LOW DOSE INTRAVENOUS MIDAZOLAM FOR PREVENTION OF PONV, IN LOWER ABDOMINAL SURGERY

- Preoperative vs Intraoperative Administration -

MOHAMMAD REZA SAFAVI* AND AZIM HONARMAND**

Abstract

Background: The aim of the present study was to compare anti-emetic efficacy of low dose midazolam premedication (35 μg/kg) 15 minutes before induction of anesthesia with midazolam (35 μg/kg) administered intravenously 30 min before conclusion of surgery, in patients undergoing lower abdominal surgery under general anesthesia.

Methods: Sixty patients were assigned to one of three equal groups: Group MP (n = 20), which received intravenous midazolam 35 μg/kg in a volume of 3 ml 15 minutes before induction of anesthesia and 3 ml normal saline 30 minutes before extubation. Group MI (n = 20), which received 3 ml normal saline 15 minutes before induction of anesthesia and intravenous midazolam 35 μg/kg in a volume of 3 ml 30 minutes before extubation. Group NS (n = 20), which received 3 ml normal saline 15 minutes before induction of anesthesia plus 3 ml normal saline 30 minutes before extubation. Assessments of the occurrence of postoperative nausea and vomiting (PONV) were made at regular intervals for the first 24h.

Results: Incidence of PONV was significantly lower in Group MI compared with Group NS and Group MP at 6, 12, 18, and 24 hours after operation ($P < 0.05$). The time for the first episode of PONV was significantly higher in Group MI compared with Group NS and Group MP ($P < 0.05$).

Conclusion: Our results indicated that midazolam 35 μg/kg (2 mg) given intravenously 30 minutes before the end of surgery was more effective in decreasing the incidence of PONV than midazolam premedication 35 μg/kg.

Keywords: Midazolam, postoperative nausea and vomiting, antiemetics, anesthetics.

From Dept. of Anesth. & Intensive Care Medicine, Isfahan Univ. of Medical Sciences, Isfahan, Iran.

* MD, Assistant Professor of Anesthesia and Intensive Care.

** MD, Assistant Professor of Anesthesia and Intensive Care.

Corresponding author: Dr. Mohammad Reza Safavi, Department of Anesthesiology and Intensive Care Medicine, Isfahan University of Medical Sciences, Isfahan, Iran. Tel: 0098 913 3152416, Fax: 0098 311 7751182, E-mail: safavi@med.mui.ac.ir

Introduction

PONV is the most frequent side effect following anesthesia[1], occurring in about 30% of unselected inpatients and up to 70% of "high-risk impatiens during the 24 h after emergence[2]. Although PONV is almost always self limiting and non-fatal[3], it can cause significant morbidity, including dehydration, electrolyte imbalance, suture tension and dehiscence, venous hypertension and bleeding, esophageal rupture, and life threatening airway compromise, although the more severe complications are rare[4,5]. Each vomiting episode delays discharge from the recovery room by about 20 min[6].

A number of treatments have been introduced to reduce PONV, such as 5-HT3 antagonists, dopamine receptor antagonists, and antihistamine drugs. However, each of these treatments is associated with critical limiting factors, namely cost with 5-HT3 antagonists, extrapyramidal symptoms with dopamine receptor antagonists and excessive sedation, and tachycardia with antihistamine drugs[7-9]. In several studies, benzodiazepines have been demonstrated to improve comfort and decrease anxiety in patients. In particular, lorazepam has been reported to be capable of reducing the severity and the duration of nausea and vomiting[10]. However, its slow onset and long duration of action can result in sedation and undesirable anxiolytic effects that last longer than necessary.

Midazolam is a short-acting benzodiazepine with a rapid onset of action, which is used for induction of general anesthesia and preoperative sedation. In recent years, midazolam has been reported to be effective for prophylaxis of PONV by bolus administration before or after induction of anesthesia or postoperative continuous infusion[11-16]. Heidari et al[12] showed that prophylactic intravenous midazolam premedication 75 microg/kg reduced the incidence and severity of PONV in adult patients subjected to cholecystectomy under general anesthesia. Lee and colleagues[17] compared the prophylactic anti-emetic efficacy of midazolam and ondansetron in patients scheduled for minor gynecological or urological procedures and showed that midazolam 2 mg (35 μg/kg) were administered intravenously 30 min before the end of surgery, was as effective as ondansetron in treating PONV.

In Heidari et al study[12], the dosage of midazolam premedication was 75 μg/kg, and it effectively reduced the incidence of nausea and vomiting up till six hours after surgery. However, it is not known whether lower dosage (35 μg/kg) of midazolam premedication has similar effect. It is also not clear of the premedicant effect of midazolam in comparison to intraoperative midazolam on PONV. In randomized double-blind placebo-controlled study we compared the effectiveness of intravenous midazolam premedication 35 microg/kg as an anti-emetic with midazolam 35 μg/kg administered intravenously 30 min before the end of surgery, in patients undergoing lower abdominal surgery under general anesthesia. Our hypothesis was that intraoperative midazolam administration before conclusion of surgery was more effective than premedicant midazolam for the prevention of PONV.

Materials and Methods

Following approval of the University Research Committee and obtaining informed consents from all subjects, 80 ASA I or II patients, aged 18-60 years, scheduled for lower abdominal procedures planned to last 1-2 h were eligible to participate in this study. Patients who had gastrointestinal disorders, histories of PONV after a previous surgery, renal or liver dysfunction, history of motion sickness, had received any opioid, steroid, or antiemetic medication in the 24 h before surgery, and those who were pregnant or menstruating, were excluded.

Before induction, patients were instructed on the use of the visual analogue scale (VAS) for pain assessment. Monitoring included continuous ECG, non-invasive blood pressure, pulse oximetry and end-tidal carbon dioxide.

Patients were randomly allocated to one of three equal groups:

Group MP (n = 20), received intravenous midazolam premedication 35 μg/kg in a volume of 3 ml, 15 minutes before induction of anesthesia

Group MI (n = 20) received intravenous midazolam 35 μg/kg in a volume of 3 ml 30 minutes before extubation at the end of surgery

Group NS (n = 20), received 3 ml normal saline 15 minutes before induction of anesthesia plus 3 ml normal saline 30 minutes before extubation at the end of surgery.

To achieve adequacy of blinding, all patients in

Group MP received 3 ml normal saline 30 minutes before extubation at the end of surgery, and the patients in Group MI received 3 ml normal saline 15 minutes before induction of anesthesia. The estimated doses of all drugs were diluted in equal volume (3 mL). The dosage of midazolam was formulated on the basis of an earlier report[17]. The randomized process and the identity of the study drugs were blinded to the anesthesiologists during surgery and the investigators who collected the postoperative data.

No premedication was given, Patients in the three groups underwent a standardized anesthesia protocol which included induction with thiopental (5 mg/kg) and fentanyl (2 μg/kg). Atracurium was used as a muscle relaxant. After tracheal intubation, anesthesia was maintained with a 50% nitrous oxide/oxygen mixture along with isoflurane in a concentration of 0.8%-1.2%. Ventilation was adjusted to produce normocapnia. At the end of surgery, reversal of residual neuromuscular blockade was accomplished using i.v. atropine 20 μg/kg and neostigmine 40 μg/kg. Assessments of patients recovery were made by a blinded observer, including the times from discontinuation of anesthesia until the time to achieve a modified Aldrete score of 10[8].

Sedation was assessed during the first 5, 15, 30, 60 and 120 min in the PACU by a physician using the five-point Observer's Assessment of Alertness/Sedation (OAA/S) scale (where 1 = awake/alert and 5 = deep sleep)[19]. All assessments were carried out by a physician who had no knowledge of the treatment patients had received. The discharge criteria in the post anaesthesia care unit (PACU) consisted of: an awake and alert patient, stable vital signs, no severe pain, and no persistent nausea and vomiting.

PONV assessment was started at extubation and was carried out hourly for the first 4 h and thereafter every 4 h until the first 24 h. PONV was evaluated by the following variables: incidences of nausea and vomiting, requirements of rescue antiemetics, and complete responses. Nausea was defined as a subjectively unpleasant sensation associated with awareness of the urge to vomit, and vomiting was defined as the forceful expulsion of gastric contents from the mouth. For the purpose of data collection, retching (same as vomiting but without expulsion of gastric contents) was considered vomiting. Nausea was recorded according to the following scale: 0 none; 1 mild (patient able to eat); 2 moderate (oral intake significantly decreased); and 3 severe (no significant oral intake necessitating i.v. fluid)[20]. The absence of nausea was defined as complete protection from nausea. An emetic episode was defined as a single vomit or retch, or any number of continuous vomiting episodes or retches (one emetic episode should be separated from another by an absence of vomiting or retching for at least 1 min). The absence of emetic episodes was defined as complete protection from vomiting. Rescue medication (metoclopramide 10 mg) was given intravenously if patient was nauseous for more than 15 min or experienced retching or vomiting during the observation periods. The treatment was repeated if necessary.

For the first 24 h after anesthesia, the levels of pain and sedation experienced by the patients were recorded by a physician who had no knowledge of the treatment patients had received. Pain intensity score was measured with a visual analog scale (VAS) from 0 (no pain) to 10 (the worst possible pain). If patients asked for analgesic or experienced pain with a VAS more than 3, meperidine 1 mg/kg was administered intravenously.

Sample size was predetermined with a power analysis based on the assumption that:

1) the total incidence of nausea and vomiting in the saline group would be 60%[21];
2) a 40% reduction (from 60% to 20%) in the total incidence of PONV in the treatment group would be of clinical relevance;
3) $\alpha = 0.05$, $\beta = 0.2$. The analysis showed that 20 patients per group would be sufficient. Statistical analyses were performed with SPSS version 15.0 (SPSS, Chicago, IL).

Data are presented as mean ± SD, median or number (%). Patient demographics, duration of surgery or anesthesia, PACU discharge eligibility, first nausea or vomiting time, rescue opioids and metoclopromide dosage were analyzed by using one-way ANOVA, and multiple comparison between pairs was done by the Bonferroni's test. VAS scores were compared among groups by two-way analysis of variance for repeated measures. Between-group differences in the numbers of patients needing rescue antiemetic were analyzed using the chi-square test. Fisher's exact test was used

Table 1
Patients characteristic and clinical data of patients

	Group MP	Group MI	Group NS
Number of patients	20	20	20
Age (year)	27.6 ± 5.3	29.8 ± 4.2	28.4 ± 5.4
Gender (F/M)	9/11	11/9	8/12
Weight (kg)	68.2 ± 8.7	72.5 ± 7.7	69.3 ± 8.2
Height (cm)	166.0 ± 4.7	165.7 ± 4.6	167.8 ± 6.5
ASA (I/II)	17/3	15/5	16/4
Duration of surgery (min)	97.5 ± 9.7	99.2 ± 8.1	98.5 ± 8.4
Duration of anesthesia (min)	107.5 ± 7.9	108.2 ± 4.9	109.5 ± 6.9
PACU discharge eligibility (min)	16.4 ± 3.3	17.3 ± 3.2	15.3 ± 2.2
Sedation level median (range)	2 (1-3)	2 (1-3)	2 (1-3)
Post-op VAS			
0-2 h	2.6 ± 1.3	2.2 ± 1.4	2.4 ± 1.1
2-24 h	1.5 ± 1.0	1.05 ± 1.0	1.5 ± 0.9
Rescue opioids (mg)	56.0 ± 9.8	58.5 ± 11.8	57.5 ± 10.4

Data are presented as mean ± SD, number of patients or median (range). Group MP = midazolam premedication; Group MI = midazolam intraoperative; Group NS = normal saline; PACU = post-anesthetic care unit; VAS = visual analogue scale. There was no significant difference between the three groups.

when appropriate. A Mann-Whitney *U*-test was applied where appropriate. Median sedation level between groups was compared with Kruskall-Wallis test. A P value less than 0.05 was considered to be significant.

Results

The three groups were comparable with respect to demographic characteristics, duration of surgery or anesthesia, the median sedation level at arrival to PACU, the postoperative pain scores (VAS) in the different time intervals, PACU discharge eligibility time, and requirement for rescue pain medication (Table 1).

The was no statistically significant difference between the three groups for SAP, DAP, MAP, HR, or SpO_2 at any time. The incidence of PONV and requirements for rescue anti-emetics during different observatory periods are presented in Table 2.

Incidence of PONV was significantly lower in Group MI when compared to Group NS and Group MP at 6, 12, 18, and 24 hours after operation ($P < 0.05$). The time for the first episode of postoperative nausea or vomiting was significantly higher in Group MI compared with Group NS and Group MP ($P < 0.05$). The metoclopromide dosage and numbers of patients needed rescue anti-emetic was significantly lower in Group MP or Group MI compared with group NS during 24 hours after operation ($P < 0.05$) (Table 2). None of the patients who had PONV required more than 1 dose of rescue medication.

Discussion

This is the first clinical trial testing of the efficacy of midazolam as an antiemetic when administered as a premedicant as compared to its i.v. administration intraoperatively in patients at intermediate risk for PONV. This study demonstrated that intravenous administration of midazolam 35 μg/kg, 30 min before the end of surgery was more effective than intravenous midazolam premedication 35 μg/kg in patients undergoing lower abdominal surgery under general anesthesia.

The causes of PONV are of multifactorial origins: age, gender, history of previous PONV, motion sickness, type of surgery and anesthetic technique, pain, and use of opioid[8].

Table 2
Severity of PONV, incidence of requiring rescue anti-emetics, first postoperative nausea or vomiting, metoclopromide dosage and numbers of patients needed rescue antiemetic during different observatory periods among three groups.

	Group MP (0/1/2/3)	Group MI (0/1/2.3)	Group NS 0/1/2.3)	P value
Number of patients	20	20	20	
0-2 h	15/3/2/0*	18/2/0/0*	8/8/4/0	0.013
6 h	15/4/1/0	1/9/1/0/0*	8/10/2/0	0.005
12 h	15/5/0/0	20/0/0/0*†	9/10/1/0	0.003
18 h	15/5/0/0	20/0/0/0*†	9/11/0/0	0.000
24 h	16/4/0/0	20/0/0/0*†	10/10/0/0	0.001
Rescue anti-emetics	8 (40)*	4 (20)*	15 (75)	0.002
First nausea or vomiting time (hr)	1.36 ± 0.2	3.1 ± 0.2*†	0.90 ± 0.2	0.000
Metoclopromide dosage (mg)	6.5 ± 2.1*	2.0 ± 0.9*	13.5 ± 2.3	0.000
Numbers of patients needing	8 (29.6)*	4 (14.8)*	15 (55.6)	0.002
rescue antiemetic (%)				

Values are number (%) of patients with each grade of PONV in each group or mean ± SEM. Group MP = midazolam premedication; Group MI = midazolam intraoperative; Group NS = normal saline; PONV = postoperative nausea vomiting. PONV was graded as: 0 none; 1 mild (patient able to eat); 2 moderate (oral intake significantly decreased); and 3 severe (no significant oral intake necessitating i.v. fluid). * $P < 0.05$ vs. Group NS. † $P < 0.05$ vs. Group MP.

In our study since the three groups were similar in patient characteristics, type of surgery, anesthetics administered, pain intensity, and analgesic used after surgery, therefore, the incidence of PONV can be attributed to the study of the drug under consideration.

We found that 3% of the patients in the MI group reported PONV in the first 24 h postoperatively, which was significantly less than group MP (24%). Also in patients who received midazolam premedication showed a higher incidence of PONV than those who received midazolam 30 minutes before conclusion of surgery in the first 2 h. This study, however, was not sufficiently powered to detect such differences. More patients were needed to detect the same relative reduction in nausea. Also, rescue antiemetic, metoclopromide dosage and numbers of patients needing rescue antiemetic was higher in MP group than MI group during 24 hours after surgery. However, due to probably small sample size, this difference was not statistically significant.

Based on our data, the incidence of PONV was significantly lower in group MI than in group MP or group NS at 12, 18, and 24 hours after surgery. In contrast, there was no significant difference between group MP and group NS in this regard. Heidari et al[12] investigated the effect of intravenous midazolam premedication on the incidence and severity of PONV in a sample of adult patients undergoing anesthesia for cholecystectomy, and showed that severity of nausea was significantly lowered in midazolam group during the first six hours after recovery period compared with placebo group. Our finding is in agreement with this study.

