The Egyptian Journal of Hospital Medicine (July 2022) Vol. 88, Page 3155-3162

Comparative Study among Gabapentin, Midazolam and Granisetron for Prevention of Postoperative Nausea and Vomiting after Middle Ear Surgery

Ahmed Mohamed Salama Al-Najjar, Dalal El-Sayed Mohammad Soud, Haitham Nuri Farg Hassan*, Nermeen Mohammad Ali Mohammed

Department of Anesthesia, Intensive Care and pain management, Faculty of Medicine Zagazig University, Egypt

***Corresponding author:** Haitham Nuri Farg Hassan, **Mobile:** (+20) 01069022954, **E-mail:** haithamnuri85@gmail.com

ABSTRACT

Background: Postoperative nausea and vomiting (PONV) is the one of the most unpleasant complications. PONV is more distressing for patients than pain.

Objective: The aim of the present study was to prevent PONV after middle ear surgery by comparing one hour preinduction use of oral gabapentin, intravenous Midazolam or Granisetron.

Patients and methods: This was a prospective double-blinded randomized placebo controlled clinical study that was conducted in Anesthesia, Intensive Care and Pain Management Department in Zagazig University Hospitals. The study was carried out within 6 months on 108 adult patients between the ages of 21 and 65 years planned for middle ear surgery. The study included 46 men and 62 women. The patients were divided into four groups: Control (C) group, Gabapentin (G) group, Midazolam (M) group and Granisetron (GR) group (27 patients in each). Patients were followed-up 24 hours postoperatively for the incidence and severity of PONV, hemodynamic changes, side effects of these drugs and the need for rescue antiemetics.

Results: Vomiting and nausea was considerably higher in Group C. Moreover, nausea was noticeably associated with Group G, It was reduced from 14.3% at 8-16 hr interval to 9.5% at 16-24 hr interval in M group. There was no significant difference among studied groups regarding side effects. Only one patient in G group felt dizziness, one patient suffered from extra pyramidal symptoms and one patient complained from vertigo. One patient in C group felt vertigo and 2 patients in GR group felt headache.

Conclusions: Using oral Gabapentin 300 mg, intravenous Midazolam 0.075 mg/kg or Granisetron 3 mg one hour before induction of anesthesia in middle ear surgeries, surely causes a substantial reduction in occurrence of PONV.

Keywords: PONV, Gabapentin, Midazolam, Granisetron.

INTRODUCTION

PONV is the one of the most unpleasant complications. PONV is more distressing for patients than pain. The etiology of PONV is multi-factorial and its occurrence depends on the type and duration of surgery, the type of drugs used during anesthesia, the technique of anesthesia, age, sex, and smoking habit. PONV increases intraocular and intracranial pressure, causes wound dehiscence and prolongs duration of stay in the recovery room and hospital. Also, PONV is an uncommon cause of aspiration, dehydration, electrolytes disorder and even death especially in children and elderly patients and increase the cost of treatment [1].

The incidence of PONV after middle ear surgeries is high. It has been reported that 50-80% of the patients who undergo middle ear surgeries experience PONV [2].

To prevent PONV, different kinds of drugs could be used including promethazine, droperidol, ondansetron, dexamethasone and propofol. Despite using different kinds of drugs, PONV is a common side effect yet [3]. The objectives of the present study were to compare the incidence and severity of PONV after using oral Gabapentin, intravenous Midazolam or Granisetron after middle ear surgery and to assess the side effects of the used drugs, which may include drowsiness, nausea, vomiting, diarrhea, blurred vision, dry mouth, headache, hiccups, stomach pain, weakness and feeling sleepy.

PATIENTS and METHODS

This prospective double-blinded randomized placebo-controlled clinical study was conducted on 108 cases planned for middle ear surgery attended the Anesthesia, Intensive Care, and Pain Management Department in Zagazig University Hospitals throughout six months started from November 2021 to May 2022.

Inclusion criteria:

Patients undergoing elective unilateral middle ear surgeries under general anesthesia with age between 21 and 65 years, both males and females, and belonging to ASA I or II. BMI 25-30 kg/m^2.

Exclusion criteria:

Patients with a known allergy, sensitivity, or any other form of reaction to gabapentin, midazolam, and granisetron. Patients with systemic comorbidities. Patients with preoperative involvement of the inner ear or intraoperative gross damage to the inner ear. Pregnant and lactating females or during menstruation period. History of motion sickness, CNS disorder especially cerebellar problems and using antiemetic drugs. Addicts receiving benzodiazepine medication.

The patients were allocated randomly using a computer-generated table into four equal groups (27 patients for each group). Group C (control) (n= 27) where patients received a placebo tablet 1 hour before induction with sips of water and 2 ml saline before induction. Group G (Gabapentin) (n=27) where patients

Received: 13/02/2022
Accepted: 12/04/2022

received oral gabapentin 300 mg 1 hour before induction with sips of water and 2 ml saline [4]. Group M (Midazolam) (n=27): Patients received oral placebo tablet 1 hour before induction and intravenous midazolam 0.075mg/kg [5]. Group GR (Granisetron) (n=27): Patients received oral placebo tablets 1 hour before induction and intravenous granisetron 3mg [6].

