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Comparison of parenteral promethazine versus midazolam effect as a preoperative medication on postoperative nausea and vomiting after appendectomy

Abstract

Background: Postoperative nausea and vomiting is a high unpleasant symptom in surgical procedures. This study compares the effectiveness of midazolam with promethazine as multipurpose drug in postoperative nausea and vomiting as a preoperative and anesthetic medication after appendectomy.

Methods: This randomized, double – blind clinical trial study was performed in patients who underwent appendectomy. These patients randomly received either placebo or midazolam or promethazine 5 minutes before appendectomy. All episodes of vomiting and nausea within 24 hours after surgery were recorded. The study population (N=75) comprised 3 comparable subgroups (N=25 in each group). A standard general anesthetic technique and postoperative analgesia were used. The data were collected and analyzed.

Results: Vomiting and nausea occurred in 19.20%, 0% and 81.80% of the patients in the midazolam, promethazine and placebo groups, respectively. The frequency of postoperative nausea and vomiting was as follows: the first 6 hours after surgery 0%, 0% and 50%, during the second 6 hours after surgery 19%, 0% and 19%, during the third 6 hours after surgery 0%, 0% and 7%, during the fourth 6 hours after surgery 0%, 0% and 4% in the midazolam, promethazine and placebo groups, respectively. There were no significant differences between promethazine with midazolam in reduction of postoperative nausea and vomiting.

Conclusion: Our study suggests that midazolam can be used as multipurpose drugs in postoperative nausea and vomiting as a preoperative medication after appendectomy and treatment using midazolam for anti-emetic, prophylaxis provide a similar effect compared to promethazine in the present study.

Key words: Midazolam, Postoperative nausea and vomiting, Promethazine.

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Postoperative nausea and vomiting (PONV) are common findings after surgery with a prevalence of 20-30%. It is the most common complaint after surgery and has undesirable side effects of anesthesia (1). It can increase the risk of re-hospitalization in outpatient and also increases cost, decreasing the consent of patients (2). The etiology of PONV is secondary to the different neurotransmitter pathways, including serotonergic, dopaminergic and cholinergic (3).

Nausea is an unpleasant feeling and vomiting explodes gastric contents through the mouth. After 1990s, studies comprised the use of anti-emetic medications for prophylaxis of PONV, aiming to decrease the side effects and hospital costs. Most of the presently used anti-emetics include butyrophenones, phenothiazines, dopamine receptor antagonists, anticholinergics, antihistamines, and benzodiazepines (4)..

Recently, several studies have found the anti-emetic properties of midazolam. Bauer et al. recorded that midazolam premedication reduces the frequency of PONV in patients undergoing outpatient surgery (5). Sanjay and Tauro suggested that midazolam can reduce vomiting undergoing cardiac surgery (6). Unlugenc et al. also demonstrated that midazolam used in sub- hypnotic dose was effective in PONV (7). Promethazine, the H1 antagonist has been used as a premedication of anesthesia and treatment of PONV (8, 9). It is estimated that midazolam can provide many advantages in preoperative period if we can demonstrate that midazolam can act as multipurpose drug for preoperative medication. The concomitant use of many drugs in operation can make more adverse drugs and more drug reactions.

Thus, this study was designed to compare the efficacy of parenteral midazolam with parenteral promethazine as multipurpose drug and anesthetic premedication on PONV after appendectomy.

Methods

This prospective, randomized, double – blind, placebo – controlled trial was performed after the institutional approval of the Ethics Committee and the written informed consent was obtained from each patient, and the data were collected. The Society of Anesthesiologists (ASA) physical status I of patients between 15 to 40 years old listed for elective appendectomy was studied.

The female patients were those who were younger than 15 years and older than 40 years, those who had systematic disease (diabetes), those who took any drugs prior to surgery, and those who had hemodynamic disturbance within surgery were excluded from the study due to the peculiarities of the incidence of PONV factors in these groups as reported in the literature. The patients were randomly allocated to receive one of the three regimens: group A (n=25) received 1 mg/kg promethazine intravenously, group B (n=25) received 0.05 mg/kg midazolam intravenously, group C (n=25) received placebo intravenously. The intravenous medications were coded and given 5 minutes prior to surgery. General anesthesia was then induced in all patients using thiopental 5 mg/kg, and Succinylcholine 1 mg/kg or Atracurium 0.5 mg/kg or Pancuronium 0.07 mg/kg administered for endotracheal intubation, and inhaled Halothane (0.5-1%) administered to maintain neuromuscular activity and depth of anesthesia during surgery, the patients were ventilated

with 50% N₂O/O₂. At the end of the operation, the muscle relaxation was reversed by intravenous administration of neostigmine 0.04 mg/kg and atropine 0.02 mg/kg. postoperative, Through the questionnaire referred to patients before their discharge from the ward, the absence or presence of all episodes of nausea and vomiting and the other side effects experienced by the patients during the first 24 hours (every 6 hours) after anesthesia were gathered and recorded by a trained investigator with no knowledge of which treatment the patients had received. The patients' data were analyzed using Chi-square test.

