Original Article

A prospective controlled study to assess the antiemetic effect of midazolam following intragastric balloon insertion

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Abstract

Background and Aims: Obesity is a chronic disease with considerable morbidity and mortality. The intragastric balloon appears attractive for a group of patients who do not respond to medical therapy and who are not surgical candidates. Postoperative nausea and vomiting (PONV) are distressing adverse effects for these patients. Midazolam has been used as an antiemetic, both as a preventive or rescue medication.The study aims at studying effect of combined use of ondansetron and midazolam to decrease the PONV following intragastric balloon insertion.

Materials and Methods: The study was conducted on 54 patients presented for intragastric balloon insertion during the period between 1st of January 2012 and 31 December 2012. Patients were randomly allocated into two groups; Ondansetron group and ondansetron/midazolam group. Patients were assessed for the incidence of nausea and vomiting, nausea and vomiting score, degree of sedation and occurrence of adverse effects during the first 24 h after the operation.

Results: Incidence of nausea and/or vomiting during the first 24 h postoperatively was 66% in the ondansetron group, while 34.5% among the ondansetron-midazolam group. There was significant reduction of nausea and/or vomiting in the second group. Degree of postoperative sedation was also significantly different between the two groups in the immediate postoperative period and 30min postoperatively.

Conclusion: Use of midazolam combined with ondansetron provides significant reduction and therefore better outcome regarding nausea and vomiting following intragastric balloon insertion.

Key words: Antiemetic, intragastric balloon, midazolam, nausea, obesity, vomiting, weight loss

Introduction

Obesity is a chronic incurable disease with considerable morbidity and mortality. Contrary to past concepts, there is general agreement that treatment should focus on sustained 10%-15% weight loss to prevent or reduce risk of cardiovascular and other obesity-related diseases. For motivated patients who seriously attempt but fail to achieve weight loss of 5%-10% in 3-6 months, pharmacotherapy is recommended. Body mass index (BMI) is used to classify overweight (BMI 25-29.9 kg/m^2) and obese (BMI ≥30 kg/m^2) individuals and further classify the severity of obesity to as class I (BMI 30-34.9 kg/m^2), class II (BMI 35-39.9 kg/m^2) and class III (BMI 40 ≥Kg/m^2).[1] Surgical approach is restricted to extremely or morbidly obese patients (BMI >40 kg/m^2, or >35 kg/m^2 with co-morbidity) and after failure of conservative weight loss measures.[2] However, the intermediate group of patients who do not respond to medical therapy but are not yet surgical candidates are attractive candidates for intragastric balloon insertion.[3]

It has been estimated that the overall incidence of postoperative nausea and vomiting (PONV) for all surgeries and patient populations is between 25% and 30%, while severe intractable PONV was estimated to occur among approximately 0.18% of all patients.[4] PONV are distressing and frequent adverse effects in patients undergoing intragastric balloon insertion for weight reduction. Ganesh *et al.*,[5] reported 20% early removal of the balloon due to intolerance which was defined as nausea, vomiting, abdominal pain, or retching, while Loffredo *et al.*,[6] reported 3.3% early removal due to such intolerance.

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Midazolam has been used as an antiemetic in adults and children, both as a preventive and rescue medication. It has been postulated that a possible mechanism for the antiemetic effect of benzodiazepines could be an action at the chemoreceptor trigger zone-reducing synthesis, release, and postsynaptic effect of dopamine.[7-10]

The research aims at studying the effect of combined use of ondansetron and midazolam to decrease the PONV following intragastric balloon insertion.

Materials and Methods

The study was conducted on all patients who presented for intragastric balloon insertion in the Medical Research Institute Hospital during the period between 1st of January 2012 and 31 December 2012. Inclusion criteria were being an obese patient with BMI of 30-35 kg/m^2, presenting for intragastric balloon insertion, American Society of Anesthesiologists physical status I or II, aged 18-40 years.

Following approval of the ethical committee in the Medical Research Institute, an informed written patient consent was obtained from each of the studied patients.

The exclusion criteria were need for emergency operation, patients with motion sickness or PONV history to control anticipated risk of PONV, patients with antiemetic drug use within 24 h before surgery, patients with regular corticosteroid use, patients who had received chemotherapy within 4 weeks or radiotherapy within 8 weeks, patients with allergy to any of the studied drugs and patients with liver dysfunction or confirmed renal impairment.