Preoperative preparation:

All patients were visited in the ward before surgery. Full medical and surgical history was taken, proper clinical examination. Detailed pre-anesthetic check-ups and investigations of all patients posted for planned middle ear surgery were done a day before surgery to decide the fitness and eligibility. The body mass index (BMI) was calculated as the patient's weight in kilograms divided by the square of height in meters. A blood sample was collected from each patient for complete blood count, bleeding time, PT, PTT, liver and kidney function tests and HCV Ab and HBV Ag.

Intraoperative preparation: On arrived to the operating room, a peripheral intravenous line (18G) was established and monitors for non-invasive blood pressure (NIBP), ECG and SPO_2 were connected to the patients, and baseline of mean blood pressure, HR, respiratory rate and SPO_2 were recorded.

Intraoperative Assessment and Treatments:

The studied drugs were given before the induction of anesthesia. General anesthesia was induced by intravenous injection of 2 mg/kg propofol and 2 bug/kg fentanyl. Tracheal intubation was facilitated by intravenous injection of 0.8 mg/kg rocuronium and controlled ventilation was started with adjustment of tidal volume and respiratory rate to maintain $EtCO_2$ 35-45 mmHg. Anesthesia was maintained with 1.5% isoflurane and muscle relaxant rocuronium 0.2 mg/kg guided by nerve stimulation.

Postoperative Assessment and Treatments:

At the end of surgery, inhalational anesthesia was stopped and muscle relaxant was reversed with a mixture of neostigmine 0.05 mg/kg and 0.01mg/kg of atropine. Extubation was performed when the patient becomes fully awake and was transferred to the PACU and monitored for mean blood pressure, heart rate, respiratory rate, and SPO_2.

Nausea is defined as a subjective unpleasant sensation associated with awareness of the urge to vomit. Vomiting is defined as forceful expulsion of gastric contents from the mouth [7]. Continuous intraoperative hemodynamics monitoring (mean blood pressure and heart rate). Incidence and severity of postoperative nausea and vomiting and the first time of occurrence were assessed in the PACU all over the 1st 24 hours. An emetic episode means single vomit or retch or any number of continuous vomit or retch. One emetic episode should be separated from another by an absence of vomiting or retching for at least one minute. The rescue antiemetic, intravenous ondansetron 4 mg was administered for severe nausea or two more episodes of vomiting. Number of doses and total consumption of antiemetics per 24 hour was recorded.

Ethical Consideration:

The study was approved by the Local Ethical Committee of Zagazig University. Written consent was obtained from every patient prior to the procedures. This study has been carried out in accordance with the code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

Data were collected, revised, coded and entered to the Statistical Package for Social Science (IBM SPSS) version 20. The comparison between two groups with qualitative data were done by using Chi-square test and/or Fisher exact test, which was used instead of Chi-square test when the expected count in any cell was found less than 5. The comparison between more than two independent groups with quantitative data and parametric distribution was done by using One Way ANOVA test. The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant ($P \leq 0.05$), highly significant ($P \leq 0.001$) or non-significant ($P > 0.05$).

RESULTS

Table (1) showed that there was no statistically significant difference found between studied groups regarding patient characteristics (age, gender, weight, height, BMI), ASA and duration of surgery. Mean age was distributed as 36.89 ± 8.02, 35.85 ± 7.75, 36.22 ± 7.84 and 36.56 ± 8.55 years among groups **C**, **G**, **M** and **GR** respectively. Males were distributed as 40.7%, 48.1%, 40.7% and 40.7% among group **C**, **G**, **M** and **GR** respectively, and females were distributed as 59.3%, 51.9%, 59.3% and 59.3% among group **C**, **G**, **M** and **GR** respectively with no considerable difference between studied groups concerning sex distribution. Surgery duration was distributed as 125.07 ± 26.51, 124.41 ± 28.40, 121.30 ± 33.25and 139.11 ± 32.29 among group **C**, **G**, **M** and **GR** respectively.

Table (1): Patient characteristics and duration of surgery among studied groups

		Group C	Group G	Group M	Group GR	Test value	P-value
		No.= 27	No.= 27	No.= 27	No.= 27		
Age (years)	Mean ± SD	36.89 ± 8.02	35.85 ± 7.75	36.22 ± 7.84	36.56±8.55	0.082	**0.969**
	Range	22 – 50	21 – 50	21 – 50	21 – 50		
Gender	Male	11 (4o.7%)	13 (48.1%)	11 (40.7%)	11 (40.7%)	0.454	**0.929**
	Female	16 (59.3%)	14 (51.9%)	16 (59.3%)	16 (59.3%)		
Weight (kg)	Mean ± SD	70.00 ± 8.89	71.12 ± 11.48	70.96 ± 7.97	71.85±12.23	0.149	**0.930**
	Range	55 – 85	55 – 95	55 – 85	60 – 95		
Height (meter)	Mean ± SD	1.59 ± 0.11	1.64 ± 0.09	1.61 – 0.10	1.65 ± 0.06	2.182	**0.095**
	Range	1.39 – 1.76	1.45 – 1.75	1.39 – 1.73	1.55 – 1.75		
BMI (kg/m^2)	Mean ± SD	27.79 ± 3.66	28.59 ± 3.63	27.71 ± 4.75	29.19 ± 2.81	0.934	**0.427**
	Range	19.96 – 34.68	22.04 – 39.41	18.93 – 39.41	22.04–35.65		
ASA (physical status)	I	21 (77.8%)	18 (66.7%)	20 (74.1%)	19 (70.4%)	0.923	**0.820**
	II	6 (22.2%)	9 (33.3%)	7 (25.9%)	8 (29.6%)		
Duration of surgery (minutes)	Mean ± SD	125.07±26.51	124.41±28.40	121.30±33.25	139.11±32.29	1.858	**0.141**
	Range	80 – 195	80 – 195	80 – 195	90 – 195		

P-value >0.05: Non significant (NS)

Table (2) showed that there was statistically significant difference found between the four groups regarding incidence and severity of PONV, (P-value < 0.05). Incidence of PONV was distributed as 77.8 %, 70.4%, 55.6 % and 44.4% respectively among group **C**, **M**, **G** and **GR**. Group **C** was considerably higher regarding occurrence of PONV followed by group **M**, **G** and **GR**, but there was no major statistical difference between group **G** and **GR**. Regarding the severity of PONV, it was divided into mild, moderate and severe, the severe cases were more in **C** group (57.1%) then **G** group (53.3%) while **M** group was the lowest in severe cases (15.8%). Also **C** group showed increase in mild cases in comparison with other groups.

Table (2): Incidence and severity of PONV among the four studied groups.

		Group C		Group G		Group M		Group GR		Test value	P-value
		No.	%	No.	%	No.	%	No.	%		
Incidence of PONV	No	6	22.2%	12	44.4%	8	29.6%	15	55.6%	7.667	0.043*
	Yes	21	77.8%	15	55.6%	19	70.4%	12	44.4%		
Severity of PONV	Mild	7	33.3%	3	20.0%	6	31.6%	3	25.0%	11.716	0.048*
	Moderate	2	9.5%	4	26.7%	10	52.6%	4	33.3%		
	Severe	12	57.2%	8	53.3%	3	15.8%	5	41.7%		

P-value <0.05: Significant(S)

Figure (1) showed P-value of > 0.05, which indicated that there was no significant statistical difference among the studied groups concerning MBP at baseline and at different postoperative times. At 15 min postoperatively MBP was 92.74 ± 7.81, 94.81 ± 7.17, 95.11 ± 7.2 and 94.37 ± 7.5 in groups **C**, **G**, **M** and **GR** respectively, MBP at 60 min was lower in group **C** than the other groups, while at 24 hr the highest reading was noted in **G** group.

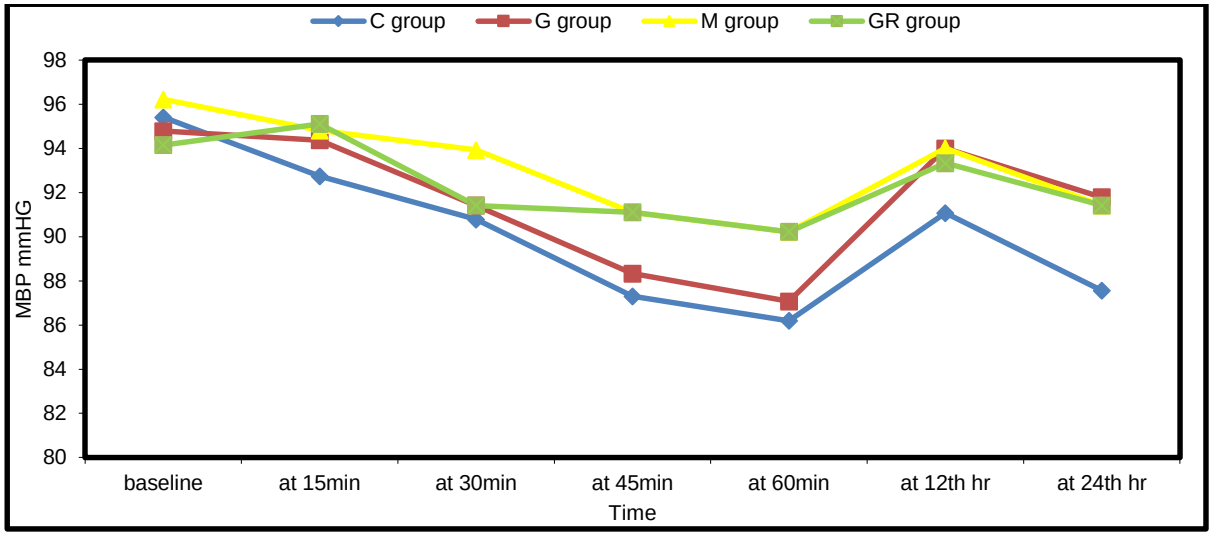

Figure (1): MBP in (mmHg) between the studied groups

Figure (2) showed that there was no statistically significant difference found among the studied groups as regards HR.

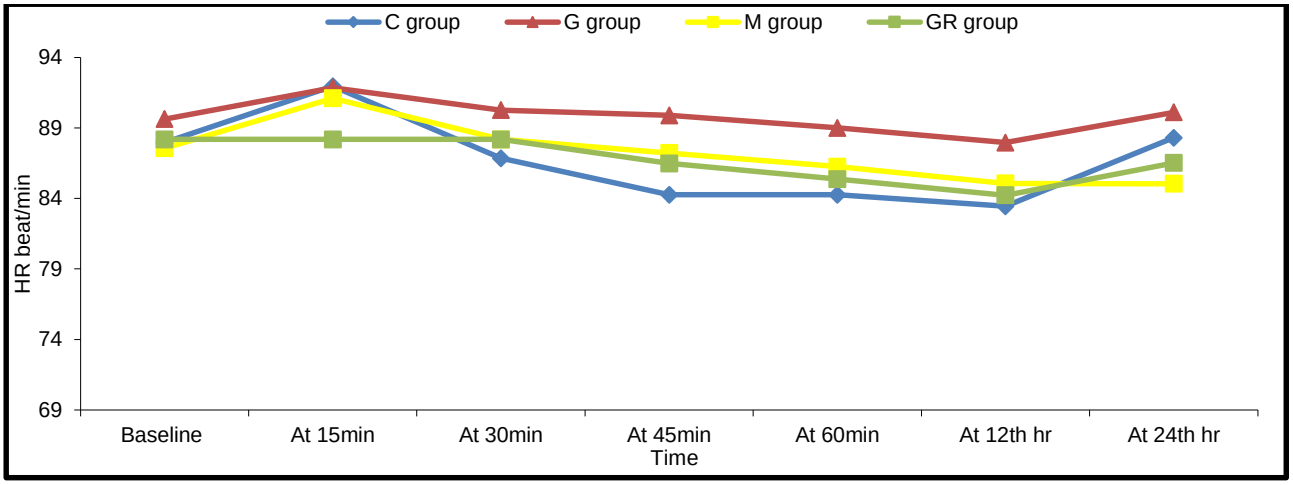

Figure (2): HR in (beat/minute) between the studied groups

Figure (3) showed that there was no statistically considerable difference between the four groups regarding RR.

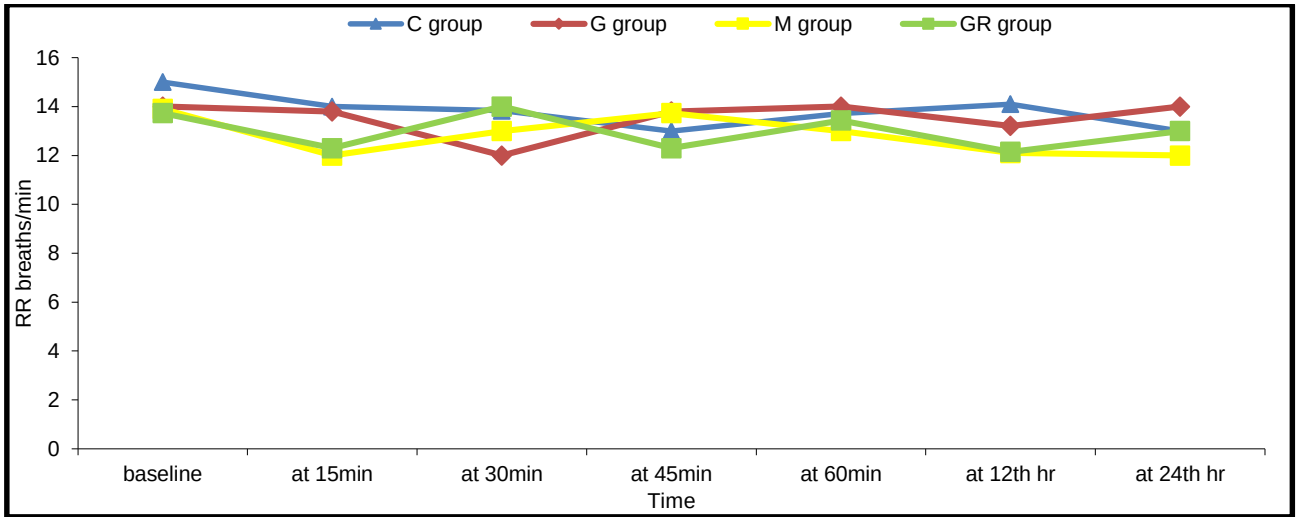

Figure (3): RR in (breath/minute) between the studied groups

Table (3) showed that there was no statistical significant difference among studied groups regarding side effects. Only one patient in G group suffered from dizziness, one patient complained from extra pyramidal symptoms and one patient felt vertigo. One patient in C group felt vertigo and two patients in GR group complained from headache.

Table (3): Side effects of used drugs in the four groups

Side effects of used drugs	Group C		Group G		Group M		Group GR		Test valu*	P-value
	No.	%	No.	%	No.	%	No.	%		
Respiratory depression	0	0.0%	0	0.0%	0	0.0%	0	0.0%	–	–
Apnea	0	0.0%	0	0.0%	0	0.0%	0	0.0%	–	–
Drowsiness	0	0.0%	0	0.0%	0	0.0%	0	0.0%	–	–
Dizziness	0	0.0%	1	3.7%	0	0.0%	0	0.0%	3.028	0.387
Extra pyramidal symptoms	0	0.0%	1	3.7%	0	0.0%	0	0.0%	3.028	0.387
Vertigo	1	3.7%	1	3.7%	0	0.0%	0	0.0%	2.038	0.565
Headache	0	0.0%	0	0.0%	0	0.0%	2	7.4%	6.113	0.106

P-value >0.05: Non significant (NS)

Table (4) showed that there was no significant difference found between studied groups regarding vomiting (P- > 0.05). There was highly statistically significant difference (P- < 0.01) found between the groups regarding first time of vomiting episode (hours). First time of vomiting episode showed statistically significant decrease in **C** group (0.80 ± 0.22) than **M**, **GR** and **G** groups (0.88 ± 0.27, 2.81±0.67, 3.42 ± 0.41 respectively). **GR** and **G** groups showed longer time to first time of vomiting episode to occur (2.81 ± 0.67 and 3.42 ± 0.41) respectively. The patients in G group took longer time to complain from vomiting than the other groups followed by GR group.

Table (4): Vomiting and first time of vomiting episode (hours) among studied groups

		Group C		Group G		Group M		Group GR		Test value	P-value
		No	%	No	%	N	%	N	%		
Vomiting	From Post to 8hr	5	(22.6%)	2	(13.3%)	4	(21.1%)	2	(16.7%)	2.361	0.501
	From 8hours to 16hr	5	(22.6%)	2	(13.3%)	4	(21.1%)	1	(8.3%)	3.750	0.290
	From 16hours to 24hr	4	(18%)	1	(6.7%)	3	(15.8%)	1	(8.3%)	3.273	0.351
First time of vomiting episode (hours)	Mean±SD	0.80 ± 0.22		3.42 ± 0.41		0.88 ± 0.27		2.81 ± 0.67		262.514	0.000**
	Range	0.5 – 1.2		2.8 – 4		0.5 – 1.29		1.92 – 3.72			

P-value >0.05: Non significant (NS), P-value< 0.01: highly significant (HS)

Table (5) showed that there was no statistically significant difference found between studied groups regarding nausea. Immediately postoperative up to 8 hr (P-value = 0.521), from 8 hr up to 16 hr (P-value = 0.739), and from 16 hr up to 24 hr (P-value = 0.932).

Table (5): Nausea among the four groups (number and percentage)

	Group C		Group G		Group M		Group GR		Test value	P-value
	No	%	No	%	N	%	N	%		
From post to 8hr	2	(10.5%)	4	(26.7%)	3	(15.6%)	3	(25.0%)	2.255	0.521
From 8hr to16hr	3	(15.8%)	4	(26.7%)	3	(15.6%)	3	(25.0%)	1.257	0.739
From 16hr to 24hr	2	(10.5%)	2	(13.3%)	2	(10.8%)	2	16.7%)	0.435	0.932

P-value >0.05: Non significant (NS)

Figure (4) showed that there were three cases in Group **C** and **M** (11.1 %) while only one case in group **G** and **GR** (3.7 %) need rescue of anti-emetic (ondansetron) with no large statistical significant difference between the four groups.

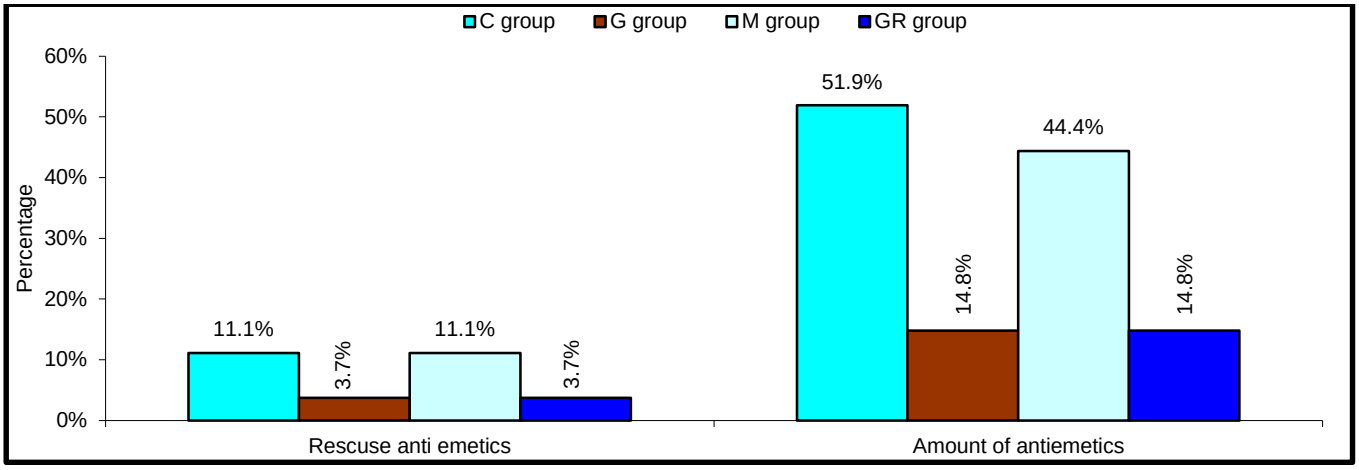

Figure (4): The difference between studied groups regarding rescue antiemetics and the total dose of antiemetics.

DISCUSSION

The present study showed that there was statistically significant difference found between control group, Gabapentin group, Midazolam group and Granisetron group regarding incidence and severity of PONV. The current work showed that there was no statistically significant difference found among the four groups regarding postoperative MBP, HR and RR. This study showed also that there was no statistically significant difference found between studied groups regarding side effects of used antiemetics. The present study showed that there was no statistically significant difference among the groups regarding nausea and vomiting, but there was highly statistical significant difference regarding first time of vomiting episode (hours). The present study also showed that there was no statistically significant difference found between the groups regarding rescue and total dose of antiemetics.

