Prophylactic antiemetic effects of midazolam, dexamethasone, and its combination after middle ear surgery

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ABSTRACT

الأهداف: تقييم ومقارنة تأثير عقار ديكساميثازون وميدازولام سويا أو كلاً على حدة في منع القئ والغثيان (PONV) بعد علميات الأذن لدى السيدات.

الطريقة: أجريت دراسة مستقبلية في مستشفى احد التعليمي – المدينة المنورة – المملكة العربية السعودية، خلال الفترة مابين مايو 2007م وحتى مايو 2008م. تم تقسيم 80 مريضة، العمر (32.6 عاماً) واللاتي سيخضعن لعمليات جراحية في الأذن الوسطى تحت التخدير العام إلى 4 مجموعات. تلقت المريضات وريدياً على محلول ملحي، ميدازولام 0.075mg/kg، ديكساميثازون 10mg، أو عقاري الميدازولام والديكساميثازون سويا قبل التخدير خضوعهن للتخدير الكامل. تمت مراقبة وتقييم المريضات خلال الـ24ساعة الأولى بعد العملية وتسجيل ما إذا حصل لهن غثيان، قئ أو كلاهما، أو أية آثار أخرى للعقارات المستخدمة في هذه الدراسة مثل الصداع أو الدوار وعدد المرات.

النتائج: كانت هناك فروقات جوهرية بين الأربع مجموعات، اقل مجموعة حصل لديها غثيان وقئ (PONV) كانت مجموعة الديكساميثازون مع ميدازولام (MD) مقارنة بالمجموعات الأخرى ($p<0.01$). أما بالنسبة للقئ لم يكن هناك فرق واضح بين تلك المجموعات الأربعة على الرغم من إن مجموعة الـ(MD) كانت اقلهم إصابتاً بالأعراض، ولم توجد فروقات واضحة بين تلك المجموعات بالنسبة إلى بقية الأعراض الأخرى مثل شدة الألم،الصداع،الدوار أو عدم التوازن.

خاتمة: إن استخدام عقار ميدازولام 0.075mg/kg، ديكساميثازون 10mg، عن طريق الوريد أعطى نتائج أفضل من استخدام العقارين كلاً على حده في التقليل من حدوث القي والغثيان المصاحب لما بعد عمليات الأذن الجراحية.

Objectives: To evaluate and compare the efficacy of the combination of midazolam and dexamethasone, with midazolam and dexamethasone alone, for the prevention of postoperative nausea and vomiting (PONV) in female patients undergoing middle ear surgery.

Methods: A prospective, randomized, double-blind, placebo-controlled study in 80 female patients (mean age 32.6 years), undergoing middle ear surgery with general anesthesia at Ohud Hospital, Madina, Kingdom of Saudi Arabia from May 2007 to May 2008. Patients were classified into 4 groups. They received intravenous normal saline (S group), midazolam 0.075 mg/kg (M group), or dexamethasone 10 mg (D group), or a combination of midazolam and dexamethasone (MD group), before the induction of anesthesia. Postoperatively for 24 hours observation and assessment of nausea, vomiting, rescue antiemetics, and side effects of the study drugs such as headache and drowsiness were carried out.

Results: There was a significant difference between the 4 groups. The MD group was the least to develop PONV compared to other groups ($p<0.01$). Regarding nausea, there was a non-significant difference between the 4 groups, although the MD group developed the least symptoms among the 4 groups, there were no significant differences in pain intensity and side effects such as, headache, dizziness, and drowsiness between the 4 groups.

Conclusions: The combination of midazolam 0.075 mg/kg and dexamethasone 10 mg intravenously is better than either drug alone in reducing the incidence of PONV in female patients after middle ear surgery.

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Postoperative nausea and vomiting (PONV) has a high incidence and frequency as a complication after surgery and general anesthesia (GA), especially after middle ear surgery (tympanoplasty or mastoidectomy).[1] Patients undergoing GA for middle ear surgery (tympanoplasty or mastoidectomy) have an incidence of PONV as high as 62-80%.[2] Due to this high incidence, a number of treatments have been introduced in order to reduce PONV such as; 5-Hydroxytryptamine3 (5-HT3) antagonists, dopamine receptor antagonists, and antihistamine drugs. However, the cost of 5-HT3 antagonists, the extrapyramidal symptoms with dopamine receptor antagonists, and the excessive sedation and tachycardia with antihistaminic drugs, limits its clinical use in PONV prophylaxis.[3] Recently, many studies had concluded that midazolam can be used as a prophylaxis of PONV by administration before or after the induction of anesthesia, or postoperatively.[4] Dexamethasone is also an effective anti-emetic in patients undergoing cancer chemotherapy. Its mode of action is not exactly known.[5] As the combination of midazolam and dexamethasone has not been used before in PONV prophylaxis after middle ear surgery, our hypothesis was this combination may be more effective than either drug alone. This study was conducted to evaluate and compare the efficacy of the combination of midazolam and dexamethasone, with midazolam and dexamethasone alone, for decreasing the incidence of PONV, and decreasing the use of postoperative antiemetics in female patients undergoing middle ear surgery (tympanoplasty or mastoidectomy).

Methods. This double blind study was conducted at Ohud Hospital, Madina, Kingdom of Saudi Arabia, from May 2007 to May 2008. After obtaining the ethical approval from the hospital ethics committee, we included in our study 80 female patients of American Society of Anesthesiologists grades 1 and 2, scheduled to undergo elective middle ear surgeries (tympanoplasty or mastoidectomy). Sample size was not determined as explained in the limitations of the study. Written informed consent was obtained from each patient. The exclusion criteria comprised of patients with history of preoperative nausea and vomiting (24 hours prior to surgery), history of PONV after previous anesthesia, patients on anti-emetic steroids within 24 hours before surgery, patients with diseases prolonging gastric emptying such as, diabetes mellitus, hiatus hernia, obese patients (body mass index >30), pregnant or menstruating females, patients with history of motion sickness, and known hypersensitivity to the study drugs. No premedication was given; the anesthetic techniques and postoperative pain management were standardized in all patients. All patients were divided randomly into 4 groups of 20 patients each. In a computer spreadsheet, a randomized list was made using a random number function. The administration of study drugs was carried out blindly by using similar syringes containing each drug with similar volumes. Immediately prior to the induction of anesthesia, the patients in each group received one of the following drugs intravenously (iv): group S - received saline as placebo, group M - received 0.075 mg/kg midazolam (CENEXI SAS, Fontenay-Sous-Bois, France),[6] group D - received 10 mg dexamethasone (EPICO-Egypt),[7] and group MD - received midazolam 0.075 mg/kg + dexamethasone 10 mg (EIPICO, Tenth of Ramadan City, Egypt). Induction of GA was carried out by propofol 2.5 mg/kg, fentanyl 2 ug/kg iv, and atracurium 0.5 mg/kg iv, to facilitate tracheal intubation, and was injected as required, to maintain neuromuscular blockade. General anesthesia was maintained by isoflurane 1-3% (inspired concentration) and oxygen (100%). Mechanical ventilation was performed to maintain the end-tidal CO_2 pressure at 35-40 mm Hg, primus model anesthesia equipment (Drager Medical, AG & Co., KGaA, Lubeck, Germany). A nasogastric tube was inserted and suction was also applied to empty the stomach with air and other contents. Intraoperative monitoring consists of continuous 5 lead ECG, blood pressure, pulse rate, respiratory rate, oxygen saturation, and capnography (Datex cardiocap vital signs detector). At the end of surgery, isoflurane was stopped and atropine 0.02 mg/kg iv and neostigmine 0.05 mg/kg iv were administered for neuromuscular block antagonism. The nasogastric tube was suctioned and removed before tracheal extubation. Extubation was carried out when the patient was awake and respiration was adequate, and regular patients were transferred to the recovery room. During the first 12 hours postoperatively, observation for nausea, vomiting, and retching was carried out every 2 hours, and every 4 hours during the next 12 hours. If more than 2 episodes of PONV occurred, a rescue anti-emetic in the form of metoclopramide 10 mg iv was given. One gram of paracetamol was given iv as a rescue analgesic. Nausea was defined as a subjectively unpleasant sensation associated with awareness of the urge to vomit,[8] was recorded on a 0-10 rating scale: (0 = no nausea, 1-3 = mild nausea, 4-6 = moderate nausea, 7-10 = severe nausea). Vomiting was defined as the forceful expulsion with gastric contents from the stomach. The spasmodic rhythmic contraction with respiratory muscles without the expulsion of gastric contents was considered as retching. Sedation was assessed according to Ramsay's sedation score.[9] There are 6 levels of sedation: level 1

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- patient is anxious, agitated or restless, level 2 - patient is cooperative, and oriented, level 3 - patient responds to commands only, level 4 - a brisk response, level 5 - a sluggish response, level 6 - no response. The first 3 levels were dependent on observation of the patients' anxiety, cooperation, and response to commands. The other 3 levels were dependent on the patient's response to a light glabellar tap. Visual analogue scale (VAS) is a tool widely used to measure pain (0 = no pain to 10 = worst pain). One gram of paracetamol was given if VAS was more than 3.

Statistical analysis. Data entry and analysis were performed using the Statistical Package for Social Sciences version 13.0 (SPSS Inc., Chicago, IL, USA) using appropriate statistical, descriptive, and analytical methods. Descriptive methods included frequency, means, and percentage. Analytical methods were the Chi-square test with confidence interval of 95% (p=0.05).

