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Is lorazepam effective at preventing nausea and vomiting after laparoscopic cholecystectomy? A randomized controlled trial

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Summary : *Background :* Nausea and vomiting are very common after surgery and anesthesia, and cause patient dissatisfaction. The aim of this study was to evaluate the effect of premedication with oral lorazepam at preventing post-operative nausea and vomiting (PONV) following cholecystectomy.
Methods : This study was conducted on 76 patients with American Society of Anesthesiologist physical status I or II, who were scheduled for laparoscopic cholecystectomy, at Razi Hospital, Ahwaz. Patients were divided randomly into a lorazepam or a control group. The incidence of PONV, the use of antiemetic drugs, and the severity of PONV according to a clinical score (NVS score) were recorded at 3 time points, namely 0, 6, and 24 hours after the procedure.
Result : Between-group comparison showed a significantly higher incidence of nausea in the control group as compared to the lorazepam group at the 6th (P = 0.003) and 24th (P = 0.007) postoperative hour. This was also true for the incidence of vomiting at time 0 (P = 0.016) and 6 (P < 0.001), whereas there was no significant difference at time 24. Antiemetic medication consumption occurred in a significantly higher number of control group patients (n = 12, 31.6%) than of lorazepam group patients (n = 10; 26.3% ; P < 0.05). The mean ± (SD) NVS score was 0.4 (0.2) in the lorazepam group, and 1.0 (0.2) in the control group (P = 0.017).
Conclusion : Premedication with lorazepam for appears to be effective at preventing PONV following laparoscopic cholecystectomy.

Keywords : Postoperative nausea and vomiting ; laparoscopic cholecystectomy ; general anesthesia ; benzodiazepines.

Postoperative nausea and vomiting (PONV) are very common following surgical procedures performed under general anesthesia. They constitute one of the most common causes of patient dissatisfaction about their anesthesia management. Such PONV occur approximately after 20 to 30 % of surgical procedures under general anesthesia (1). Causes risk factors of PONV are numerous and depend both on the type of surgery and on the anesthesia technique. Laparoscopic surgery is frequently followed by PONV. Age, female gender, pregnancy, menstrual cycle, previous experience of nausea and vomiting, history of motion sickness, non-smoking, duration of anesthesia, obesity, use of nitrous oxide, use of opioids, and use of inhaled anesthetic agents are all 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 too common postoperative morbidity that can delay patient discharge from the post-anesthesia care unit, and increase the rate of unanticipated hospital admissions in outpatients (2, 3).

The main classes of medications for the management of PONV are anticholinergic medications, antihistaminic medications, dopamine antagonists, serotonin antagonists, benzamides, phenothiazines, butyrophenones, corticostroids, canabinoids, and benzodiazepines. However, due to the multiple possible routes of vomiting center activation, no single drug or class of drug is entirely effective at controlling PONV (4). A meta-analysis has been recently published on the efficacy of adding dexamethasone to antiemetic medications at preventing PONV after laparoscopic cholecystectomy (5).

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Lorazepam is used alone or in combination with other medications as an antiemetic agent in patients receiving chemotherapy. The antiemetic effect of lorazepam may occur through its ability to decrease anxiety, induce sedation, and provide anterograde amnesia, in addition to its specific antiemetic effects (6, 7, 8). To the best of our knowledge, recent studies on the effects of antiemetic medications after surgery are scarce, and most previous studies on the antiemetic effect of lorazepam were not conducted in surgical patients. Therefore, the purpose of this study was to evaluate the efficacy of oral lorazepam administered as a premedication at preventing PONV following laparoscopic cholecystectomy.

Methods

This study was a double blind randomized clinical trial, and was conducted from December 21, 2015, to January 20, 2016 at the Razi Hospital in Ahvaz, Iran, an Iranian governmental educational hospital. Approval was obtained from our local Ethics Committee (Ahvaz Jondishapour University of Medical Sciences, Ahvaz, Iran) under the reference number ajums.REC.1394.3 and IRCT2014051917742N2. All patients provided written informed consent. Seventy six ASA 1 or 2 patients, aged between 20 and 60 years, with a BMI < 30 and scheduled for laparoscopic cholecystectomy were recruited and randomly assigned to two groups: the lorazepam (1 mg) (group 1) and the placebo (group 2), according to a 1:1 ratio (parallel design) (Fig. 1). The randomization method used random permuted blocks of size 4. The exclusion criteria were complicated surgery, hemodynamic changes after lorazepam usage and defined as systolic blood pressure < 90mmhg or >160, previous PONV; use of an antiemetic agent within 24 hours before surgery, and conversion of laparoscopy into laparotomy. Patients were assigned using a computer-generated random list.

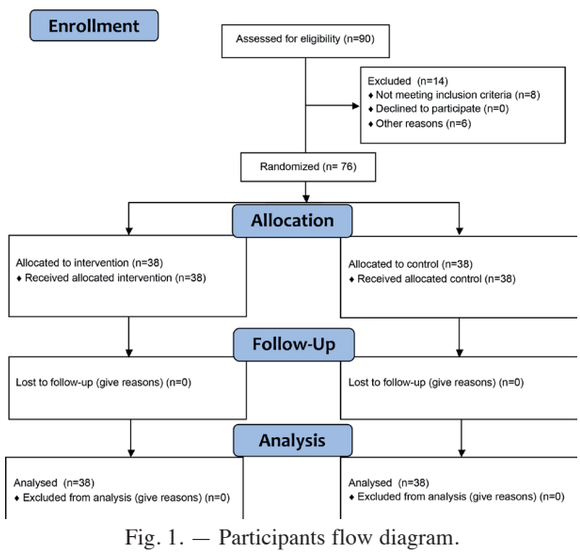

Fig. 1. — Participants flow diagram.

All procedures were performed by the same team of anesthesiologists and surgeons. Different anesthesiologists carried out data collection. Both participants and anesthesiologists were blinded to the received treatment. Patients fasted for 8 hours before surgery. Patients of group 1 received 1 mg oral lorazepam as a premedication, while group 2 patients were given a placebo in the form of 10 mL of water 60 minutes before induction of anesthesia (dosage and time of administration were determined according reference (6)). In the operation room, heart rate (HR), non-invasive systolic arterial pressure (SAP), diastolic arterial pressure (DAP), mean arterial pressure (MAP), and peripheral oxygen saturation (SpO_2) were monitored on a Passport 2 Data scope (Data scope Corp, Mahwah, New Jersey). Anesthesia for all patients in both groups was induced with propofol 1.5 mg/Kg (IV bolus dose), followed by a remifentanil infusion at a rate of 0.1 µg/Kg/min, and isoflurane at an inspired concentration of 1 %. Muscle relaxation was achieved using 0.5 mg/Kg of IV atracurium. All patients had orotracheal intubation of their trachea, and were mechanically ventilated using a O_2/air gas mixture (50/50), and a 4 L/min fresh gas flow.

Successful ventilation was defined as a square-wave tracing on capnography, with end-tidal CO_2 ($EtCO_2$) values ranging from 30 to 45 mmHg. The maintenance doses of remifentanil and isoflurane were adjusted for hemodynamic stability. Hydration was maintained using an infusion of isotonic or Ringer's lactate solution at a rate between 3 and 5 mL/Kg throughout the procedure.

At termination of the surgical procedure, all anesthetic maintenance agents were terminated, and the time was recorded. The lungs were manually ventilated with 100% oxygen (4 L/min) until spontaneous ventilation recovered. Residual muscle relaxation was antagonized using 0.03 mg/Kg neostigmine, and 0.02 mg/Kg atropine, before extubation of the trachea. All patients were transferred to the post-anesthesia care unit, for careful monitoring, at least for 1 hour.

The primary end points of this study were the incidence of nausea and vomiting, frequency of antiemetic medication use, as well as severity of nausea and vomiting according to a clinical

scoring system, namely the nausea and vomiting scale (NVS score, Table I). Those data were recorded at 0, 6, and 24 hours after the procedure. An additional antiemetic medication (10 mg of metoclopropamide) was administered intravenously when the NVS score was ≥ 3.

Table I

NVS score

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

NVS = nausea and vomiting scale

Statistical analysis

The sample size was calculated according to Khalil et al. study (6) by assuming a power of 80 % and a 95% confidence interval, using the formula: $n = ((Z1\text{-}\alpha/2 + Z1\text{-}\beta)^2 ((P1\ (1\text{-}P1) + P2 \times (1\text{-}P2)))/(P1 - P2)^2$; where n = sample size for each group, $Z1\text{-}\alpha/2 = 1.96$ when $\alpha = 5$ % , $Z1\text{-}\beta = 1.28$ when $\beta = 10\%$ (power = 90%), and P1 or 2 = probability of outcome 1 or 2. In this case, P1 was considered to be 0.54, and P2 0.2. This yielded an n of 38 in each group.

Statistical analyses were performed using SPSS (Version 19). Data were expressed as mean (SD) unless otherwise stated. A two-sided P value < 0.05 was considered significant.
Nonparametric variables were compared using the Mann-Whitney U tests. Proportions were compared using χ^2 tests.

