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**Research Article**

# Evaluation of combination antiemetic prophylaxis in high risk emetogenic patients undergoing thyroid surgery: A randomized double-blind study

**Alaa El-Deeb [a,*], Yasser Ali [b], Hosam Rashdy [b]**

[a] *Department of Anesthesia, Faculty of Medicine, Mansoura University, Egypt*
[b] *Department of Surgery, Faculty of Medicine, Mansoura University, Egypt*

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**KEYWORDS**

Thyroid surgery;
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**Abstract** *Background:* This study was designed to find out the effective antiemetic drug for prevention of postoperative nausea and vomiting in high risk emetogenic patients undergoing thyroid surgery.

*Patients and methods:* One hundred twenty patients, ASA I, II, subjected to elective thyroid surgery were enrolled in this study. Patients were randomly assigned, according to antiemetic prophylaxis, into three groups, each consisted of 40 patients. Patients received 4 mg ondansetron plus 8 mg dexamethasone (Group II) i.v. or 2 mg midazolam plus 8 mg dexamethasone (Group III) i.v. or saline (Group I) just after induction of anesthesia. Frequency of nausea, vomiting, the use of antiemetics, the complete response (defined as no PONV and no administration of rescue antiemetic drug) were recorded at three time points (6 h, 12 h, 24 h) postoperatively.

*Results:* We found that ondansetron/dexamethasone or midazolam/dexamethasone significantly increased the complete response, compared with placebo, with an incidence of 90%, 85%, and 22.5%, respectively at 6 h, 90%, 87.5%, 25%, respectively, at 12 h and 95%, 92.5%, 47.5%, respectively at 24 h postoperatively.

* Corresponding author.
E-mail address: alaaeldeep9@hotmail.com (A. El-Deeb).

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*Conclusion:* We conclude that the prophylactic use of ondansetron/dexamethasone or midazolam/dexamethasone, compared with placebo, was effective for reducing nausea and vomiting in patients undergoing thyroid surgery. Midazolam/dexamethasone is preferred due to its cost relative to ondansetron/dexamethasone.

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## 1. Introduction

Nausea, vomiting and pain are the most important perioperative concerns from the patients' point of view. PONV can lead to delayed discharge from postanaesthetic care unit (PACU) and recovery room and readmission to hospital [1]. Previous studies, has reported the average incidence of PONV to be 40–60% [2,3]. Thyroidectomy is associated with relatively high incidences of PONV, ranging from 60% to 84% [4].

Postoperative nausea and vomiting are disagreeable complication that can be effectively managed. The risk must be suitably assessed and acted on accordingly [5].

Apfel's score predicting postoperative nausea and vomiting (PONV) in potentially high-risk patients considered four risk factors: female gender, previous history of PONV or motion sickness, non-smoking status and postoperative use of opioids [6,7]. Sinclair score included, in addition to these factors, duration, type of anesthesia and surgery [8].

Several studies demonstrated that dexamethasone has a potent antiemetic effect for the prophylaxis of PONV in a dose of 8–10 mg IV [9]. Also, midazolam has been reported to be a good antiemetic in controlling postoperative nausea and vomiting [10]. The clinical efficacy of anti-emetic combination of different classes is better than single drug therapy [11].

So far, the use of antiemetic combination for prevention of PONV in high risk emetogenic patients undergoing thyroid surgery has not been studied .The aim of this study was to investigate the efficacy and cost of two anti emetic combinations for the prevention of PONV in high risk group of surgical patients. We postulated that the use of i.v. midazolam/dexamethasone would reduce PONV after thyroid surgery.

## 2. Patients and methods

After institutional ethical committee approval and written informed consent, we studied 120 ASA (American society of anesthetists) physical status I or II patients, undergoing general anesthesia for elective thyroidectomy. Risk factors for PONV include adult female gender, previous history of PONV, history of motion sickness, non-smoking status, and duration of surgery more than 1 h. Inclusion criteria include patients with 3 or more risk factors. Exclusion criteria include age less than 17 years or more than 60 years, smoking, and surgery lasting less than 1 h and known allergy or previous adverse reaction to any of the study drugs.

Patients were randomly allocated using computer-generated code to receive 2 ml saline i.v. (Group I, $n = 40$), or ondansetron 4 mg/plus dexamethasone 8 mg i.v. (Group II, $n = 40$) or midazolam 2 mg plus dexamethasone 8 mg i.v. (Group III, $n = 40$). All solutions were 5 ml volume, looked identical, prepared by personnel blinded to the study and were given immediately after the induction of anesthesia. After the placement of standard monitors (ECG, non invasive arterial blood pressure, oxygen saturation), anesthesia was induced with i.v. propofol (2–2.5 mg/kg), and fentanyl (1 μg/kg) and vecuronium 0.15 mg/kg to facilitate tracheal intubation. After intubation, anesthesia was maintained with 2–2.5% sevoflurane and 50% oxygen in 50% air. Ventilation was mechanically controlled and adjusted to keep an end-tidal concentration of carbon dioxide 30–40 mm Hg throughout surgery. At the end of the operation, i.v. atropine (0.02 mg/kg) and neostigmine (0.04 mg/kg) were administered for reversal of the residual paralysis, and the trachea was extubated.