Results. The 4 groups were matched in terms of gender distribution, age, weight, and duration of surgical procedures. The difference in demographic data between the 4 groups was not statistically significant (**Table 1**). Postoperative nausea and vomiting in the 4 groups is summarized in **Table 2**. The sedation score was between 2 and 4 in 95% (p>0.05) of the patients in all groups. One patient in group S showed a sedation score of one, one patient in group M showed a sedation score of one, one patient in group D showed a sedation score of 5, and one patient in group MD shows a sedation score of 5. Ten percent (2 patients) of patients in each group required rescue analgesic because the VAS score was >30. Between the 4 groups there were no statistical differences in the VAS scores, or in the number of patients who needed rescue analgesic. No hemodynamic or respiratory adverse effects were observed related to the studied drugs in the 4 studied groups.

Discussion. Postoperative nausea and vomiting is a distressing symptom for patients after surgical procedures.[6] In our study, we compared the efficacy of the combination of midazolam and dexamethasone, with either midazolam or dexamethasone alone for the prevention of PONV in female patients undergoing middle ear surgery. This is the first clinical trial testing the efficacy of a combination of midazolam with dexamethasone in comparison to either drug alone after middle ear surgery. The rationale behind giving the study drugs at induction, rather than just prior to extubation, was to get the benefit of PONV immediately at recovery from anesthesia.

Our study showed that the incidence of PONVwas 70% in the S group. Our results are in agreement with the results of several studies.[10,11] Honkavaara et al[10] found that the incidence of PONV was 43% in the S group, in comparison with 27% in the hyoscine group in their study to evaluate the value of transdermal hyoscine in PONV prophylaxis during the first 24 hours after anesthesia. The incidence of PONV was also consistent with the study of Reinhart et al[11] who reported that the incidence of PONV after middle ear surgery was from 62-80% when no prophylactic anti-emetic is provided. Recently, Jung et al[6] found the incidence of PONV was 65% for patients in the S group (control group). Anti-emetics used for the prevention of PONV for 24

Table 1 - Demographic data of the 4 study groups.

Demographic data	Saline group	Midazolam group	Dexamethasone group	Midazolam and Dexamethasone group
Number of patients	20	20	20	20
Mean age, years	30.6	33.1	34.2	32.7
Mean weight, kg	52.3	55.2	56.2	54.6
Mean anesthesia duration, minutes	130.5	136.5	140.5	134.5

Table 2 - Postoperative nausea and vomiting (PNOV) in the 4 groups.

Observed items	Saline group	Midazolam group	Dexamethasone group	Midazolam + Dexamethasone group	Chi-square χ^2	*P*-value
			n (%)			
PONV	14 (70)	5 (25)	7 (35)	3 (15)	14.8	<0.01
Nausea	8 (40)	3 (15)	4 (20)	2 (10)	6.2	>0.05
Vomiting	6 (30)	2 (10)	3 (15)	1 (5)	5.4	>0.05
Rescue antiemetics	7 (35)	2 (10)	4 (20)	1 (5)	7.27	>0.05

hours are divided into traditional anti-emetics (such as anticholinergics, phenothiazines, butyrophenones, and benzamide), and nontraditional anti-emetics (propofol, dexamethasone, tandospirone, midazolam, ondansetron, granisetron, and ramosetron).[12] The prophylactic effect of dexamethasone against PONV was shown in patients undergoing chemotherapy,[13] gynecological surgery and thyroidectomy.[7] This study showed a decrease in the incidence of PONV during the first 24 hours after middle ear surgery in patients who received dexamethasone 10 mg iv immediately before induction of anesthesia, compared with those who received placebo. Our results are in agreement with several studies that demonstrated a prophylactic effect of dexamethasone on the incidence of PONV after various types of surgical procedures.[14,15] In a study conducted by Wang et al,[14] using 4 doses of dexamethasone to find the most effective dose in the prevention of PONV, a dose of 5 mg was concluded as effective as a 10 mg dose, and better than saline. The dose of 10 mg dexamethasone was chosen in our study, although some studies have shown even lower doses to be effective in reducing PONV. In a quantitative systematic review by Henzi et al,[16] the commonly used doses for PONV prophylaxis are 8-10 mg for adults, and we applied the higher limit of the dose to get the benefit of the analgesic effect of this dose of dexamethasone. Chu et al[15] in their study for the evaluation of the PONV prophylactic effect of dexamethasone in comparison with other anti-emetics in patients undergoing laparoscopic vaginal hysterectomy, concluded that dexamethasone was effective in PONV prophylaxis (incidence of 38%), compared with saline (incidence of 65%).