Several investigations have indicated that midazolam may have anti-emetic properties. Splinter et al[14] observed that administering midazolam 0.05 mg.kg after induction of anesthesia has antiemetic effects that are similar to the same dose of droperidol in children undergoing strabismus surgery. Bauer et al[11] found that pre-operative intravenous midazolam 0.04 mg.kg is an effective way to reduce the frequency of PONV and increase patient satisfaction. Unlugenc et al[16] demonstrated that midazolam used in subhypnotic dose was as effective as ondansetron in treating PONV without untoward sedative effects. The prophylactic

administration of midazolam was also reported to be effective in reducing vomiting after tonsillectomy in children[13]. Midazolam is an effective antiemetic in patients having chemotherapy[22].

The mechanism of action of midazolam has not been fully understood. It is thought that midazolam decreases dopamine input at the chemoreceptor trigger zone (CRTZ)[23] and decreases adenosine re-uptake[24]. This leads to an adenosine-mediated reduction in synthesis, release, and postsynaptic action of dopamine at the CRTZ[23]. It may also decrease dopaminergic neuronal activity and 5-HT3 release by binding to the gamma-aminobutyric acid (GABA) receptor[25].

In our study, we reported a significant (P = 0.002) lower use of rescue antiemetics (20%) in the MI group when compared with the NS (75%) group. This is consistent to the study by Lee et al[17], who reported a 23% use of rescue antiemetics in their midazolam group.

Clinical practitioners may be cautious of using hypnotic agents for anti-emetic purposes because of the risk of delayed recovery. The sedation scores recorded in our trial have clearly demonstrated that the patients in three study groups had similar scores and laid to rest the speculation that the patients in the midazolam group were failing to report nausea because they were more sedated than the patients who received ondansetron. Moreover, midazolam has been stated to be a sedative in a larger dose range than that used in our trial[26].

We also observed that midazolam as a premedicant or intraoperative bolus administration did not prolong the duration of anesthesia, increase the degree of sedation, increase the postoperative stay in the PACU, or alter the postoperative pain scores. Also, administration of midazolam preoperatively did not significantly affect perioperative vital signs, a finding that is consistent with previous studies[12-14].

Lerman[27] has suggested that PONV is approximately two to three times more frequent in women than in men. In our study, PONV was predominant in women (49% vs. 35% in men). In common with most other studies on PONV, we found that PONV was associated significantly with the female sex[28,29]. This overwhelming incidence of PONV in women suggests that women should be a target population to receive antiemetics after lower abdominal surgery.

There are few limitations in our trial. First, plasma levels of midazolam were not measured. Second, meperidine was used for pain relief in the postoperative period. Meperidine being an opioid could *per se* cause PONV, and it was used in three study groups.

In conclusion, the results of this study indicated that patients undergoing lower abdominal surgery under general anesthesia, midazolam 35 μg/kg (2 mg) given intravenously 30 minutes before the end of surgery was more effective than midazolam premedication 35 μg/kg, in decreasing the incidence of PONV without increasing recovery time and the level of sedation. Further prospective randomized studies with varying doses of midazolam to evaluate its antiemetic properties are needed before drawing any firm conclusions.

