</td>
<td>49.1±7.3</td>
</tr>
<tr>
<td>Duration of CO2 insufflation (minute)</td>
<td>33.4±4.1</td>
<td>34.57±6.81</td>
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</tbody>
</table>

### Table 2: Overall incidence of PONV after 8 hours.

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>Clinical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>15 60%</td>
<td>16 64%</td>
<td>NS  P &gt; 0.05</td>
</tr>
<tr>
<td>Incomplete response</td>
<td>3 12%</td>
<td>1 4%</td>
<td>NS  P &gt; 0.05</td>
</tr>
<tr>
<td>Failure of response</td>
<td>7 28%</td>
<td>8 32%</td>
<td>NS  P &gt; 0.05</td>
</tr>
<tr>
<td>Total</td>
<td>25 100%</td>
<td>25 100%</td>
<td></td>
</tr>
</tbody>
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NS: not significant; N: number; %: percentage
CONCLUSION:
After all these evidences, we conclude there is no significant clinical difference between preoperative or postoperative Ondansetron administration of the same dosage in prevention of postoperative nausea and vomiting.

REFERENCES:

