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CLINICAL TRIAL REPORT

Promethazine Combined with Metoclopramide for the Prevention of Postoperative Nausea and Vomiting in Patients Undergoing Laparoscopic Colorectal Cancer Surgery: A Randomized Controlled Trial

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Purpose: Postoperative nausea and vomiting (PONV) are undesirable postoperative problems in patients undergoing surgery. However, there is currently no satisfactory solution to this problem.

Patients and Methods: This prospective, single-center, randomized, double-blind, pilot study was conducted at Gansu Provincial Hospital in China. Patients aged 18–65 years who underwent elective colorectal tumor resection were randomly assigned to receive 6.25 mg promethazine or 1 mL saline intravenously before induction of anesthesia. All patients then received postoperative patient-controlled intravenous analgesia and a continuous metoclopramide infusion at 50 mg. The primary endpoint was the incidence and severity of PONV at 6 h, 24 h, 48 h, and 72 h postoperatively.

Results: Between June 2021 and March 2022, 96 eligible patients were included in the final analysis, with 48 patients in the promethazine group and 46 in the saline group. The incidence and severity of nausea during the early period (the first 6 hours postoperatively) were significantly different between groups ($P = 0.031$ and $P = 0.036$). A statistically significant difference was found in the incidence and severity within 24 hours postoperatively ($P = 0.023$ and $P = 0.020$). The incidence and severity of vomiting were significantly different between groups at 6 h postoperatively ($P = 0.043$ and $P = 0.048$). Vomiting incidence and severity were statistically different during the 24 hours postoperatively ($P = 0.012$ and $P = 0.046$). A significant statistical difference was found in the satisfaction between the two groups during the postoperative observation period ($P = 0.004$).

Conclusion: Preoperative prophylactic promethazine significantly reduced the incidence and severity of PONV within 24 hours postoperatively, with few adverse effects and no serious adverse reactions. Additionally, patient satisfaction was also improved.

Keywords: promethazine, colorectal tumor, laparoscopic surgery, nausea, vomiting

Introduction

Laparoscopic surgery has the advantages of a low postoperative infection rate, a short hospital stay, and less trauma, and is therefore becoming increasingly popular in abdominal surgery. However, in laparoscopic surgery, insufficiency of gastrointestinal perfusion caused by pneumoperitoneum may damage gastrointestinal function and promote the occurrence of postoperative nausea and vomiting (PONV). PONV refers to the discomfort symptoms that occur within 24 hours after operation, with nausea and vomiting constantly occurring at the same time, but isolated nausea or infrequent vomiting without accompanying nausea may also occur.[1] PONV is one of the most common complications,[2] ranking second only to postoperative pain, and has a high incidence in the perioperative period: about 30% for general surgery,[3] 40%-80% for laparoscopic surgery,[4] and as high as 80% in

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the high-risk population who has not received prevention,[3] which seriously hampers patients' postoperative recovery. PONV not only results in unpleasant psychological feelings for patients, but also triggers a series of physiological changes, such as incision dehiscence, dehydration, anxiety, acid-base imbalance, electrolyte disorder, and other severe complications (including esophageal tear, hernia, respiratory pneumonia, pneumothorax, etc)., which may lead to prolonged stay in the anesthesia recovery room or hospitalization, readmission and increased medical burden of patients.[5] Although PONV is common after operation, it is not inevitable At present, the Apfel simplified scoring system is widely used to predict PONV,[6] which is based on four independent risk predictors, namely, female, non-smoking, a history of motion sickness or PONV, and postoperative opioid use. The longer the duration of surgery, the higher the incidence of PONV. Prolonging surgery by 30 minutes may increase the risk of PONV by 60%.[7] The types of surgery such as cholecystectomy, gynecological surgery, and laparoscopic surgery are associated with the high incidence of PONV.[8] According to the Apfel simplified scoring system, a multimodal approach to the prevention and treatment of PONV has been proposed. For patients with moderate to high risk, drugs from different categories and with different mechanisms of action should be used in combination. For patients with a high risk of PONV, a multimodal approach combining pharmacological and non-pharmacological prophylaxis with interventions to reduce baseline risk should be adopted.[9,10] However, a study showed that 8% of patients with high risk of PONV did not receive any antiemetic prevention at all, and they still frequently experienced PONV.[11]

At present, the treatment of PONV still focuses on drug therapy, mainly including histamine blockers (promethazine, chlorpheniramine, etc)., 5-HT3 receptor antagonists (ondansetron, dolostone, granisetron, tropisetron, ramosetron and palonosetron, etc)., neurokinin −1 (NK-1) receptor antagonists (aripitan, etc.) and corticosteroids.[12] The combination of multiple drugs for prevention and treatment can reduce the incidence of PONV; however, even with the combined use of antiemetic agents, the incidence of PONV among high-risk patients is still higher than 20%. Effective management of PONV is an important component of postoperative recovery, especially for abdominal colorectal surgery, and therefore, more effective prophylactic regimens are needed for PONV.

Promethazine, a histamine receptor blocker, is a time-tested antiemetic agent that primarily exerts its anti-nausea and vomiting effects through dopamine receptor antagonism, as well as with moderate histaminergic and anticholinergic activities.[13,14] Metoclopramide, a dopamine receptor blocker, is one of the preferred drugs for anesthesiologists in treating PONV.[15] Metoclopramide acts mainly by antagonizing central and peripheral dopamine-two receptors (D2), decreasing the sensitivity of visceral afferent nerves, and thereby exerting anti-nausea and vomiting effects.[16] Although these two agents have been widely used in clinical practice, the effect of their combination has not been reported yet.

Therefore, we designed a randomized controlled trial to assess the effect of promethazine as a prophylactic intervention prior to the induction of anesthesia, in combination with postoperative continuous infusion of metoclopramide, on the prevention and treatment of PONV in patients with colorectal cancer.

Methods

Study Design and Patients

This prospective, single-center, randomized, double-blind, pilot study was done at Gansu Provincial Hospital in China (ChiCTR2100054495), and was approved by the ethics committee of Gansu Provincial Hospital. The study was conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice Guideline. All patients provided written informed consent before enrollment.

Patients were eligible if they were 18–65 years old; had colorectal cancer and underwent general anesthesia in the elective colorectal tumor resection; had a body mass index (BMI) of 15–30 kg/m^2; had an American Society of Anesthesiologists (ASA) physical status of I–II; understood and signed the informed consent form; and cooperated with the interventions and evaluations. The operation time was 1–4 hours, and the postoperative hospital stays were more than 72 hours. Exclusion criteria included asthma, mechanical intestinal obstruction, angle-closure glaucoma, a confirmed/suspected history of alcohol, opioid, or other drug abuse within the first three months of the study, preoperative coma, mental disorders, cardiovascular diseases, hepatic or renal insufficiency, prolonged ST segment on preoperative electrocardiogram, postoperative admission to intensive care unit (ICU), allergy to promethazine, and a history of chemotherapy within four weeks before surgery, and participation in other clinical studies. During the

study, patients who were unable or unwilling to continue treatment due to serious adverse events, discontinuation of an analgesic pump, any reason unrelated to the study, conversion to laparotomy during surgery, and mistaken inclusion were also excluded.

Randomization, Masking and Procedures

Eligible patients were assigned randomly in a 1:1 ratio to receive promethazine 6.25 mg or saline 1 mL intravenously before the induction of anesthesia by SPSS 25.0. Following surgery, all patients received a continuous infusion of PCIA (Patient Controlled Intravenous Analgesia), with a formulation of sufentanil 1.5μg/kg, flurbiprofen 200 mg, metoclopramide 50 mg, dexmedetomidine 1 μg/kg, and 0.9% normal saline 150 mL. The pump was configured with an initial bolus dose of 2 mL, a continuous basal infusion rate of 2 mL/h, a self-controlled bolus dose of 2 mL and a lockout interval of 15 min. Patients, anesthesiologists, and assessors were masked to treatment assignment.

Both groups were anaesthetized using the uniform standard method. Upon admission to the operating room, patients were monitored using routine electrocardiogram, non-invasive blood pressure, heart rate (HR), oxygen saturation, and bispectral index (BIS). Anaesthesia was induced with intravenous administration of flurbiprofen ester 50 mg, midazolam 0.05 mg/kg, sufentanil 0.4–0.6 ug/kg, etomidate 0.15–0.3 mg/kg, and rocuronium 0.6 mg/kg. After the induction of anaesthesia, radial artery puncture was performed, and invasive arterial blood pressure was monitored. Central venous pressure was monitored via the right internal jugular vein. Both groups were administered additional sufentanil 0.5 μg/kg before excision to maintain a BIS of 40–60 and to maintain blood pressure fluctuations of no more than 20% of the basal value, and vasoactive drugs could be administered if necessary. Atropine 0.5 mg was administered if the HR was lower than 50 beats/min, and phenylephrine 50–100 μg was administered if the blood pressure dropped by more than 20% of the basal value.

After surgery, patients were admitted to PACU (Post-anesthetic care unit) with an endotracheal tube. The Ramsay score was used to evaluate the depth of sedation and agitation during PACU admission. The extubation time and duration of PACU stay were recorded. PONV was monitored, with the frequency and severity of nausea and vomiting recorded at 6, 24, 48, and 72 hours postoperatively. Nausea severity was assessed using a 5-point numerical rating scale (NRS: 1 = none, 2 = mild, 3 = moderate, 4 = severe, 5 = refractory),[17] and vomiting was assessed using a vomiting scale (0 = no vomiting, 1–2 times/day = mild vomiting, 3–5 times/day = moderate vomiting, ≥6 times = severe vomiting).[17] Patients who required remedial antiemesis with dexamethasone were recorded, and decisions regarding additional nausea and vomiting management after 72 hours were left to the clinical judgment of the clinicians. Pain intensity at 24 hours postoperatively was assessed using a visual analogue scale (0 being no pain and 10 being intolerable pain).

Promethazine-related adverse effects, such as drowsiness, coma, or extrapyramidal reactions, were recorded in detail. Patient satisfaction with the PONV management was evaluated 72 hours postoperatively using a 4-point rating scale (1 = poor, 2 = fair, 3 =good, 4 = excellent). After surgery, in cases of severe nausea and vomiting, patients received an intravenous injection of dexamethasone 8 mg as the initial rescue drug for PONV. The choice of subsequent antiemetic agents was determined at the discretion of the attending clinician.

Outcomes

The incidence and severity of PONV were observed at 6, 12, 24, 48 and 72 hours after surgery. A complete response to promethazine was defined as the absence of PONV without the need for postoperative remedial antiemetic intervention. The extubation time, duration of stay in the post-anesthesia care unit (PACU), intraoperative fluid volume, Visual Analog Scale (VAS) analgesic score, effective pressing times of postoperative patient controlled intravenous analgesia (PCIA) pump, time to first press, time to first deflation, time to first getting out of bed, number of remedial antiemetic administration, and adverse effects (eg, sedation, dizziness, lethargy, extrapyramidal reaction, etc) were recorded. Patient satisfaction was also investigated.

Statistical Analysis

Based on our pre-trial results, the PASS 15 software was adopted for sample size calculation. With the β value of 0.2 and the α value of 0.05, 27 patients were needed per group. Considering the dropout rate, 46 patients in the saline group and 48 patients in the promethazine group were finally included in the study.

In this study, SPSS (Statistical Package for the Social Sciences) 25.0 software was used for statistical analysis of all data. The measurement data included age, BMI, operation time, in-and-out volume, PCIA first compression time and effective compression times, VAS score, first exhaust time, first time out of bed activity time. Normal distribution test was performed, and the measurement data that conformed to the normal distribution was expressed as x±s, and two independent samples were used for comparison between the two groups. *T*-test was used for the data that did not conform to the homogeneity of variance, and the counting data included gender and PONV incidence, and X^2-test or Fisher exact probability method was used. The grade data included the severity of nausea and vomiting, and the nonparametric test (Mann–Whitney *U*-test) was used. All the results were statistically significant with $P < 0.05$.

Results

Between June 2021 and March 2022, 120 patients were screened for eligibility, of which 10 did not meet the inclusion criteria, and four patients refused to participate in the study. Of the 106 eligible patients who were randomly assigned, nine patients (six in the promethazine group vs three in the saline group) required postoperative nerve block analgesia, and three patients (two in the promethazine group vs one in the saline group) discontinued the use of PCIA. Finally, 48 patients in the promethazine group and 46 patients in the saline group were included in the analysis (Figure 1). Baseline characteristics of patients were generally balanced between the promethazine and saline groups, including age, gender, BMI, operation duration, intraoperative volume, Apfel score, ASA grade and operation type (Table 1).