References

1. Eberhart LH, Hogel J, Seeling W, et al: Evaluation of three risk scores to predict postoperative nausea and vomiting. *Acta Anaesthesiol Scand*; 2000, 44:480-8.
2. Gan TJ: Postoperative nausea and vomiting: can it be eliminated? *JAMA*; 2002, 287:1233-6.
3. Tramer MR: Treatment of postoperative nausea and vomiting. *BMJ*; 2003, 327:762-3.
4. Apfel CC, Kranke P, Katz MH, et al: Volatile anaesthetics may be the main cause of early but not delayed postoperative vomiting: a randomized controlled trial of factorial design. *Br J Anaesth*; 2002, 88:659-68.
5. Scuderi PE, Conlay LA: Postoperative nausea and vomiting and outcome. *Int Anesthesiol Clin*; 2003, 41:165-74.
6. Gan TJ, Meyer T, Apfel CC, et al: Consensus guidelines for managing postoperative nausea and vomiting. *Anesth Analg*; 2003, 97:62-71.
7. Fujii Y, Tanaka H, Kobayashi N: Prevention of nausea and vomiting after middle ear surgery: granisetron versus ramosetron. *Laryngoscope*; 1999, 109:1988-1990.
8. Kovac AL: Prevention and treatment of postoperative nausea and vomiting. *Drugs*; 2000, 59:213-243.
9. Fujii Y, Toyooka H, Tanaka H: Prophylactic antiemetic therapy with a combination and dexamethasone in patients undergoing middle ear surgery. *Br J Anaesth*; 1998, 81:754-756.
10. Laszlo J, Clark RA, Hanson DC, et al: Lorazepam in cancer patients treated with cisplatin: a drug having antiemetic, amnesic, and anxiolytic effects. *J Clin Oncol*; 1985, 3:864-869.
11. Bauer KP, Dom PM, Ramirez AM, et al: Preoperative intravenous midazolam: benefits beyond anxiolysis. *J Clin Anesth*; 2004, 16:177-183.
12. Heidari SM, Saryazdi H, Saghaei M: Effect of intravenous midazolam premedication on postoperative nausea and vomiting after cholecystectomy. *Acta Anaesthesiol*; Taiwan, 2004, 42:77-80.
13. Splinter WM, MacNeill HB, Menard EA, et al: Gould MH. Midazolam reduces vomiting after tonsillectomy in children. *Can J Anaesth*; 1995, 42:201-203.
14. Splinter W, Noel LP, Roberts D, et al: Antiemetic prophylaxis for strabismus surgery. *Can J Ophthalmol*; 1994, 29:224-226.
15. Sanjay OP, Tauro DI: Midazolam: an effective antiemetic after cardiac surgery – a clinical trial. *Anesth Analg*; 2004, 99:339-343.
16. Unlugenc H, Guler T, Gunes Y, Isik G: Comparative study of the antiemetic efficacy of ondansetron, propofol and midazolam in the early postoperative period. *Eur J Anaesthesiol*; 2003, 20:668-673.
17. Lee Y, Wang JJ, Yang YL, Chen A, Lai HY: Midazolam vs ondansetron for preventing postoperative nausea and vomiting: a randomized controlled trial. *Anaesthesia*; 2007, 62, 18-22.
18. White PF, Song D: New criteria for fast-tracking after outpatient anesthesia: a comparison with the modified Aldrete's scoring system. *Anesth Analg*; 1999, 88:1069-72.
19. Chernik DA, Gillings D, Laine H, et al: Validity and reliability of the Observer's Assessment of Alertness/Sedation (OAA/S) scale: study with intravenous midazolam. *Journal of Clinical Psychopharmacology*; 1990, 10:244-51.
20. Mandalà M, Cremonesi M, Rocca A, Cazzaniga M, Ferretti G, Di Cosimo S, et al: Midazolam for acute emesis refractory to dexamethasone and granisetron after highly emetogenic chemotherapy: a phase II study. *Support Care Cancer*; 2005, 13:375-380.
21. Honkavaara P, Saarinvaara L, Klemola UK: Prevention of nausea and vomiting with transdermal hypocine in adults after middle ear surgery during general anaesthesia. *Br J Anaesth*; 1994, 73:763-766.
22. Olynyk J, Cullen SR, Leahy MF: Midazolam: an effective antiemetic agent for cytotoxic chemotherapy. *Med J Aust*; 1989, 150:466.
23. Di Florio T: The use of midazolam for persistent postoperative nausea and vomiting. *Anaesth Intensive Care*; 1992, 20:383-386.
24. Phillis JW, Bender AS, Wu PH: Benzodiazepines inhibit adenosine uptake into rat brain synaptosomes. *Brain Res*; 1980, 195:494-498.
25. Takada K, Murai T, Kanayama T, et al: Effects of midazolam and flunitrazepam on the release of dopamine from rat striatum measured by in vivo microdialysis. *Br J Anaesth*; 1993, 70:181-185.
26. Peter SAG, Steven LS, Reeves JG: Intravenous drug delivery systems. In: Miller RD, ed. *Anesthesia*. 5th ed. Philadelphia: Churchill Livingstone, 2000, 398.
27. Lerman J: Surgical and patient factors involved in postoperative nausea and vomiting. *Br J Anaesth*; 1992, 69:24S-32.
28. Grebenik CR, Allman C: Nausea and vomiting after cardiac surgery. *Br J Anaesth*; 1996, 77:356-9.
29. Koizumi Y, Matayoshi Y, Kondoh K, et al: Postoperative nausea and vomiting after open heart surgery. *Masui*; 2002, 51:638-41.