Among 61 admitted patients during the period of the study, 57 patients were eligible to participate in the research as 4 patients were excluded after applying the exclusion criteria. Patients were randomly allocated into two groups; ondansetron group and ondansetron/midazolam group. Patients with odd hospital file numbers were included in the first group, while those with even hospital file numbers were allocated in the second group. A total of three patients were excluded from the first group due to episodes of continuous vomiting (balloon intolerance) and balloon was removed within 24 h postoperatively. Thus, the total participants were 54 patients.

The first group composed of 25 patients, who received ondansetron 8 mg, and the second group composed of 29 patients, received ondansetron 8 mg with midazolam 0.075 μg/kg based on ideal body weight. Anesthesia induction was conducted using fentanyl 1 μg/kg, propofol 2-2.5 mg/kg, cisatracurium 0.15 mg/kg, followed by tracheal intubation 2 min later and maintenance with propofol 100 μg/kg/min based on total body weight. Patients were assessed for the occurrence of nausea and vomiting, scores of nausea and vomiting (0 = no nausea, 1 = only nausea, 2 = only vomiting, 3 = nausea and vomiting), degree of sedation immediately, 30 min, and 1 h postoperatively (awake, mild, moderate, and deep) and occurrence of adverse effects during the first 24 h after the procedure.

Statistical analysis

Power of the study was calculated (using Open Epi software) to be 81.8% based on prevalence of vomiting of 86 %[11] and detection of reduction in vomiting to 50% (36% reduction) at 95% level of confidence.

Data were analyzed using SPSS system files (SPSS package version 18). The following statistical measures were used: Descriptive statistics including frequency, distribution, mean, and standard deviation were used to describe different characteristics.Kolmogorov-Smirnov test was used to examine the normality of data distribution. Univariate analyses including: *t*-test was used to test the significance of results of quantitative variables. Chi-square test, Monte Carlo test and, Fisher's exact test were used to test the significance of results of qualitative variables. The significance of the results was at the 5% level of significance.

Results

Demographic characteristics among the studies groups revealed that male patients constituted 60% of the first group and 44.8% of the second group.

Age of patients enrolled in the first group ranged between 18 and 35 years with a mean of 26.3 ± 4.9 years compared with patients in the second group with their age ranged from 20-32 years with a mean of 27.0 ± 3.3 years.

BMI of the first group ranged from 30.5-34.8 kg/m^2 with a mean of 32.9 ± 1.4 kg/m^2, while BMI of the second group ranged between 30.3 and 34.9 kg/m^2, with a mean of 32.8 ± 1.3 kg/m^2.

None of the studied demographic characteristics showed statistically significant difference between the two groups.

As regards occurrence of nausea and or vomiting in the first 24 h postoperatively, it was 56% in the first group (ondansetron), compared with 34.5% in the second group (ondansetron-midazolam). Still, the difference observed was statistically insignificant (P = 0.113) [Table 1].

On the contrary, significant differences were evident in nausea and vomiting score recorded in both groups, where 10 (40%) patients in the first group suffered from both nausea and vomiting compared with 7 (24.1%) among the second group. Moreover, four patients (16%) of the first group experienced only vomiting compared with none of the second group. The differences observed were statistically significant ($P = 0.015$) [Table 2].

Regarding the degree of immediate postoperative sedation, the majority of the patients in the first group (80%) were mildly sedated as compared to a lower percentage among the second group (58.6%). A higher percentage of moderate sedation was encountered in the second group (34.5%) as compared to the first group (4%). The differences observed were statistically significant ($P = 0.018$).

Thirty minutes later, all patients of the first group (100%) and the majority of the second group (75.9%) were awake. Again, the difference was statistically significant ($P = 0.012$). However, 60min postoperatively, all patients of both groups were awake [Table 3].

Table 1: Occurrence of nausea, vomiting in 24 h among the studied groups

Occurrence of nausea/ vomiting during 24 h postoperative	Group I (ondansetron) (n = 25)		Group II (ondansetron/ midazolam) (n = 29)		Significance
	No.	%	No.	%	
Present	14	56.0	10	34.5	X^2=2.52
Absent	11	44.0c	19	65.5	P=0.113

X^2 = Chi-square test

Table 2: Nausea and vomiting score among the studied groups

Nausea/ vomiting score	Group I (ondansetron) (n = 25)		Group II (ondansetron/ midazolam) (n = 29)		Significance
	No.	%	No.	%	
No nausea, no vomiting	11	44.0	19	65.5	MCP=0.015*
Only nausea	0	0.0	3	10.3	
Only vomiting	4	16.0	0	0.0	
Nausea and vomiting	10	40.0	7	24.1	

