

LORAZEPAM EFFECT FOR PREVENTING POSTOPERATIVE NAUSEA AND VOMITING AFTER LAPAROSCOPIC CHOLECYSTECTOMY

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Article Received on
09 Aug. 2016,

Revised on 29 Aug. 2016,
Accepted on 19 Sept. 2016

DOI: 10.20959/wjpr201610-7130

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ABSTRACT

Background: Postoperative nausea and vomiting (PONV) are the most common symptoms affecting patients after surgery under general anesthesia and that is one of the most common causes of patient dissatisfaction after anesthesia. **Objective:** the purpose of this study was to evaluate the effect of oral lorazepam in reducing PONV after laparoscopic cholecystectomy. **Methods:** This double blind clinical prospective study was conducted on 76 patients aged 20-60 years, with American Society of Anesthesiologist physical status I or II who were scheduled for laparoscopic cholecystectomy, at Razi Hospital, Ahwaz, Iran from December 21, 2015 to January 20, 2016. Patients were divided into lorazepam (Group 1) or control group (Group 2). Patients were assigned using a computer-generated random number table. The incidence of nausea and vomiting, use of antiemetic drugs and severity

of nausea vomiting according to NVS score during the first 24 hours post anesthesia in 3 time periods (0, 6 and 24 hours post anesthesia). were recorded. **Result:** The comparisons of the groups for the number of patients with nausea showed a significant difference at 6(3.437times in group 2 more than group 1, p-value=0.003) and at 24 hours (4.391 times in group 2 more than group 1, p-value=0.007), also The comparisons of the groups for the number of patients with vomiting showed a significant difference at 0(3.954times in group 2 more than group 1,

p-value=0.016) and at 6 hours (12.397 times in group 2 more than group 1, p-value<0.001), whereas there were no statistically significant differences at 24. Regarding to antiemetic uncovered a significant difference at recovery 10 patients in group 1 (26.3%) vs 12 patients in group 2 (31.6%) hours ($P < 0.05$). The mean \pm (SD) NVS score was 0.4 (0.2) in group 1 and 1.0 (0.2) in group 2 ($P = 0.017$) that is significant. **Conclusion:** We concluded that effectiveness of premedication with lorazepam for prevention of PONV after laparoscopic cholecystectomy. **Trial registration:** The trial was registered at the Iranian Registry of Clinical Trials (<http://www.irct.ir>) with the Irct ID: IRCT2014051917742N2. **Funding:** The authors received no financial support for the research, authorship and/or publication of this article.

KEYWORDS: Post operative nausea and vomiting, Laparoscopic cholecystectomy, Lorazepam.

1. INTRODUCTION

Postoperative nausea and vomiting (PONV) are the most common symptoms affecting patients following surgical procedure under anesthesia, and that is one of the most common causes of patient disappointment after anesthesia, with an occurrence of approximately 20 to 30%.^[1] The causes of PONV are numerous and varied based on enduring, operation type and anesthesia related factors. PONV occurs commonly in patients undergoing laparoscopic surgery. Age, female gender, pregnancy, menstrual cycle, experience of nausea and vomiting, history of motion sickness, smoking, duration of anesthesia, obesity, use of N₂O, narcotics, inhaled drugs for anesthesia and surgery are risk factors for PONV. While suture dehiscence, aspiration of gastric contents, esophageal rupture and other serious complications associated with PONV are rare, nausea and vomiting is still an unpleasant and all-too-common postoperative morbidity that can delay patient discharge from the post-anesthesia care unit and increase unanticipated hospital admissions in outpatients.^[2,3]

There are main classes of drugs used in the management of PONV: anticholinergics, antihistamines, D₂ antagonists and 5HT₃ antagonists, Benzamides, Phenothiazines, Butyrophenones, Corticosteroids, Cannabinoids and Benzodiazepines. However, because of the many ways in which the vomiting centre can be triggered, no single drug or class of drug is completely effective in controlling PONV.^[4]

Lorazepam is used by itself and combined with other agents as an antiemetic in patients having chemotherapy. The antiemetic effect of lorazepam may be secondary to its ability to decrease anxiety, induce hypnosis and provide antrograde amnesia and/or simply provide a specific antiemetic effect.^[5] Since most previous studies on the antiemetic effect of lorazepam were after chemotherapy^[6,7] and enough studies on the effects of antiemetic medication after the surgery is not performed, the purpose of this study was to evaluate the effect of oral lorazepam in reducing PONV after laparoscopic cholecystectomy.

2. MATERIAL AND METHODS

2.1. Trial design

This study was a randomized clinical trial that was conducted from Desember21, 2015 to January 20, 2016.

2.2. Participants

This clinical trial was conducted in an Iranian governmental educational hospital (Razi Hospital, Ahwaz, Iran).

2.3. Selection criteria

The inclusion criteria for participation in this study were: Scheduled for laparoscopic cholecystectomy; Anesthesiologist physical status I or II; BMI<30; Age20 to 60 years.

The exclusion criteria included: Complicated surgery, Hemodynamic change after lorazepam usage; Systolic blood pressure<90mmhg or>160; Previous postoperative emesis; Use of an antiemetic agent within 24 hours before surgery; And laparoscopy replaced by laparotomy.

2.4. Interventions

This randomized, double-blind, controlled clinical study was carried out at the Razi Hospital in Ahvaz, Iran. Approval was obtained from the Ethics Committee at Ahvaz Jondishapour University of Medical Sciences, Ahvaz, Iran. All patients provided written informed consent. Seventy six patients with BMI<30, scheduled for laparoscopic cholecystectomy (aged 20 to 60 years) with an American Society of Anesthesiologists (ASA) physical status classification system risk of 1 or 2 were randomly assigned to 1 of 2 groups: the lorazepam (1mg) (group 1) and the placebo (group 2). Patients were assigned using a computer-generated random number table.

Exclusion criteria included

Complicated surgery, Hemodynamic change after lorazepam usage; systolic blood pressure <90 mmHg or >160; previous postoperative emesis; use of an antiemetic agent within 24 hours before surgery; and laparoscopy replaced by laparotomy. All procedures were performed by the same team of anesthesiologists and surgeons. Different anesthesiologists carried out the data collection and treating roles in this study. Patients fasted for 8 hours before surgery. 60 minutes before induction of anesthesia, patients in group 1 were given 1 mg oral lorazepam tab with 10 cc water. Group 2 patients were given placebo tab with 10 cc water. In the operation room, heart rate (HR), systolic arterial pressure (SAP), diastolic arterial pressure (DAP), mean arterial pressure (MAP) and peripheral oxygen saturations (SpO₂; Datascope Passport 2, Datascope Corp, Mahwah, New Jersey) were monitored. Anesthesia for all patients in both groups was induced with propofol 1.5 mg/kg (IV bolus dose) followed by remifentanyl infusion at 0.1 µg/kg/min and isoflurane inspiration at 1% concentration. After patients received atracurium (0.5 mg/kg), all were ventilated mechanically with O₂/air (50%/50%), 4 L/min end tidal carbon dioxide (ETCO₂) 35 to 40 mm Hg through orotracheal intubation (TMS Maxi 2200 M, Penlon AV 900, Oxford, United Kingdom). The maintenance doses of remifentanyl and isoflurane were adjusted for hemodynamic stability. Throughout surgery, hydration was maintained with an infusion of isotonic or Ringer's lactate solution at a rate of 3 mL/kg to 5 mL/kg.

At the time of the last surgical suture, all anesthetic maintenance agents were terminated and the time was recorded. The lungs were manually ventilated with 100% oxygen (4 L/min) until spontaneous respiration was achieved. Residual muscle relaxation was antagonized with 0.03 mg/kg neostigmine and 0.02 mg/kg atropine, and the patients were appropriately extubated. All patients were removed to postoperative recovery and remonitored after extubation. Patients remained for evaluation of potential postoperative complications and recovery for at least 1 hour.

2.5. Outcomes

The incidence of nausea, vomiting, use of antiemetic drugs, severity of nausea and vomiting according to nausea-vomiting scale (NVS), were recorded during the first 24 hours after anesthesia in 3 time periods (0, 6 and 24 hours post anesthesia). Additional antiemetic (10 mg metoclopropamide) was administered intravenously when the NVS score was ≥3.

2.6. Sample size

The sample size was calculated by assuming the test power of 80% and a confidence level of 95% and using the following formula:

$$n = (Z_{1-\alpha/2} + Z_{1-\beta})^2 \times ((P_1 \times (1-P_1) + P_2 \times (1-P_2)) / (P_1 - P_2)^2)$$

Where:

n = Sample size

$Z_{1-\alpha/2} = 1.96$ when $\alpha = 5\%$ for two-sided test

$Z_{1-\beta} = 0.842$ when $\beta = 20\%$ (test power = 80%)

P = Probability of the main outcome.

2.7. Randomization and blinding

Patients were divided in lorazepam (Group 1) or control group (Group 2) Patients were assigned using a computer-generated random number table. Then, the participants in each of the groups were assigned randomly to receive either lorazepam or control on a 1:1 ratio. Randomization was done by one of researchers, who did not have a role in the treatment of the participants.

2.8. Statistical methods

Statistical analyses were performed by SPSS 19. Parametric values were evaluated with the Student *t*-test. Nonparametric values were compared using the Mann-Whitney U test. Side effects and gender were compared using χ^2 and Fisher exact tests. A $p < 0.05$ was considered statistically significant.

2.9. Research ethics.

This research was supported by Pain Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran. Proposal No ajums.REC.1394.3and IRCT2014051917742N2.

Indeed, in this study, for ethical considerations, the participants were informed about the objective and nature of the study and each participant provided her or his written consent in her or his native language (Persian) prior to the study. Also, we were committed to keeping all of the participants' information confidential.

Table I: Nausea vomiting scale.

NVS	Severity
0	No complaints
1	Mild nausea
2	Moderate nausea
3	Frequent vomiting (4 times)
4	Severe vomiting (continuous)

NVS = nausea vomiting scale.

3. RESULTS

A total of 76 patients were approached for study inclusion. No statistically significant between-groups differences were found in the patients' demographic and clinical characteristics (Table II).

Table 2: Demographics characteristics.

Parameter	Group 1 (Lorazepam)	Group 2(placebo)	P
Age. (Mean \pm SD), y	36.92 \pm 9.24	36.13 \pm 8.93	0.539
Smoking, no. (%)	11(28.9)	10(26.3)	0.798
Gender (F/M), no. (%)	22(57.9)/ 16(42.1)	25(65.8)/ 13(34.2)	0.479

Data are mean (\pm SD).

The comparisons of the groups for the number of patients with nausea showed a significant difference at 6(3.437 times in group 2 more than group 1, p-value=0.003) and at 24 hours (4.391 times in group 2 more than group 1, p-value=0.007), whereas there were no statistically significant differences at 0.

The comparisons of the groups for the number of patients with vomiting showed a significant difference at 0(3.954 times in group 2 more than group 1, p-value=0.016) and at 6 hours (12.397 times in group 2 more than group 1, p-value<0.001), whereas there were no statistically significant differences at 24.

Comparison of groups regarding to need for antiemetic drug uncovered a significant difference at recovery; 10 patients in group 1 (26.3%)vs 12 patients in group 2(31.6%) (p <0.05), but no significant differences at 6 and at 24 hours.

The mean \pm (SD) NVS score was 0.4 (0.2) in group 1 and 1.0 (0.2) in group 2 (P = 0.017) that is significant.

4. DISCUSSION

Our findings indicated that premedication with lorazepam effective for prevention of PONV after laparoscopic cholecystectomy. In this study, patient demographics, type of surgical procedure and anesthetic administered were similar between groups. Numerous agents have been used to prevent from PONV at varying dosages and time intervals.^[4] Parameters such as nausea and vomiting scores for 4 hours in the early postoperative period or in the postoperative 24 hours, number of episodes and severity of vomiting, number of antiemetics required, amount of antiemetics used, hospitalization time and problems caused by nausea and vomiting are studied to evaluate the effectiveness of these agents.^[8-13]

PONV develops as a complication after anesthesia and if not prevented, recovery and hospitalization time can be prolonged, leading to unpleasant hospital experiences and increased health care costs.^[13] Prolonged vomiting may result in electrolyte imbalance (hypocalcaemia, hypochloremia, hyponatremic metabolic alkalosis) and dehydration, Mallory-Weis tears, esophageal rupture, wound opening and hematoma formation under skin flaps after abdominal, vascular, eye, or plastic surgery.^[8,9]

The effect of intraperitoneal insufflations of carbon dioxide (CO₂) on residual stretching and irritation of the peritoneum and duration of surgery are other factors that affect PONV after LC(11). In our study, however, treatment groups were similar for patient demography, types of LC, anesthetics administered and analgesics used postoperatively.

Benzodiazepines have been involved during the years in the prevention and treatment of Post-Operative Nausea and Vomiting (PONV). It has been postulated that a possible mechanism for the anti-emetic effect of benzodiazepines could be an action at the chemoreceptor trigger zone reducing synthesis, release and postsynaptic effect of dopamine⁹. Whether benzodiazepines reduce dopamine release centrally, or by blocking the re-uptake of adenosine, causing an adenosine-mediated reduction of dopamine release, has been matter of debate¹⁰⁻¹⁴. Dopaminergic neuronal activity and 5hydroxytryptamine release may also be reduced by binding of midazolam to the GABA benzodiazepine complex^{9, 12 and 15}: thus, anxiolysis as a secondary effect may also contribute to antiemetic. However, Wang and Klein¹⁶, in a cross-sectional study exploring a possible association between preoperative anxiety and PONV in a group of children undergoing outpatient surgery did not find any predictive value of children's anxiety for the occurrence of PONV.^[3] Lorazepam is used by itself and combined with other agents as an antiemetic in patients having chemotherapy. The

antiemetic effect of lorazepam may be secondary to its ability to decrease anxiety, induce hypnosis and provide antrograde amnesia and/or simply provide a specific antiemetic effect.^[5]

In our study, the severity of nausea and vomiting was measured using the NVS for the postoperative 24 hours and the number of patients with nausea, vomiting, or need for antiemetics was compared for postoperative hours 0, 6 and 24 hours; the results were expressed in percentages. We determined that the administration of 1mg oral lorazepam 60 minutes before surgery was effective for control of PONV during the first 6 postoperative hours ($p=0.003$ for nausea and $p\text{-value}=0.016$ for vomiting).

Khalil et al. demonstrated that premedication with lorazepam was effective for PONV in strabismus surgery.^[5]

In addition to in our study incidence of PONV was in women more than men, but there was no significant. That is Consistent with other studies.^[4,5]

To reduce the effect of patient- and anesthesia-specific factors, we homogenized study groups for age, body weight, height, ASA group, duration of operation and anesthesia. Such differences may account for differences observed in some studies.

Our study had potential limitations. First, these data may not be applicable to different surgical procedures or anesthetic techniques. Second, no pre study power analysis was performed.

5. CONCLUSIONS

We concluded that effectiveness of premedication with lorazepam for prevention of PONV after laparoscopic cholecystectomy.

ACKNOWLEDGMENT

This research was supported by Pain Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran. With proposal No ajums. REC.1394.3. The authors appreciate the assistance and of the patients who participated in the study.

Trial Registration

The trial was registered at the Iranian Registry of Clinical Trials (<http://www.irct.ir>) with the Irct ID:IRCT2014051917742N2.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Conflict of Interest

There is no conflict of interest to be declared.

REFERENCES

1. Acalovschi I. Postoperative nausea and vomiting. *Curr Anaesth Crit Care*. 2002; 13: 37–43.
2. Watcha MF, White PF. Postoperative nausea and vomiting. Its etiology, treatment and prevention. *Anesthesiology*. 1992; 77: 162–184. [PubMed].
3. Fredman B, Nathanson MH, Smith I, Wang J, Klein K, White PF. Sevoflurane for outpatient anesthesia: a comparison with propofol. *Anesth Analg*. 1995; 81: 823–828.
4. Chandrakantan, A. and P. S. A. Glass. "Multimodal therapies for postoperative nausea and vomiting and pain." *British journal of anaesthesia*, 2011; 107.suppl 1: i27-i40.
5. Khalil, Samia N., et al. "The antiemetic effect of lorazepam after outpatient strabismus surgery in children." *Anesthesiology*, 1992; 77.5: 915-919.
6. 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*, 1985; 3(6): 864-9.
7. Malik, Imtiaz A., et al. "Clinical efficacy of lorazepam in prophylaxis of anticipatory, acute and delayed nausea and vomiting induced by high doses of cisplatin: a prospective randomized trial." *American journal of clinical oncology*, 1995; 18.2: 170-175.
8. Isik B., Cekmen N., Arslan M. Comparison of the antiemetic effects of ondansetron and dexamethasone on middle ear surgery. *Saudi Med J*. 2006; 27: 646–651. [PubMed].
9. DeBalli P. The use of propofol as an antiemetic. *Int Anesthesiol Clin*. 2003; 41: 67–77. [PubMed].
10. Tramer M.R. Strategies for postoperative nausea and vomiting. *Best Pract Res Clin Anaesthesiol*. 2004; 18: 693–701. [PubMed].

11. American Society of Health System Pharmacists ASHS Therapeutic guidelines on the management of nausea and vomiting in adult and pediatric patients receiving chemotherapy or radiation therapy or undergoing surgery. *Am J Health Syst Pharm.* 1999; 56: 729–764. [PubMed].
12. Fujii Y., Tanaka H., Kobayashi N. Small doses of propofol, droperidol, and metoclopramide for the prevention of postoperative nausea and vomiting after thyroidectomy. *Otolaryngol Head Neck Surg.* 2001; 124: 266–269. [PubMed].
13. Unal Y., Ozsoylar O., Arslan M. comparison of the efficacy of propofol and metoclopramide in preventing postoperative nausea and vomiting after middle ear surgery. *Saudi Med J.* 2009; 30: 778–782. [PubMed].