Postoperatively, Nausea and vomiting were evaluated every 3 h for 6 h then every 6 h up to 24 h by an observer who is blinded to group assignment. Data were reported at three time points (6 h, 12 h, 24 h). Retching (same as vomiting but without expulsion of gastric contents) was considered vomiting. Nausea was assessed using numerical scale (0 = no nausea; 10 = worst imaginable nausea). An antiemetic ''rescue'' drug (1 mg granisetron intravenously) was administered in case severe nausea (scale 4or more) or vomiting within the study period. The complete response was defined as no vomiting and no antiemetic drug. Data were also collected regarding the duration of surgery and side effects of dexamethasone, (e.g., wound infection), midazolam (e.g., respiratory depression) and ondansetron (e.g., headache, dizziness) were reported. Sedation was assessed with modified Ramsey sedation score (where 1 = Anxious, agitated or restless, 2 = Co-operative, orientated, and tranquil, 3 = semi sleep but responds to commands only, 4 = Brisk response to a light glabellar tap, 5 = Sluggish response to a light glabellar tap, 6 = No response to a light glabellar tap) [12] at 2 h postoperatively.

Postoperative pain was assessed with a 10-cm visual analog scale (0 = no pain to 10 = most severe pain) score. Postoperative analgesia was achieved with IV paracetamol 500 mg every 6 h. Diclofenac 75 mg IM is the rescue analgesic. Patient satisfaction regarding antiemetic prophylaxis was evaluated and recorded (10 point verbal numeric scoring system, 0 = not at all satisfied, 10 = fully satisfied).

## 3. Statistical analysis

The power analysis before the study showed that each group should be composed of 35 patients for detecting a 50% relative reduction in the incidence of postoperative nausea and/or vomiting in high risk patients, with a confidence interval of 95% (an error was set at 0.05). Forty patients were included in each study group for more statistic validity. The statistical analysis of data was performed using the SPSS for Windows (version 11; SPSS Inc., Chicago, IL) statistical software package. Data are tested for normality using Kolmogorov–Smirnov test. One way ANOVA test was performed to compare the parametric values of the studied groups, followed by Post Hoc test (Turkey's test). The Kruskal–Wallis test was used for the non-parametric analysis among the groups. $P$ is

significant if $<0.05$. Data are presented as number of the patients (percentage) or median (range) or mean ± standard deviation (SD).

## 4. Results

The three groups showed no significant differences regarding patient characteristics such as age, body mass index and duration of anesthesia (Table 1).

Nausea and vomiting were statistically significant less in groups II, III, compared to group I (placebo) up to 24 h. The incidence of complete response in group I was 22.5% compared with 90%, 85 in group II and III, respectively, at 6 h, whereas, it was 25%,90%, 87.5%, respectively, at 12 h and 47.5%, 95%, 92.5%, respectively, at 24 h postoperatively (Table 2). Although complete response in group II was less than that of Group III, it did not reach statistical significance.

The antiemetic rescue and incidence of nausea and vomiting were comparable between groups II, III during the study period (Table 2). No patient reported wound infection or respiratory depression in any group. Sedation score and other side effects of the study drugs were comparable among the three groups ( Table 3). Patient satisfaction with PONV control was statistically significant higher in groups II, III compared with group I (Table 3).

**Table 1** Patient characteristics and duration of anesthesia.

| | Group I | Group II | Group III |
|---|---|---|---|
| Age (year) | 32.1 ± 3.5 | 29.1 ± 3.4 | 30.2 ± 2.1 |
| Body mass index | 26 ± 1.2 | 27 ± 1.2 | 29 ± 1.3 |
| Duration of anesthesia (min) | 134 ± 4.2 | 132 ± 3.1 | 133 ± 5.1 |

Data are presented as mean ± standard deviation.

**Table 2** Incidence of nausea and vomiting, rescue antiemetic and complete response.

| | Group I | Group II | Group III |
|---|---|---|---|
| *6 h postoperative* | | | |
| Nausea | 27 (67.5%) | 10 (25%)* | 9 (22.5%)* |
| Vomiting | 16 (45.5%) | 4 (10%)* | 5 (12.5%)* |
| Rescue antiemetic | 21 (52.5%) | 4 (10%)* | 6 (15%)* |
| Complete response | 9 (22.5%) | 36 (90%)* | 34 (85%)* |
| *12 h postoperative* | | | |
| Nausea | 22 (55%) | 8 (20%)* | 7 (17.5%)* |
| Vomiting | 12 (30%) | 3 (7.5%)* | 4 (10%)* |
| Rescue antiemetic | 10 (25%) | 4 (10%)* | 6 (15%)* |
| Complete response | 10 (25%) | 36 (90%)* | 35 (87.5%)* |
| *24 h postoperative* | | | |
| Nausea | 10 (25%) | 2 (5%)* | 3 (7.5%)* |
| Vomiting | 6 (15%) | 1 (2.5%)* | 1 (2.5%)* |
| Rescue antiemetic | 9 (22.5%) | 2 (5%)* | 3 (7.5%)* |
| Complete response | 19 (47.5%) | 38 (95%)* | 37 (92.5%)* |

Values are presented as number of patient (percentage of study group).
*P* value $< 0.05$ is significant.
* Significant when compared to group I.