In the current study, incidence of PONV was statistically lower among **G**R group (44.4%) than **G**, **M** and **C** groups (55.6%, 70.4%, and 77.8% respectively). Generally, there was statistically significant difference found between the four groups regarding incidence and severity of PONV. Regarding the severity of PONV, it was divided in to mild, moderate, and severe, the severe cases were more in **C** group (57.1%) then **G** group (53.3%) while **M** group was the lowest in severe cases (15.8%). Also **C** group showed increase in mild cases in comparison with other groups. This agrees with **Heidari *et al.*** [8] who showed that using oral Gabapentin 300 mg or intravenous Granisetron 3 mg 1 hour before induction of general anesthesia significantly reduced the incidence and severity of PONV in comparison with placebo. Also, in another study performed by **Ganjare and Kulkarni** [9] where they showed that Granisetron 1 mg administered before induction of anesthesia was effective for prevention of PONV.

In this study the percentage of Gabapentin in prevention of PONV was (55.6%) and this somehow agrees with **Khademi *et al.*** [10] who showed that administration of oral Gabapentin 2 hours before surgery significantly reduced the incidence of PONV after open cholecystectomy. Also, **Kong and Irwin** [11]**,** showed that oral Gabapentin had significant effect in reducing the incidence and severity of PONV after laparoscopic surgery. While, **Sussan and Mirsadegh** [12] observed that none of the patients in Gabapentin group had vomiting. This disagree with **Anuradha and Balakrishnan** [13] who observed that the incidence of PONV between the oral Gabapentin and intravenous Granisetron groups were statistically insignificant.

It has been shown that combination of Granisetron and Dexamethasone has more beneficial effect than using each drug individually [14]**.** Also, **Kim *et al.*** [15] found lower incidence of PONV in combination therapy than using each drug individually. The incidence was declined from 52.1% to 23%.

Studies have shown that Granisetron and Ondansetron are better antiemetics for preventing PONV compared to a placebo [15-17]**.** In this regard, **Kim *et al.*** [17] found that oral Gabapentin 300 mg administered 1 h before induction of anesthesia and intravenous Ramosetron 0.3 mg given at the end of surgery were associated with comparable PONV-preventive effects in patients undergoing laparoscopic gynecologic surgery. In addition, the combination of these two drugs was more effective in preventing PONV than using each one individually after gynecologic laparoscopic surgery. Furthermore, Gabapentin is a relatively inexpensive medication, the use of which can result in significant cost savings [18]**.** Also, **Jahromi *et al.*** [19] found that oral premedication with Gabapentin 300 mg Chlorpromazine 25 mg, and Metoclopramide 10 mg before maxillofacial trauma surgery could lead to a significantly reduced incidence of PONV. A previous study by **Achuthan *et al.*** [4] who used Gabapentin in patients undergoing abdominal surgery demonstrated the differential antiemetic efficacy of Gabapentin with respect to the use of Propofol, either as an induction or maintenance agent. Preoperative Gabapentin as pharmacotherapy for preventing PONV was effective when Propofol was not used.

This study revealed that, incidence of PONV was 70.4% among **M** group that was more than **G** and **GR**

groups (55.6% and 44.4%, respectively). This agrees with **Heidari *et al.*** [20] who found that Midazolam administration before induction of general anesthesia was effective in prevention of PONV. Midazolam has been used in preventing PONV and its beneficial effect has been shown**.** In addition, this is in accordance with **Sanjay and Tauro** [21] who showed that Midazolam in comparison with control group had more efficacies in preventing PONV after cardiac surgery.

In a meta-analysis conducted by **Ahn *et al.*** [22] fifteen of the 16 relevant studies reported that there were ***no significant differences*** between Midazolam and control groups and this does not agree with the results of this study, which showed that there was statistically significant difference between control versus Midazolam in the incidence of PONV. In this regard, **Amr *et al.*** [23] showed that Midazolam had preventive effects on PONV similar to Ondansetron or Haloperidol in high-risk patients after gynecological laparoscopic surgery. Also, **Lee *et al.*** [24] reported that there is no preference of Ondansetron on Midazolam in the prevention of PONV. They compared between Midazolam 2 mg and Ondansetron 4 mg for preventing PONV and showed that the proportions of patients who did not experience PONV in the first 24 h were similar in the two groups. **Heidari *et al.*** [20] showed that combination therapy with Midazolam and Dexamethasone prevents PONV more effectively than Midazolam alone. The frequency of vomiting was significantly less in recovery room and after 6 h during the first postoperative day.

In The present study, there was no statistically significant difference found between studied groups regarding side effects of used drugs. Only one patient in **G** group felt dizziness, one patient felt extra pyramidal symptoms and one patient felt vertigo. Also, one patient in **C** group felt vertigo and 2 patients in **GR** group felt headache. This is in agreement with **Kim *et al.*** [17] who reported that, the use of PONV prophylactic agents is accompanied by the risk of various adverse events. In their study, combining Gabapentin and Ramosetron did not increase the incidence of adverse events, such as dizziness, drowsiness and headache. In the same line, **Savant *et al.*** [25] reported that, in the Ondansetron group, three patients (10.0%) complained of headache whereas one patient (3.3%) reported similar in the Granisetron group.