Before this study, the number of patients needed in each group was settled after power analysis 0.8 ($\beta= 0.2$, $\alpha= 0.05$) based on previous studies. The number of patients in each group was estimated as P₀= 40% in placebo group and P₁=0.05 in treatment group. A p-value less than 0.05 was considered statistically significant.

Results

The characteristics of the patients in the three treated groups are shown in table 1. The frequency of nausea and vomiting alone and nausea with vomiting during the first 24 hours after recovery from anesthesia was shown in table 2. Regarding the whole study period, the incidence of nausea and vomiting was almost similar in patients receiving midazolam and promethazine. No significant differences were found between midazolam compared to promethazine during the 6-12 hour, 12-18 hour and 18-24 hour observation periods, only during the 0-6 hour observation after surgery the differences between midazolam compared to promethazine in vomiting was seen. The incidence of PONV during different observatory periods (0-6 hour, 6-12 hour, 12-18 hour and 18-24 hour after surgery) are presented in table 2. There were no side effects in the first 24 hour after surgery in the three groups.

Table 1. Demographic data for the patients

| | Midazolam (n=25) | Promethazine (n=25) | Placebo (n=25) |
|--------------------------------|---------------------|------------------------|-------------------|
| Age; years | 23.1±4.4 | 27.3±5.3 | 23.5±5.8 |
| Sex; male; % | 100% | 100% | 100% |
| Weight; kg | 55±5.6 | 56±6.1 | 57±5.2 |
| Duration of anesthesia; min | 35±4.4 | 44±3.8 | 27±6.2 |

p<0.05

Table 2. Comparison of frequency distribution of PONV and side effects during the first 24 hours after appendectomy surgery

| | Midazolam (n=25) | Promethazine (n=25) | Placebo (n=25) |
|------------------------|---------------------|------------------------|-------------------|
| 0-6h PON | 0% | 0% | 50% |
| 0-6h POV | 19% | 0% | 19% |
| 6-12h PON | 0% | 0% | 38.4% |
| 6-12h POV | 0% | 0% | 7% |
| 12-18h PON | 0% | 0% | 23.10% |
| 12-18 h POV | 0% | 0% | 4% |
| 18-24h PON | 0% | 0% | 15.30% |
| 18-24 PON | 0% | 0% | 0% |
| During 24h PONV | 18.20% | 0% | 96.20% |
| Gastrointestinal | 0% | 0% | 0% |
| Respiratory | 3.81% | 0% | 0% |
| Central nervous system | 0% | 0% | 0% |
| Cardiovascular | 0% | 0% | 0% |

PONV; Postoperative nausea and vomiting; Hour; h; PON; Postoperative nausea; POV; Postoperative vomiting.

Discussion

Postoperative nausea and vomiting are complications under general anesthesia and a significant side effect of surgery (1, 2). Our results showed that preoperative intravenous administration of promethazine is effective for reducing postoperative nausea and vomiting in men having general anesthetics for operations on appendicitis. The result of this study exhibited that administration of midazolam 5 minutes before surgery was effective for reducing the incidence of postoperative nausea and vomiting after appendectomy. However, previous studies have shown that the promethazine apart from the histamine-receptor blocking effect also has dopaminergic, and cholinergic-receptor blocking effect on the receptors in the central trigger zone (CTZ), reducing nausea and vomiting and has a antiemetic effect. It significantly lowers the rate of postoperative nausea and vomiting in the first 24 hours after surgery compared with placebo (8, 10).

Several investigations have implied that midazolam has antiemetic properties (11). Splinter et al. noted that administration of midazolam 0.05 mg/kg after anesthesia has anti-vomiting properties similar to droperidol in children under strabismus surgery (12). Bauer et al. reported that the

administration of midazolam 0.04 mg/kg before operation is effective in decreasing the frequency of nausea and vomiting and increases the consent of patients (5). Recent study suggests that midazolam administered in sub-hypnotic dose was effective in treating nausea and vomiting without sedative effects (7).

In conclusion, our results suggest that both drugs have the same effect and better than placebo in postoperative nausea and vomiting. There were no significant differences between promethazine with midazolam in reduction of postoperative nausea and vomiting. The serious disadvantages were not noticed in our study compared with placebo. The concomitant use of many drugs in operation can make more adverse drug reactions and more drug interactions. Our study suggests that midazolam may be used as multipurpose drug in the treatment of postoperative nausea and vomiting as a preoperative medication after appendectomy.

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