

A Clinical Trial to Determine the Preventive Effective Dose of Promethazine on Postoperative Nausea and Vomiting after Laparoscopic Gastric Plication

Farhad Etezadi¹, Naser Ghasnejad Omrani¹, Mohammad Talebpour², Farsad Imani¹, Reza Shariat Moharari¹, Pejman Pourfakhr¹, Mohammad Reza Khajavi^{1*}

Background: Laparoscopic gastric plication (LGP) is a technique in the restrictive category of bariatric procedures that reduces the gastric volume. Nausea and vomiting are the most common complications after this procedure.

The goal of this research is to determine the preventive effective dose of promethazine on postoperative nausea and vomiting (PONV) after laparoscopic gastric plication

Methods: After induction of general anesthesia the patients were divided into two groups, the promethazine 50mg group, which was given promethazine 50mg IM plus dexamethasone 8mg IV and the promethazine 25mg group, which was given promethazine 25mg IM plus dexamethasone 4mg IV. The primary endpoints were the incidence and intensity of nausea and vomiting, and severity of abdominal pain score in postoperative periods.

Results: Sixty-four morbid obese patients were enrolled into the study. Promethazine 50mg group was found to significantly reduce the incidence of PONV in the first 12hrs compared with the other group, (21.87% vs 37.5%, $P=0/068$). At the same time the intensity of PONV in base of numeric rating scale was lower in promethazine 50mg group compared to another group (2.63 ± 0.85 vs 4.65 ± 1.23 , $P=0/089$). The mean severity of abdominal pain was higher in promethazine 25mg group, thus these patients needed more analgesia in comparison with another group.

Conclusion: In morbidly obese patients undergoing laparoscopic gastric plication, prophylactic administration of dexamethasone 8mg and promethazine 50mg was more effective in the first 12 hours after surgery in reducing the incidence of PONV, and severity of abdominal pain.

Keywords: laparoscopic gastric plication; nausea; vomiting; promethazine; dexamethasone; metoclopramide

Bariatric surgery is sometimes an effective method for weight loss in morbidly obese individuals, however, it is not without potential complications. Laparoscopic gastric plication (LGP) is a restrictive technique that reduces the gastric volume by plication of the greater curvature [1]. Postoperative nausea and vomiting (PONV) is the most common problem that disturbs patients in the immediate post operative hours [2]. The incidence of PONV according to technique of bariatric surgery and the size of gastric lumen that remains after surgery are different and may reach to 40% in some of the studies [3].

Traditionally, a combination of antiemetic drugs such as

metoclopramide, ondansetron and dexamethasone are used to manage PONV, but the incidence of PONV has not been reduced. Promethazine and dexamethasone are commonly used as an antiemetic drugs which act on the central nervous system and are very effective for the prevention of PONV [4-5]. In this prospective control clinical trial we try to determine which dose of promethazine 50mg or 25 mg is effective for prevention of nausea/vomiting after LGP.

Methods

After being approved by the Ethical Board Committee of Anaesthesiology Department of Tehran University of Medical Sciences (TUMS), this interventional, randomized clinical controlled trial, was conducted on 64 morbid obese patients candidates for LGP surgery. After explaining different aspects of the procedure, a written informed consent was obtained from all the participating patients. This trial was conducted in Sina Hospital affiliated with Tehran University of Medical Sciences.

Exclusion criteria were any contraindication to receiving dexamethasone, promethazine, uncontrolled hypertension and/or diabetes; and any patient that received any antiemetic drugs in the preoperative period.

From the ¹Department of Anesthesiology and Critical Care, Sina Hospital, Tehran University of Medical Sciences, Tehran, Iran.

²Department of Surgery, Sina Hospital, Tehran University of Medical Sciences, Tehran, Iran.

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*Corresponding author: Mohammad Reza Khajavi, MD. Department of Anesthesiology and Critical Care, Sina Hospital, Tehran University of Medical Sciences, Tehran, Iran. E-mail: khajavim@tums.ac.ir

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All surgeries were done by two general surgeons who had completed a fellowship in advanced laparoscopic surgery. The technique of LGP used, was based on the standard method in the last paper of the author [6].

All patients received general anesthesia; they were induced with propofol 1.5mg/kg, fentanyl 2µg/kg, midazolam 0.06 mg/kg, and atracurium 0.5mg/kg. For anesthesia maintenance a combination of isoflurane, fentanyl 1µg/kg/hr, and propofol was used. Propofol was the standard drug between two groups and these patients were morbid obese with BMI>40. In some situations we added less than one MAC isoflurane to decrease blood pressure during surgery.

After induction the patients were randomly allocated by using a computer-generated table into two following groups, the promethazine 50mg group, which was given promethazine 50mg IM plus dexamethasone 8mg IV and the promethazine 25mg group, which was given promethazine 25mg IM plus dexamethasone 4mg IV.

Prior to extubation all patients received propacetamol 1g IV. The study was double-blinded and the anesthesiologist responsible for the postoperative patient evaluations was not involved in drug administration. The evaluations were performed q12hrs for the first 48hr following the surgery.

The primary endpoints were the incidence of nausea and vomiting, in postoperative periods. The intensity of nausea and vomiting score was evaluated as a scale comparable to a numeric rating scale (NRS).