The odds of nausea and vomiting according to group (lorazepam or placebo), taking account of covariates, were estimated using the generalized estimating equation (GEE), where the correlation between individual data is taken into account at different times, and where nausea and vomiting are considered ordinal variables.

Table II

Demographics characteristics

Parameter	Group 1 (n = 38)	Group 2 (n = 38)	P
Age. (Mean±SD), y	36.92 (9.24)	36.13 (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 (SD) or n (%).

Results

A total of 76 patients were approached for study inclusion and no one was excluded (Fig. 1). There were no statistically significant between-group differences in terms of patients' demographic and clinical characteristics (Table II).

The odds of nausea in the group 2 (control group) was 3.437 times the one of group 1 (lorazepam group) at time 6 (95 % CI 1.552-7.757), P = 0.003) and 4.391 at time 24 (95 % CI 1.489-12.931, P = 0.007), whereas there were no statistically significant between-group difference at time 0 (OR = 1.385, 95 % CI 0.575-3.333), P = 0.467). The odds of vomiting in group 2 was 3.954 times the one of group 1 at time 0 (95 % CI 1.293-12.087, P = 0.016) and 12.397 at time 6 (95 % CI 3.813 - 40.304, P < 0.001), whereas there were no statistically significant between-group differences at time 24 (OR = 7.114, 95 % CI 0.941-53.768, P = 0.057). The odds of antiemetic drug use in group 2 was 13.053 times the one of group 1 at time 0 (95 % CI 2.128-80.095, P = 0.006), but no between-group significant differences were found at time 6 and 24 (OR = 2.974, 95 % CI 0.338 - 26.154, P = 0.326).
The mean NVS score was 0.4 (0.2) in group 1 and 1.0 (0.2) in group 2 (P = 0.017).

Discussion

Our findings indicate that premedication with lorazepam is effective at preventing PONV following laparoscopic cholecystectomy. In this study, patient demographics, type of surgical procedure and administered anesthetic agents were similar between groups.

Numerous agents have been used to prevent PONV, at varying dosages and time intervals (4, 5). Several parameters have been studied to evaluate the effectiveness of these agents, such as nausea and vomiting scores for 4 hours in the early postoperative period or during the first 24 postoperative hours, the number of episodes and severity of vomiting, the number and amount of antiemetic medications used, the hospitalization length of stay, and the complications of nausea and vomiting (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 (14). 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 the skin flaps after abdominal, vascular, eye, or plastic surgery (8, 9).

The effect of intraperitoneal insufflations of carbon dioxide (CO_2) on residual stretching and irritation of the peritoneum, as well as duration of surgery are other factors that affect PONV after laparoscopic cholecystectomy (11, 14).

Benzodiazepines have been involved in the prevention and treatment of 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 dopamine (10). Whether benzodiazepines reduce dopamine release centrally, or by blocking the re-uptake of adenosine, causing an adenosine-mediated reduction of dopamine release, has been a matter of debate (10-14). Dopaminergic neuronal activity and 5-hydroxytryptamine release may also be reduced following the binding of midazolam to the GABA benzodiazepine complex. Anxiolysis may also contribute to the antiemetic effect of benzodiazepines (9, 12, and 14). However, Wang and Klein, in across-sectional study exploring a possible association between preoperative anxiety and PONV in a group of children undergoing out-patient surgery, did not find any predictive value of children's anxiety on 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 sedation, and provide anterograde amnesia, in addition to a probable intrinsic antiemetic effect (6).

In our study, the severity of nausea and vomiting was measured using the NVS score during the first 24 postoperative hours, as well as by counting and the number of patients with nausea, vomiting, or need for antiemetics. We determined that the administration of 1mg oral lorazepam 60 minutes before surgery was effective for the control of PONV during the first 6 postoperative hours. This may be related to the fact that the incidence of postoperative nausea and vomiting at that time was the highest.

Khalil et al. demonstrated that premedication with lorazepam was effective at preventing PONV following strabismus surgery (6). Our results are in line with Khalil et al's findings.

Of note, in our study, the incidence of PONV in females was higher than in males, but this difference was not significant. This is consistent with previous findings (4, 6).

In a meta-analysis by Awad et al. constructed from 14 RCT, the conclusion was that dexamethasone combined with other antiemetic agents provides stronger prophylaxis than a single antiemetic agent against PONV after laparoscopic cholecystectomy(5). Our recommendation for future trials would therefore be to assess the preventive effect of lorazepam combined with dexamethasone for preventing PONV.

Some limitations of our study should be acknowledged. First, our sample size was small, and this can have affected the results. This study also lacks a comparison with other methods of PONV prevention.

Conclusions

We conclude that premedication with lorazepam for the prevention of PONV following laparoscopic cholecystectomy may be effective.

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