

## Comparison of the Efficacy of Midazolam Vs. Ondansetron in Preventing Post Operative Nausea and Vomiting in Gynecologic Laparoscopic Surgeries: Double-blinded Randomized Clinical Trial Study

Leili Hafizi<sup>1</sup>, Mahsa Kiafar<sup>2</sup>, Arash peyvandi<sup>3</sup>, Alireza Sepehri Shamloo<sup>4</sup>, Samira Andalibizadeh<sup>5</sup>, Masoume Nouri<sup>6</sup>, Nahid Zirak<sup>7\*</sup>

<sup>1</sup>Assistant professor of Obstetrics and Gynecology, Imam Reza Hospital, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.

E-mail: [hafizil@mums.ac.ir](mailto:hafizil@mums.ac.ir)

<sup>2</sup>Obstetrician and Gynecologist, Imam Reza Hospital, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.

E-mail: [Kiafarm@mums.ac.ir](mailto:Kiafarm@mums.ac.ir)

<sup>3</sup>Assistant professor of Anesthesiology, Imam Reza Hospital, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.

E-mail: [PeyvandiA@mums.ac.ir](mailto:PeyvandiA@mums.ac.ir)

**Corresponding Author:** <sup>4</sup>Student Research Committee, School of medicine, Mashhad University of Medical Sciences, Mashhad, Iran

E-mail: [Sepehria871@mums.ac.ir](mailto:Sepehria871@mums.ac.ir)

<sup>5</sup>Medical student, Imam Reza Hospital, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.

E-mail: [andalibizadehs861@yahoo.com](mailto:andalibizadehs861@yahoo.com)

<sup>6</sup>Medical student, Imam Reza Hospital, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.

E-mail: [nourim861@mums.ac.ir](mailto:nourim861@mums.ac.ir)

<sup>7\*</sup>Associated professor of Anesthesiology, Imam Reza Hospital, Faculty of Medicine, Cardiac Anesthesia Research Center, Faculty of Medicine, Mashhad University of Medical Sciences, and Mashhad, Iran.

E-mail: [zirakn@mums.ac.ir](mailto:zirakn@mums.ac.ir)

Accepted 1st November, 2013

### Abstract

#### Introduction

Post operative nausea and vomiting (PONV) can be seen more commonly in women and especially in gynecologic and laparoscopic surgeries. One of the drugs suggested as a pre-treatment is midazolam. This study investigated the effect of midazolam in reducing post operative nausea and vomiting in comparison with ondansetron.

#### Method

In this double blind randomized clinical trial 80 patients who were met inclusion and exclusion criteria were randomly allocated in two equal groups of 40, each receiving either midazolam (received 15 mg/kg during induction of anesthesia) or ondansetron (4 mg IV, 15 min before extubation). Information regarding occurrence of nausea and vomiting in 0, 2, 6 and 24 hours after extubation were recorded in a questionnaire.

#### Results

The nausea score in the recovery, 2, 6 and 24 hours after extubation, was not significantly different between the two groups. Frequency of vomiting was higher in midazolam group than ondansetron group at 2 and 6 hours post recovery, but was the same at 24 hours.

#### Conclusion

Although midazolam premedication was not more effective than ondansetron in reducing postoperative nausea and vomiting but in many intervals the effect was similar to ondansetron; in which justifies its use with other anti-nausea medications.

**Key words:** ondansetron, nausea, vomiting, laparoscopic, gynecologic, midazolam

### Introduction

Postoperative nausea and vomiting (PONV) is common problem which affecting 20-30% of the patients undergoing surgery (1-2). It is an unpleasant experience that some patients reported it even worse than postoperative pain (3). It may increase risk of some complications such as dehydration and electrolyte disturbances, stitch opening, aspiration and pulmonary complications, late-onset of oral feeding and delayed recovery, which may lead to increase time of hospitalization and waste cost and time (4).

Factors that can affect risk of PONV include: gender (women is more likely than men), drug addiction, motion sickness, history of PONV, type of surgery, prolonged surgery and type of anesthetic drugs that is used (5-6). However PONV is more related to the patient condition and type of anesthesia than type of surgery; in gynecologic surgeries it has a higher incidence (6-7). Prevention of PONV in high risk patients has been advised in some guide lines. Use of anti-nausea drugs such as ondansetron, metoclopramide and droperidol due to those side effects such as weakness and extra pyramidal symptoms is limited (8).

The anti-nausea effect of midazolam as an anesthetic medication has investigated previously (9-13). Although in our country, general anesthesia is a usual method of anesthesia but no specific protocol for PONV management has been provided. We designed this study to investigate the effect of a single dose of midazolam in reducing nausea and vomiting after surgery, in comparison with ondansetron as a potent anti nausea agent.

### Method

In this double-blinded randomized clinical trial study, patients in Gynecology Department of Imam Reza hospital in Mashhad, Iran, who underwent elective laparoscopic gynecological surgery, were studied from February 2011 and November 2011. Mashhad University of Medical Sciences Research Ethics Council approved the project and the consent was freely and knowingly filled by the patients. The exclusion criteria were ASA physical status more than II, chronic cough, pregnancy, suggestive history of malignant hyperthermia, breast feeding, psychiatric problems, smoking or drug abuse, history of motion sickness disease, chronic use of benzodiazepines, and allergy to medications that were used in study. As well patients with history of moderate to severe nausea and vomiting or antiemetic

treatment 24 hours prior to surgery were excluded from the study.

Monitoring included continuous ECG, non-invasive blood pressure, pulse oximetry, end-tidal carbon dioxide (Sa'adat, Iran).

All patients underwent same general anesthesia with endotracheal intubation. General anesthesia was induced by injection of fentanyl at doses of 2 µg/kg, atracurium 0.5 mg/kg and Thiopental 5 mg/kg. Intravenous midazolam 15 µg/kg (Exir Pharmaceutical Company, Iran) was injected with the induction of anesthesia and intravenous Ondansetron 4mg (Tehran chemic pharmaceutical company, Iran) was injected 15 minutes before extubation. Maintenance of anesthesia was included by Isoflurane 1% and Oxygen.

A computer-generated randomization list was used to allocate subjects to receive either Midazolam or Ondansetron. Two groups regarding age, duration of anesthesia, history of migraines and smoking were homogeneous. At the end of the surgery, the Isoflurane was discontinued, the oxygen flow was set to 6-8 l/min, after reverse of neuromuscular block with combination of Neostigmin and Atropine the endotracheal tube was removed.

All procedures were made by one board certified anesthesiologist. A ten-point visual analogue scale (VAS) was used to assess nausea, with scores ranging from 1 (no nausea) to 10 (nausea as bad as it could be). The patients were got familiar with visual analogue scale (VAS) for nausea assessment before the anesthesia. The trained investigator who was unaware of patient grouping assessed and recorded the nausea scores during three postoperative time period, 0, 2, 6 and 24 hours after extubation. If the patient had nausea for more than 15 min or experienced retching or vomiting during the observation intravenous metoclopramide 10 mg was given. No placebo group was compared for ethical reasons. While the primary endpoint of this study was the incidence of PONV but the safety of the treatment assumed as the other endpoint.

Determining of sample size was done by using results of Lee Y et al study by Comparison of two Average formula (12). The  $\alpha$  error was set at 0.05 (two-sided) and the  $\beta$  error at 0.2 (power = 0.8). 80 patients were selected in each group for possible dropouts. The independent Samples t-test, Mann-Whitney test and Fisher's exact test were used for statistical analysis. The values were presented as the mean  $\pm$  standard deviation (SD).  $P < 0.05$  was taken as significant. Commercial SPSS 16.0 software for Windows (SPSS Inc., Chicago, IL) was used for the data analysis.

## Results

Eighty patients who underwent elective laparoscopic gynecological surgery, were randomly placed in two groups of treatment; Midazolam (n=40) and Ondansetron (n=40) and no patients were withdrawn. Patient characteristics, duration of anesthesia, and the risk factors for PONV were not different between groups (Table 1). None of the patients,

had nausea during recovery stay. Score of nausea at 2nd, 6th, and 24th hours after extubation is demonstrated in table 2. Frequency of vomiting was higher in Midazolam group than Ondansetron group at 2nd hour after extubation, but it was the same in two groups at 6th and 24th hours. (Table 3) In this study, no adverse effect associated with the drugs was detected. Totally, the use of Ondansetron, in combination with other anesthetic drugs, has a better significant effect on reducing postoperative nausea and vomiting in comparison with Midazolam. (Fig 1)

## Discussion

PONV is a common entity with multi factorial origin (2, 4). Incidence of PONV in patients depend on some factors such as age, history of motion sickness disease or previous PONV, gender, anxiety level before surgery, obesity, duration of surgery, presence of postoperative pain, timing of oral intake in the postoperative period, menstrual cycle, type of surgery and anesthetic technique (14-15). In this study, in order to reduce interfering factors, we excluded those patients with psychiatric problems, smoking or drug abuse, obesity (BMI>30), history of motion sickness disease and chronic use of benzodiazepines then two groups were matched regarding age, history of migraines and anesthetic technique. Benzodiazepines has been performed, both for prophylaxis and for treatment of PONV(13). Midazolam is a water soluble short- acting medication in benzodiazepine class that was used frequently as an antiemetic medication to prevent PONV (16). There were many studies in the literature that compared midazolam with placebo for PONV management (17-18). Heidari SM et al (19) compared anti emetic effects of premedication of intravenous midazolam with placebo after cholecystectomy and found the severity of nausea and number of vomiting significantly in midazolam group were lower than the placebo group.

They concluded that prophylactic intravenous midazolam is effective to reducing the incidence and severity of PONV. Elhakim M and colleagues (20) compared the prophylactic antiemetic effect of midazolam with placebo on 80 patients that they had received epidural morphine for pain relief after hysterectomy. Their study demonstrated that infusion of midazolam in preventing PONV after injection of epidural morphine is effective. Midazolam was also compared with potent anti emetic drugs such as droperidol, ondansetron, perphenazine, and metoclopramide (2, 21). Ondansetron is a potent anti emetic medication that was performed frequently but its side effects such as cardiac effects (acute myocardial ischemia and arrhythmias), headaches, constipation, dizziness, diarrhea and allergic reactions limited its common use (22, 23). Lee Y et al (12) compared the prophylactic antiemetic effect of midazolam with ondansetron for preventing PONV.

They found the incidence of PONV was similar in both groups and two drugs did not have advantage to each other. Pain after surgery is very important factor that affect patients satisfaction (27). Midazolam has been traditionally used in combination with other anesthetic drugs to more sedation of the patients before surgery (29). There are several studies in the literature that showed midazolam is efficient

medication to relief pain after surgery (28). In a randomized clinical trial that performed by C.K.S Ong on 125 Patients, cases were divided in to two groups that received either midazolam or not. Their pain after third molar surgery was assessed by VAS and the score of pain in patients who received midazolam was significantly lower than the other group (30). So in our purpose the anti pain effect of midazolam is other merits of this medication. There is an ongoing debate regarding the most cost effective strategy for the management of PONV (31). Although new anti emetic medications are effective, their high price restricted their use especially in low economic countries. Midazolam is relatively not expensive medication that is available in many countries. The cost of IV midazolam for a 5mg vial at the University Hospital of Mashhad is approximately 6000 IRAN Rials. Midazolam can be used by intra venous administration and has also been administered sublingually, intra nasally, and intra muscular to alleviate PONV (13, 24).

All of these types of administration have been reported to be relatively successful but its IV administration gives more acceptability due to its rapid onset of effects and more rapid rate of distribution (32) so in the current study midazolam was administered intra venous. There was challenge regarding the time of administration of antiemetic medications to patients to prevent PONV. Some authors advised prophylactic administration of midazolam immediately prior to anesthetic Induction but others prefer its administration at the end of surgical procedure. Finally it

can be concluded that premedication with midazolam, even with low doses, can be effectively used to reduce PONV and reduce the duration of hospitalization and medical expenses after laparoscopic and gynecological surgery that is associated with high rates of nausea and vomiting. Regards midazolam with mentioned dose in this study don't have any side effects and on the other hand is a relatively cheap.

## Conclusion

Although midazolam premedication was not more effective than ondansetron in reducing postoperative nausea and vomiting but in many intervals the effect was similar to ondansetron; in which justifies its use with other anti-nausea medications.

## Acknowledgements

The authors would like to express their sincere thanks to Women health research center Mashhad University of Medical Sciences, for the financial support and Ms. Vida Arbab and Ms. Atefe Akbar Abadi for their cooperation. This manuscript is derived from gynecologic residency thesis number 2515 and a research project with code 89595 with financial support of vice chancellor for research, Mashhad University of Medical Sciences.

## Financial Disclosure

Table 1. Patient characteristics and variables related to PONV. Values are mean (SD) or number

	Midazolam (n = 40)	Ondansetron (n = 40)	P value
Age; years	29.3±5.8	30±6.5	NS
Weight; kg	58±2.1	56±1.9	NS
History of PONV; n	13	14	NS
History of motion sickness; n	2	3	NS
Duration of anesthesia; min	92±14.1	90±12.2	NS

Table 2. Postoperative nausea scores (VAS) in Midazolam and Ondansetron groups during different observatory periods

Postoperative nausea scores (VAS)	Midazolam (n = 40)	Ondansetron (n = 40)	P value
2 h	1.1	0.3	0.09
6 h	0.7	0.1	0.35
24 h	0.1	0.1	0.97

Table 3. Incidences of postoperative vomiting in Midazolam and Ondansetron groups during different observatory periods

Postoperative nausea scores (VAS)	Midazolam (n = 40)	Ondansetron (n = 40)	P value
2 h	12.5	0	0.01
6 h	10	0	0.01
24 h	0	0	0.86