**Table 3** Perioperative data.

| | Group I | Group II | Group III |
|---|---|---|---|
| Sedation score | 1 (1–1) | 1 (1–1) | 1 (1–2) |
| Side effects | | | |
| Dizziness | 4 (10%) | 3 (8.5%) | 4 (10%) |
| Headache | 6 (15%) | 5 (12.5%) | 5 (12.5%) |
| Satisfaction score | 5 (2–6) | 10 (8–10)* | 10 (7–10)* |

Values are presented as number of patient (percentage of study group) or median (range).
*P* value $<0.05$ is significant.
* Significant when compared to group I.

## 5. Discussion

PONV are among the most common side effects after surgery. Increased incidence of PONV has been associated with many factors including age, gender, obesity, prior history of motion sickness or PONV, non-smoking, anesthetic techniques, surgical procedure and duration of surgery and the use of postoperative opioids [7,8]. Patients at high risk of postoperative nausea and vomiting often receive more than one prophylactic antiemetic drug [13]. In this study, patients with high risk factors were the target of this study. Other risk factors that cannot be included in patient's selection e.g. duration of surgery and the anesthetic technique were comparable among the study groups, So that the differences between the groups were more likely to be caused by antiemetic prophylaxis.

Dexamethasone, ondansetron and midazolam have been shown to be an effective antiemetic effect for the prophylaxis of PONV [10,13]. The antiemetic effect of midazolam is due to decrease in the dopaminergic neuronal activity and 5-HT3(5-hydroxy-tryptamine3) release by binding to the gamma-amino butyric acid (GABA) receptor [14]. Also, the mechanism of antiemetic effect of dexamethasone is due to central inhibition of prostaglandin synthesis and/or a decrease in serotonin turnover in the central nervous system [15]. Other antiemetics, such as antihistamines (e.g., hydroxyzine), anticholinergics (e.g., scopolamine), and dopamine receptor antagonists (e.g., droperidol, metoclopramide) have undesirable side effects of excessive sedation, tachycardia, drug mouth, dysphoria, and extra pyramidal symptoms [16,17].

The results of this study indicate that intravenous administration of 4 mg ondansetron/8 mg dexamethasone or 2 mg midazolam/8 mg dexamethasone during thyroid surgery reduced the incidence of PONV and improved the patient satisfaction in high risk emetogenic patients.

This study showed that the complete response (the primary outcome) at 24 h postoperatively in controlled patients (placebo) undergoing thyroid surgery was 47.5%. Wang et al. [9], reported higher incidence (65%) which can be explained by the type of patients. As patients included in this study are at high risk of PONV. Also, patients in the placebo group showed a high incidence of nausea at 6 h, 12 h, 24 h postoperatively (67.5%, 55%, 25% respectively)and of vomiting (45%, 30%, 15% respectively). This was in accord with recent clinical study evaluating antiemetic prophylaxis in thyroid [18].

Administration of i.v 4 mg ondansetron/8 mg dexamethasone or 2 mg midazolam/8 mg dexamethasone resulted in increase in the complete response at 24 h to 95%, 92.5%,

respectively. Wang et al. [9], reported lower incidence (88%, 89%) with 5, 10 mg dexamethasone which can be attributed to the use of antiemetic combination in this study.

Our results demonstrated that ondansetron/dexamethasone or midazolam/dexamethasone was effective in decreasing the incidence of PONV from 69% to 44% during the 24 h after surgery, which is comparable with the previous reports of ondansetron use for the prevention of PONV [19,20,2]. Single intravenous 8 mg dexamethasone, in this study, was not associated with side effects. In accord with our results, a comparative study of different antiemetic after acute abdominal surgery showed similar results [21].

This study showed that 4 mg ondansetron/8 mg dexamethasone or 2 mg midazolam/8 mg dexamethasone was shown to be comparable in preventing nausea and vomiting, and use of antiemetic during the first 24 h in high risk patients undergoing thyroid surgery. However, midazolam/dexamethasone would be better from the point of cost/effectiveness. Midazolam 2 mg and Dexamethasone 8 mg cost 7, 2.5 Egyptian bounds, respectively, whereas ondansetron costs 26 Egyptian bounds per 4 mg ampoule. Adverse events observed in our study were similar among all three groups.

The limitation of this study was that we used only two drug combination for PONV prophylaxis; further studies are needed to investigate other possible drug or non pharmacological combination.

In conclusion, ondansetron/dexamethasone or midazolam/dexamethasone was equally effective in decreasing incidence of PONV, need for rescue antiemetic, or patient satisfaction in high-risk female patients during the first 24 h after thyroid surgery.

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