To explain why dexamethasone was effective in PONV prophylaxis, many theories have been proposed such as, prevention of serotonin production centrally or peripherally, prevention of prostaglandins synthesis, and a central effect changing blood brain barrier permeability to proteins.[7]

In our study, we found that dexamethasone was effective for preventing PONV after a middle ear surgery, which was in agreement with several studies.[3,17,18] Isik et al[17] concluded that no difference in the incidence of PONV was found after 4 hours of administration of dexamethasone compared with ondansetron. Furthermore, dexamethasone was found to cost less compared with ondansetron. Ahn et al[18] in their study, concluded that compared to the placebo group, the dexamethasone group showed reduced postoperative nausea at 24 hours postoperatively. A recent study had shown that midazolam, which is a short-acting benzodiazepine can be used for the prevention and treatment of PONV.[11] However, there are few reports on its use for prophylaxis of PONV in patients who undergo middle ear surgery. It has been used for the prophylaxis of PONV after tonsillectomy[19] and strabisthmus surgery[20] in children.

This anti-emetic effect of midazolam can be attributed to a dopaminergic effect at the chemoreceptor trigger zone (CRTZ) by decreasing the synthesis, release (by decreasing adenosine reuptake), and action of dopamine at the CRTZ. Also by binding to the gamma-aminobutyric acid (GABA) receptor, it can reduce 5-HT3 release, and decreases dopaminergic neuronal activity.[6] In our study, the dose of midazolam was 0.075 mg/kg iv, and this dose was selected because in previous studies, the dose suggested for the prevention of PONV was 0.05-0.075 mg/kg without adverse effects, or delayed recovery.[19] The higher limit of the dose range was chosen in our study because of the high incidence of PONV in female patients undergoing middle ear surgery, likewise, to obtain the benefit of relieving anxiety in these female patients, which may contribute to the antiemetic effect of midazolam.

Our results found that midazolam reduced the incidence of vomiting, and the number of patients requiring rescue anti-emetics after middle ear surgery in comparison to group S. These results are in agreement with that of Jung et al[6] who compared midazolam with saline for prophylaxis of PONV after middle ear surgery. They concluded that midazolam 0.075 mg/kg is effective for reducing nausea and vomiting after middle ear surgery. Our results showed that there was no significant difference in the sedation score between the 4 studied groups. This finding is in agreement with the previous studies.[6,19,20] Recently, Fujii[12] in his trial to study clinical strategies for preventing postoperative nausea and vomiting after middle ear surgery in adult patients concluded that combined anti-emetics blocking different types of receptors would be more effective than one drug alone for preventing PONV, as most of the used anti-emetics produce its antiemetic effect by blocking only one receptor type. In line with this hypothesis, we studied the effect of combined dexamethasone and midazolam for PONV after middle ear surgery in comparison to placebo or either drug alone. Our results showed that during the first 24 hours after anesthesia, PONV occurred in 70% in group S, 35% in group D, 25% in group M, and in 15% in the MD group.

The PONV etiology is affected by many factors related to patient data, surgical procedure, and anesthesia factors including duration, technique, and postoperative management.[8] All these factors are matched in our 4 groups. They are different only in the tested drug for PONV prophylaxis. Our results are in agreement with other reports using dexamethasone in combination with other antiemetics.[1,3,8,21,22] Fujii et al[21] found that the combination of granisetron with dexamethasone had a lower incidence of PONV than granisetron or dexamethasone alone after gynecological surgery.

A combination of granisetron with dexamethasone in middle ear surgery, was more effective than granisetrone or dexamethasone alone in decreasing the incidence of PONV.[1] Henzi et al[16] concluded that the combination of dexamethasone with an anti-emetic leads to reduced risk of PONV. Riad et al[22] evaluated the efficacy of midazolam alone, or in combination with dexamethasone in reducing the incidence of PONV in children undergoing strabisthmus repair, but they administered the studied drugs after the induction of anesthesia. They concluded that prophylactic midazolam with, or without dexamethasone reduced the incidence of PONV. In comparison to our study the factors responsible for PONV were not standardized in both studies. Also, the anesthesia technique and the demographic data of patients was different. Bauer et al[23] explained how the anti-emetic effect of a short acting-agent like midazolam lasts for as long as 24 hours. They concluded that intravenous premedication of midazolam 0.04 mg/kg reduced PONV for 24 hours postoperatively. The anti-emetic effect of midazolam was suggested to last longer than the sedative effect.[24]

The limited number of patients, and non determination of the serum levels of the studied drugs limited this study.

In summary, we suggest that the combination of midazolam 0.075 mg/kg and dexamethasone 10 mg iv is better than either drug alone, in reducing the incidence of PONV in female patients after a middle ear surgery. As the studied drugs are safe with no adverse effects, cheap, and most of the anesthesiologist are familiar with their use, it is recommended to be used as a prophylaxis of PONV in female patients undergoing middle ear surgery. Further studies are needed to prove the efficacy of the same combination in other operations and in morbidly obese patients.

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