In the present work, there was no statistical difference concerning hemodynamic variations (HR or MBP) among the studied groups and the MBP range was within normal, so hemodynamic changes did not affect the results of the present study. This is in agreement with a study achieved by **Malini *et al.*** [26] who reported that, HR and MBP among Gabapentin and Granisetron groups were comparable throughout the study period. Also, **Anuradha and Balakrishnan** [13] showed no statistically significant difference between the Gabapentin and Granisetron groups regarding HR and MBP. The present study revealed that there were no statistically substantial differences concerning RR among the studied groups at different times postoperatively. These results agree well with that of **Amr *et al.*** [23] who reported that, there was no statistically significant difference between the study groups for RR at any time. While **Malini *et al.*** [26] reported that, Gabapentin is known to have non serious side effect such as dizziness but none of their patients receiving Gabapentin experienced dizziness. In a previous meta-analysis of patients receiving Gabapentin as antiemetic prophylaxis found that Gabapentin in doses of 300, 600 and 900 mg produced no statistically significant sedation, whereas preoperative administration of Gabapentin 1200 mg was associated with significantly greater postoperative sedation than controls [6]. **Huh *et al.*** [27] reported that the incidence of mild sedation in Midazolam group was higher than levels in the control group.

The present study revealed that there was no significant difference found between studied groups regarding vomiting (P-value>0.05), and there was highly statistically significant difference (P-value< 0.01) found between the groups regarding first time of vomiting episode. First time of vomiting episode showed statistically significant decrease in **C** group (0.80 ± 0.22) than **M**, **GR** and **G** groups (0.88 ± 0.27, 2.81±0.67, 3.42 ± 0.41 respectively). **GR** and **G** groups showed longer time to first time of vomiting episode to occur (2.81 ± 0.67 and 3.42 ± 0.41 respectively). The patients in G group took longer time to complain from vomiting than the other groups followed by GR group. **Malini *et al.*** [26] reported that, 6.25% patients of Granisetron group had vomiting at 0 hour as compared to 12.5% patients in Gabapentin group. 3.12% patients of both the groups had vomiting at first hour, which was mild in category. None of the patients had vomiting after the 1st hour in either of the groups. No significant difference was observed between the groups in terms of vomiting, that agrees with the present study.

In the current study, there was no statistically significant difference found among studied groups regarding frequency of nausea. It was reduced from 14.3% at 8-16 hr interval to 9.5% at 16-24 hr interval in **M** group. **Malini *et al.*** [26] showed that, 9.37% of patients in Granisetron group had nausea at 0 hour as compared to 18.75% patients in Gabapentin group and 9.37% patients had nausea at 1 hour in both groups. None of the patients had nausea after the 1st hour in either of groups and no significant difference was observed between the groups in terms of frequency of nausea, which is in accordance with the current results. **Anuradha and Balakrishnan** [13]**, Bestas *et al.*** [28] observed no incidence of nausea after 1st hour postoperatively among Gabapentin and Granisetron groups. While in this present study, it was reduced from 25% at 8- 16 hours to 16.7% at 16-24 hours in **GR** group and from 26.7% at 8-16 hours to 13.3% at 16-24 hours in **G** group.

CONCLUSIONS

Using oral Gabapentin 300 mg, intravenous Midazolam 0.075 mg/kg or Granisetron 3 mg one hour before induction of anesthesia in middle ear surgeries caused a substantial reduction in occurrence of PONV. The incidence of PONV was lower among Granisetron group than the other groups in our study. There was substantial significant difference found among C group compared to other groups regarding severity of PONV. No much difference was found between the studied groups as regards hemodynamic changes and side effects of used drugs.

Conflict of interest: The authors declared no conflict of interest.

Sources of funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author contribution: Authors contributed equally in the study.