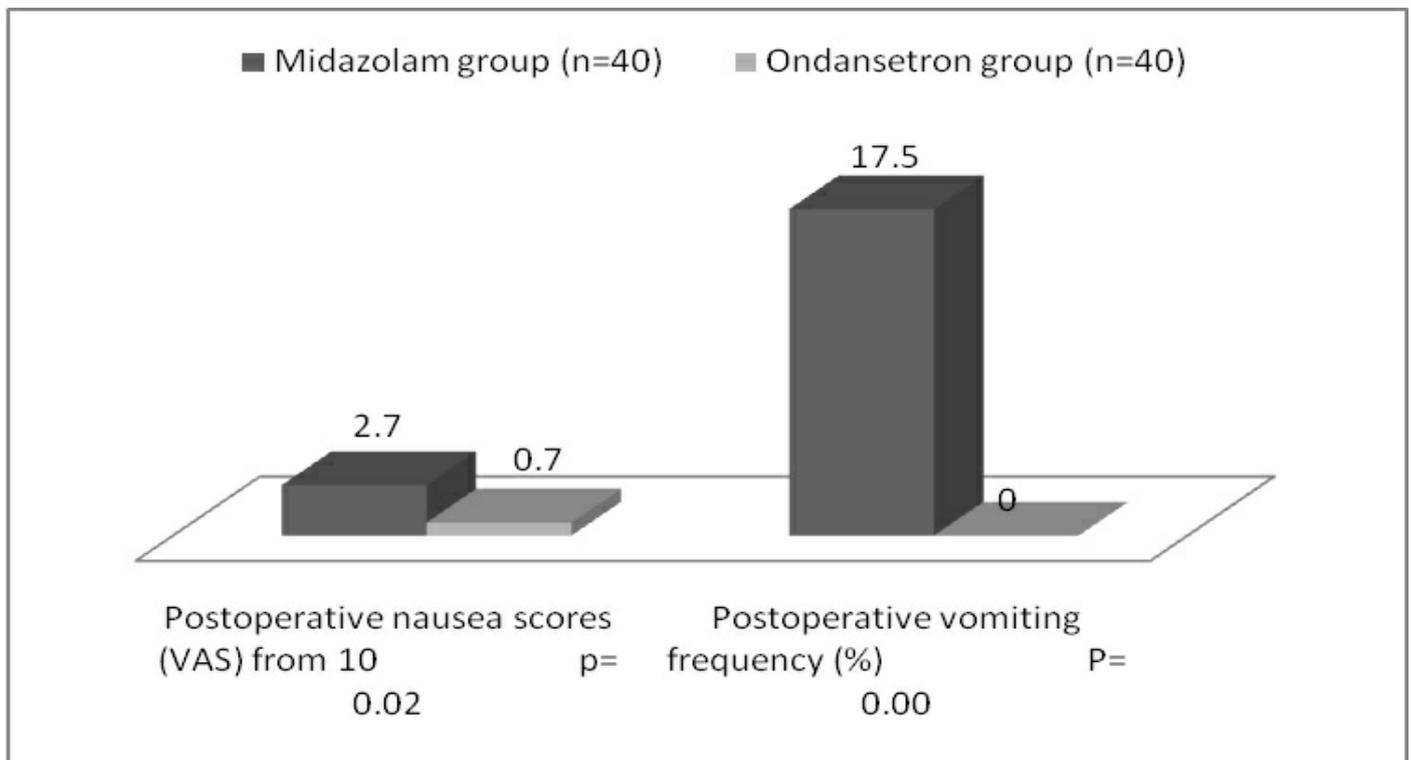


Figure 1. Comparison of midazolam and ondansetron effects on the incidence of postoperative nausea and vomiting

This manuscript has been read and approved by all of the Authors and there is not potential conflict of interest for them.

## References

- Biedler A, Wermelt J, Kunitz O, Muller A, Wilhelm W, Dethling J, et al. A risk adapted approach reduces the overall institutional incidence of postoperative nausea and vomiting. *Can J Anaesth*. 2004 Jan;51(1):13-9.
- Desilva PH, Darvish AH, McDonald SM, Cronin MK, Clark K. The efficacy of prophylactic ondansetron, droperidol, perphenazine, and metoclopramide in the prevention of nausea and vomiting after major gynecologic surgery. *Anesth Analg*. 1995 Jul;81(1):139-43.
- Macario A, Weinger M, Truong P, Lee M. Which clinical anesthesia outcomes are both common and important to avoid? The perspective of a panel of expert anesthesiologists. *Anesth Analg*. 1999 May;88(5):1085-91.
- Golembiewski JA, O'Brien D. A systematic approach to the management of postoperative nausea and vomiting. *J Perianesth Nurs*. 2002 Dec;17(6):364-76.
- Gan TJ. Risk factors for postoperative nausea and vomiting. *Anesth Analg*. 2006 Jun;102(6):1884-98.
- Eberhart LH, Hogel J, Seeling W, Staack AM, Geldner G, Georgieff M. Evaluation of three risk scores to predict postoperative nausea and vomiting. *Acta Anaesthesiol Scand*. 2000 Apr;44(4):480-8.
- Fujii Y, Tanaka H, Toyooka H. The effects of dexamethasone on antiemetics in female patients undergoing gynecologic surgery. *Anesth Analg*. 1997 Oct;85(4):913-7.
- Mishriky BM, Habib AS. Metoclopramide for nausea and vomiting prophylaxis during and after Caesarean delivery: a systematic review and meta-analysis. *Br J Anaesth*. 2012 Mar;108(3):374-83.
- Elhakim M, Abd-Elfattah H, El-Din DN, El-Kabarity R, Atef A, El-Fakey A. Midazolam as an antiemetic in patients receiving epidural morphine for postoperative pain relief. *J Opioid Manag*. 2009 Jul-Aug;5(4):189-95.
- Fujii Y, Itakura M. Antiemetic efficacy of low-dose midazolam in patients undergoing thyroidectomy. *Otolaryngol Head Neck Surg*. 2011 Feb;144(2):206-9.
- Heidari SM, Saryazdi H, Saghaei M. Effect of intravenous midazolam premedication on postoperative nausea and vomiting after cholecystectomy. *Acta Anaesthesiol Taiwan*. 2004 Jun;42(2):77-80.
- Lee Y, Wang JJ, Yang YL, Chen A, Lai HY. Midazolam vs ondansetron for preventing postoperative nausea and vomiting: a randomised controlled trial. *Anaesthesia*. 2007 Jan;62(1):18-22.
- Sanjay OP, Tauro DI. Midazolam: an effective antiemetic after cardiac surgery--a clinical trial. *Anesth Analg*. 2004 Aug;99(2):339-43, table of contents.
- Murphy MJ, Hooper VD, Sullivan E, Clifford T, Apfel CC. Identification of risk factors for postoperative nausea and vomiting in the perianesthesia adult patient. *J Perianesth Nurs*. 2006 Dec;21(6):377-84.
- Kehlet H. Effect of postoperative pain treatment on outcome-current status and future strategies. *Langenbecks Arch Surg*. 2004 Aug;389(4):244-9.
- Tang J, Wang B, White PF, Watcha MF, Qi J, Wender RH. The effect of timing of ondansetron administration on its efficacy, cost-effectiveness, and cost-benefit as a prophylactic antiemetic in the ambulatory setting. *Anesth Analg*. 1998 Feb;86(2):274-82.
- Bauer KP, Dom PM, Ramirez AM, O'Flaherty JE. Preoperative intravenous midazolam: benefits beyond anxiolysis. *J Clin Anesth*. 2004 May;16(3):177-83.
- Di Florio T, Goucke CR. The effect of midazolam on persistent postoperative nausea and vomiting. *Anaesth Intensive Care*. 1999 Feb;27(1):38-40.
- Heidari SM, Saryazdi H, Saghaei M. Effect of intravenous midazolam premedication on postoperative nausea and vomiting after cholecystectomy. *Acta Anaesthesiol Taiwan*. 2004 Jun;42(2):77-80.
- Elhakim M, Abd-Elfattah H, El-Din DN, El-Kabarity R, Atef A, El-Fakey A. Midazolam as an antiemetic in patients receiving epidural morphine

- for postoperative pain relief. *J Opioid Manag.* 2009 Jul-Aug;5(4):189-95.
21. Habib AS, White WD, Eubanks S, Pappas TN, Gan TJ. A randomized comparison of a multimodal management strategy versus combination antiemetics for the prevention of postoperative nausea and vomiting. *Anesth Analg.* 2004 Jul;99(1):77-81.
  22. Jones EA. Relief from profound fatigue associated with chronic liver disease by long-term ondansetron therapy. *Lancet.* 1999 Jul 31;354(9176):397.
  23. Rhodes VA, Johnson MH, McDaniel RW. Nausea, vomiting, and retching: the management of the symptom experience. *Semin Oncol Nurs.* 1995 Nov;11(4):256-65.
  24. Crevoisier C, Ziegler WH, Eckert M, Heizmann P. Relationship between plasma concentration and effect of midazolam after oral and intravenous administration. *Br J Clin Pharmacol.* 1983;16 Suppl 1:51S-61S.
  25. M. S. Sniadach and M. S. Alberts. A comparison of the prophylactic antiemetic effect of ondansetron and Droperidol on patients undergoing gynecologic laparoscopy. 1997 ;
  26. R. A. Steinbrook, J. L. Gosnell and D. Freiburger. Prophylactic antiemetics for laparoscopic cholecystectomy: a comparison of perphenazine, droperidol plus ondansetron, and droperidol plus metoclopramide, *Journal of clinical anesthesia*, 1998.
  27. D. J. Pavlin, C. Chen, D. A. Penaloza, N. L. Polissar and F. P. Buckley .Pain as a factor complicating recovery and discharge after ambulatory surgery, *Anesthesia & Analgesia*, 2002
  27. A. P. Tucker, J. Mezzatesta, R. Nadeson and C. S. Goodchild .Intrathecal midazolam II: combination with intrathecal fentanyl for labor pain , *Anesthesia & Analgesia*, 2004
  28. B. P. Kinirons, H. Bouaziz, X. Paqueron, A. Ababou, C. Jandard, M. M. Cao, M. L. Bur, M. C. Laxenaire and D. Benhamou. Sedation with sufentanil and midazolam decreases pain in patients undergoing upper limb surgery under multiple nerves block, 2000