Abdominal pain was evaluated at the same time by using a visual analogue scale (VAS) (0 = no pain and 10 = worst possible pain). Postoperative pain score and the total analgesic requirement for the first 48 hours were recorded. Meperidine 50 mg IV was used as rescue analgesia in both groups when pain score exceeded 3. In patients in whom nausea and vomiting wasn't tolerable ondansetron 4mg IV was used as rescue treatment.

The sample size was determined prospectively with 30 patients in each group. In regards to high incidence of PONV after laparoscopic gastric plication, a 50% reduction in the incidence of PONV at any time within the first 48hrs of treatment could be determined with a statistical power of 80% ($\beta=0.85$).

Statistical analysis was performed using SPSS version 14. Student's t-test was used to compare the continuous variables between the groups. Repeated measure test (General Linear Model), Fisher's exact test, and chi-2 were used to compare the incidence and the severity of nausea, vomiting, and pain at multiple time points. A P-value < 0.05 was considered statistically significant. Data are presented as mean [standard deviation (SD)], numbers, or percentages.

Results

Sixty four morbid obese patients were enrolled in this study from May 1, 2015 to 30 October 2016 with similar demographic characteristics in both groups (Table 1). The incidence of ponv in first 12 hour after operation in patients that took promethazine 50mg was lower than the other group, 21.87% vs 37.5% (P=0/068). At the same time the intensity of ponv in base of numeric rating scale was lower in promethazine 50mg group in compare to other group 2.63±0.85 vs 4.65± 1.23 (P=0/089). The incidenc and severity of ponv was similar and reduced in the next following times after operation in both groups. The mean

severity of abdominal pain was higher in promethazine 25mg group, thus these patients needed more analgesia in comparison with the other group.

Table 1- Patient's characteristic between two groups

Variable	Promethazine 50mg (n=34)	Promethazine 25mg (n=34)	p-value
Age (years)	32.41±12.05	30.58±13.37	0.4
Male/Female	20/12	22/10	0.1
BMI (kg/m ²)	40.87±3.38	40.67±3.68	0.3
FBS (mg/dl)	100.23±19.54	102.05±21.91	0.1
Triglyceride (mg/dl)	187.38±39.59	197.95±58.85	0.2
Cholesterol (mg/dl)	201.51±38.84	229.20±50.82	0.01
Mean severity of pain (vas)	3.23±0.45	4.85±1.67	0.06
Total pethidine Use (mg)	32.1±2.6	68.5±4.6	0.00

MAP=mean arterial pressure BMI=body mass index

Discussion

This study shows that from recovery to 12 hr following surgery the combination of dexamethasone 8mg and promethazine 50mg achieved a greater total response rate than dexamethasone 4mg and promethazine 25mg. During this period the incidence and severity of nausea and vomiting in the combination dexamethasone 8mg and promethazine 50mg group was lower than the other group.

Laparoscopic gastric plication as a surgical restrictive therapy for treatment of morbid obesity has been shown to have acceptable results since its application 12 years ago [6]. One of the most common problems with this operation is PONV. LGP, like other gastric restrictive therapies, induces increased intra gastric pressure. The degree of plication and the rate of increased intra gastric pressure is higher in patients who undergo LGP, in comparison to patients who underwent other gastric restriction procedures (such as sleeve gastrectomy) [6]. The feeling of postoperative gastric fullness is a potential etiology for nausea in LGP cases, which would be corrected after patient adaptation to the reduced stomach volume [7]. The mechanism for nausea after LGP is that the vagal input from the plicated stomach can activate the emetic center of the brainstem and can also activate afferent action from the chemoreceptor trigger zone (CTZ).

The patients in this study have multiple risk factors that can increase the incidence of PONV, such as female gender, younger age, general anesthesia with volatile anesthetics, and gastric surgery. These risk factors were similar between the two study groups and therefore do not affect the results significantly.

Promethazine is a centrally acting drug with antihistamine and anticholinergic properties that are effective for the prevention of PONV [8]. It also helps reduce nervousness, restlessness, and agitation, all of which are common after any surgery. Co-administration of promethazine with opioids or codeine increase subjective happiness in patients [9]. Deep IM injections of promethazine have a 4-6hr effect and have been shown to be safe in most patients. In this study the anticholinergic effect of promethazine is the likely

etiology that reduced the gastric irritability and frequency of PONV. In some current guidelines promethazine, in combination with other antiemetics, was found to be more effective in reducing PONV, severity of nausea, and pain than promethazine monotherapy [10]. A combination prophylactic therapy of PONV with promethazine and other drugs has been published by some authors [11-12].

Dexamethasone is a well documented anti-inflammatory drug which is also centrally acting [13]. It is absorbed rapidly following IM injection and reaches maximum plasma concentration at 1 hour, with a half-life about 190 minutes. It also potentiates euphoric effects of opioids and reduces the postoperative pain intensity, nausea, vomiting and need for rescue analgesia as compared to placebo [14-16].

In our previous study administration of promethazine 50mg /dexamethasone 8mg during the postoperative period significantly controlled ponv after surgery [17].

In a study by Benevides et al combination of dexamethasone with haloperidol and ondansetron reduced PONV, the necessity of rescue antiemetics and opioid consumption after Laparoscopic Sleeve Gastrectomy [18].

Conclusion

To conclude, in patients undergoing LGP, prophylactic administration of dexamethasone 8mg and promethazine 50mg was more effective in the first 12 hours after surgery in reducing the incidence of PONV, and severity of abdominal pain.

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