REFERENCES

1. **Heidari M, Honarmand A, Safavi M *et al.* (2015):** Granisetron versus gabapentin in preventing postoperative nausea and vomiting after middle ear surgery in adults: a double-blinded randomized clinical trial study. Advanced Biomedical Research, 26 (2): 422-6.
2. **Jung J, Park J, Kim S *et al.* (2007**): Prophylactic antiemetic effect of midazolam after middle ear surgery. Otolaryngeal Head Neck Surg., 137: 753-6.
3. **Miller R, Egan T, Warner D (2010):** Anesthesia. In: Fleisher LA, Macario A, editors. The postanesthesia care unit. 6th ed. Pennsylvania, Elsevier, Pp: 703–727. https://doi.org/10.1097/00000542-200509000-00044
4. **Achuthan S, Singh I, Varthya S *et al.* (2015):** Gabapentin prophylaxis for PONV in abdominal surgeries: a quantitative analysis of evidence from randomized controlled clinical trials. Br J Anaesth., 114 (4): 588–97.
5. **Kranke P, Eberhart L (2011):** Possibilities and limitations in the pharmacological management of postoperative nausea and vomiting. Eur J Anaesthesiol., 28 (11): 758–65.
6. **Grant M, Betz M, Hulse M *et al.* (2016):** The effect of preoperative pregabalin on postoperative nausea and vomiting: a meta-analysis. Anesth Analg., 123 (5): 1100–7.
7. **Hegde H, Yaliwal V, Annigeri R *et al.* (2014**): Efficacy of orally disintegrating film of ondansetron versus intravenous ondansetron in prophylaxis of postoperative nausea and vomiting in patients undergoing elective gynaecological laparoscopic procedures: A prospective randomised, double-blind placebo-controlled study. Indian J Anaesth., 58 (4): 423–9.
8. **Heidari S, Rahimi M, Saeb F *et al.* (2011):** Comparison of the effect of intravenous midazolam, metoclopramide and their combination on the treatment of postoperative nausea and vomiting: a double-blinded randomized clinical trial. Pak J Med Sci., 27 (4): 847–50.
9. **Ganjare A, Kulkarni A (2013):** Comparative electrocardiographic effects of intravenous ondansetron and granisetron in patients undergoing surgery for carcinoma breast: A prospective single-blind randomised trial. Indian J Anaesth., 57: 41–5.
10. **Khademi S, Ghaffarpasand F, Heiran H *et al.* (2010):** Effects of preoperative gabapentin on PONV after open cholecystectomy: A prospective randomized double-blind placebo-controlled study. Med Princ Pract., 19: 57–60.
11. **Kong V, Irwin M (2007):** Gabapentin: a multimodal perioperative drug? British Journal of Anaesth., 99: 775–86.
12. **Sussan S, Mirsadegh S (2008):** Comparing oral Gabapentin versus clonidine as premedication on early postoperative pain, nausea and vomiting after general anaesthesia. International Journal of Pharmacology, 4 (2): 153-6.
13. **Anuradha S, Balakrishnan V (2018):** A prospective, randomized study comparing the antiemetic effect of inravenous granisetron and oral gabapentin in preventing PONV after middle ear surgeries in adults. Int J Adv Res., 6 (5): 1258-60.
14. **Fujii Y, Saitoh Y, Tanaka H *et al.* (2000):** Granisetron/dexamethasone combination for the prevention of postoperative nausea and vomiting after laparoscopic cholecystectomy. Eur J Anaesthesiol., 17 (1): 64-8.
15. **Kim E, Lee S, Choi D (2007):** Combination of antiemetics for the prevention of PONV in high-risk patients. J Korean Med Sci., 22: 878-82.
16. **Liberman M, Howe S, Lane M (2000):** Ondansetron versus placebo for prophylaxis of nausea and vomiting in patients undergoing ambulatory laparoscopic cholecystectomy. A J Surg., 179: 60–62.
17. **Kim K, Huh J, Lee S *et al.* (2017):** Combination of gabapentin and ramosetron for the prevention of postoperative nausea and vomiting after gynecologic laparoscopic surgery: a prospective randomized comparative study. BMC Anesthesiol., 17: 65-71.
18. **Guttuso J (2014):** Gabapentin's anti-nausea and anti-emetic effects: a review. Exp Brain Res., 232 (8): 2535–9.
19. **Jahromi H, Gholami M, Rezaei F (2013):** A randomized double-blinded placebo controlled study of four interventions for the prevention of PONV in maxillofacial trauma surgery. J Craniofac Surg., 24 (6): 623–7.
20. **Heidari S, Talakoub R, Yaraghi Z (2012):** Comparing the preventive effect of midazolam and midazolam-dexamethasone on postoperative nausea and vomiting in elective middle ear surgery. Adv Biomed Res., 1: 9.63-8.
21. **Sanjay O, Tauro D (2004):** Midazolam: An effective antiemetic after cardiac surgery–a clinical trial. Anesth Analg., 99: 339–43.
22. **Ahn E, Kang H, Choi G *et al.* (2016):** The effectiveness of midazolam for prevention of PONV: A systematic review and meta-analysis. Anesthesia and Analgesia, 122 (3): 644-76.
23. **Amr A, Abd al-fatah S, Salah El-Deen I *et al.* (2019):** Comparative Study of Ondansetron, Haloperidol or Midazolam in Prevention of PONV in Laparoscopic Gynecological Operations. The Medical Journal of Cairo University, 14: 93-8.
24. **Lee Y, Wang J, Yang Y *et al.* (2007):** Midazolam vs ondansetron for preventing PONV: A randomised controlled trial. Anaesthesia, 62: 18-22.
25. **Savant K, Khandeparker R, Berwal V *et al.* (2016):** Comparison of ondansetron and granisetron for antiemetic prophylaxis in maxillofacial surgery patients receiving general anesthesia: a prospective, randomised, and double blind study. Journal of the Korean Association of Oral and Maxillofacial Surgeons, 42 (2): 84-9.
26. **Malini M, Akshata T, Sujay T (2021):** An Observational Study of Intravenous Granisetron Vs Oral Gabapentin in Preventing Postoperative Nausea and Vomiting after Middle Ear Surgery. Indian Journal of Forensic Medicine and Toxicology, 15 (3): 367–75.
27. **Huh B, Jung S, White W *et al.* (2010):** Antiemetic effect of midazolam added to morphine patient controlled analgesia after total abdominal hysterectomy. Anaesth Intensive Care, 38: 481-5.
28. **Bestas A, Onal S, Bayar M *et al.* (2007):** Effects of Ondansetron and Granisetron on PONV in Adult Patients Undergoing Laparoscopic Cholecystectomy: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial. Current Therapeutic, 68 (5): 303-12.