*MCP = Monte carlo test, *significant at P ≤ 0.05*

Table 3: Postoperative degree of sedation among the studied groups

Degree of sedation	Group I (ondansetron) (n = 25)		Group II (ondansetron/ midazolam) (n = 29)		Significance
	No.	%	No.	%	
Immediately postoperative					
Awake	4	16.0	2	6.9	MCP=0.018*
Mild sedation	20	80.0	17	58.6	
Moderate sedation	1	4.0	10	34.5	
30 min postoperative					
Awake	25	100.0	22	75.9	FEP = 0.012*
Mild sedation	0	0.0	7	24.1	
60 min postoperative					
Awake	25	100.0	29	100.0	–

Discussion

Intragastric balloon insertion is a nonsurgical procedure available for weight loss.[12] Once the balloon is inserted into the stomach, the empty balloon is filled with sterile saline, occupying a large part of the stomach, creating a feeling of fullness, causing postoperative nausea vomiting.[13]

In the current study, there were no significant statistical differences between the two studied groups regarding gender, age, or BMI of patients.

Incidence of nausea and/or vomiting was 56% in the first group (ondansetron group), compared with 34.5% in the second group (midazolam-ondansetron), and that was statistically insignificant between both groups. In agreement with our results, Byon *et al.*,[14] compared the antiemetic effect of ramosetron alone or combined with midazolam. He showed that adding midazolam to ramosetron had no advantages compared to ramosetron alone in reducing the incidence of PONV in patients undergoing strabismus surgery.[14] Contrary to our results, Jung *et al.*,[15] used midazolam in similar dose of 0.075 mg/kg after induction in middle ear surgery. They found that the incidence of nausea and vomiting significantly decreased compared to placebo. Safavi and Honrmand described the use of midazolam (35 μg/kg) intravenously before induction or before extubation compared to placebo. They found that indicated that midazolam 35 μg/kg (2 mg) given intravenously 30 min before the end of surgery was more effective in decreasing the incidence of PONV than midazolam premedication. They also found that the incidence of first attack of PONV was lower in group if dose was given before extubation as compared to group using the same premedication dose of midazolam.[16] Kim *et al.*,[17] compared the antiemetic effect of midazolam and/or ondansetron added to intravenous patient-controlled analgesia using fentanyl in gynecologic patients undergoing pelviscopic surgery. He concluded that the incidence of PONV in midazolam-ondansetron group (MO) was significantly lower than in group ondansetron (O) at postanaesthesia care unit, 24 h after recovery ($P < 0.05$).[17]

Our results showed significant differences in the nausea and vomiting score between the two groups. Significant differences between the two groups, were observed in the degree of sedation in the immediate postoperative period, and 30 min after the procedure, but not after 60 min following the procedure. Sanjay and Tauro[18] compared the effect of midazolam versus ondansetron after cardiac surgery. They reported a 6% incidence of nausea and no incidence of vomiting in the midazolam group, compared with a 21% incidence of PONV in the ondansetron group. They also reported a significant ($P < 0.001$) use of rescue antiemetics (21%) in the ondansetron group compared with the midazolam group. Jabalameli *et al*.,[19] compared the effect of each of the drugs; ondansetron and midazolam, and in combination. They found that added together, midazolam and ondansetron produce significantly less nausea and vomiting.[19] In a study by Shahriari *et al*.,[20] 80 women undergoing elective cesarean section under spinal anesthesia (using 0.5% bupivacaine 10 mg) were allocated randomly to receive midazolam 2 mg or metoclopramide 10 mg at the beginning of surgery before skin incision. They observed that the frequency of intraoperative nausea and vomiting was lower in the midazolam group compared with metoclopramide (15% versus 52.5%). Sedation scores within 3 h postoperatively were significantly lower in the metoclopramide group. On the contrary, Kim *et al*.,[17] showed in his trial that sedation scores were not statistically different between the groups. Makhdoom and Farid[21] compared midazolam 0.075 μg/kg alone or in combination with dexamethasone or dexamethasone alone and found no statistical differences between the groups regarding postoperative drowsiness.

Conclusions

We conclude that the use of midazolam combined with ondansetron provides significant reduction and therefore a better outcome in the severity of PONV compared to ondansetron alone, with mild degree of sedation in the early postoperative period, following intragastric balloon insertion.

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