Incidence and Severity of PONV

In the promethazine group, only two patients (4.2%) had nausea within 6 hours after surgery, compared to eight patients (17.4%) in the saline group, with a significant difference between the two groups (P=0.031). Seven patients (14.6%) and

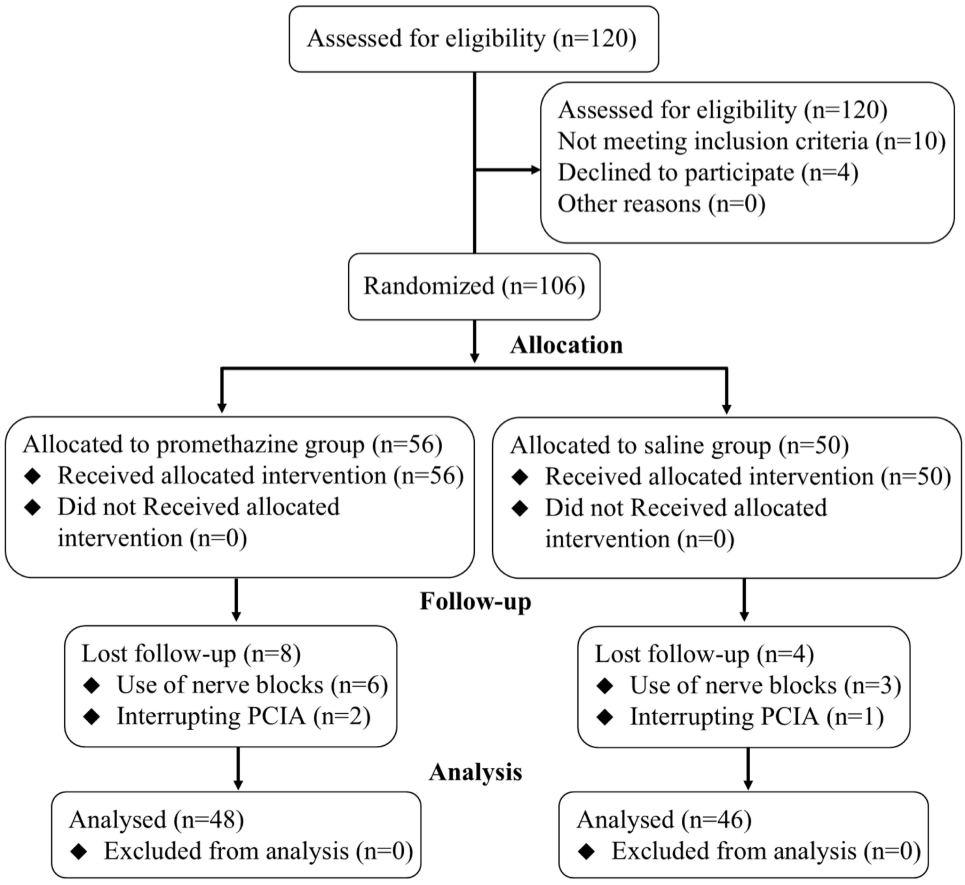

Figure 1 Trial Profile.

Table 1 Patient Characteristics

	Promethazine Group (n = 48)	Saline Group (n = 46)	*P*-value
Age, years	58.04±6.53	56.52±7.99	0.314
Gender			0.065
Female	18 (37.5%)	26 (56.5%)	
Male	30 (62.5%)	20 (43.5%)	
Body mass index, kg/m^2	22.92±3.32	22.95±2.89	0.959
Operation duration, minutes	263.15±65.0	247.41±60.46	0.228
Intraoperative access, mL	1161.04±392.35	999.78±449.0	0.067
Apfel score			0.602
1	7 (14.6%)	10 (21.7%)	
2	20 (41.7%)	11 (23.9%)	
3	15 (31.3%)	16 (34.8%)	
4	6 (12.5%)	9 (19.6%)	
ASA classification			0.69
I	22 (45.8%)	22 (47.8%)	
II	26 (54.2%)	24 (52.2%)	
Type of surgery			0.701
Laparoscopic abdominoperineal rectomy	4 (8.3%)	8 (17.4%)	
Laparoscopic right hemicolectomy	5 (10.4%)	4 (8.7%)	
Laparoscopic partial colectomy	7 (14.6%)	4 (8.7%)	
Laparoscopic mesolectal excision	6 (12.5%)	3 (6.5%)	
Laparoscopic radical resection of rectal cancer	13 (27.1%)	11 (23.9%)	
Laparoscopic anterior rectal excision	9 (18.8%)	12 (26.1%)	
Laparoscopic sigmoidectomy	4 (8.3%)	4 (8.7%)	

Note: Data are n (%) or mean±standard deviation.
Abbreviation: ASA, American Society of Anesthesiologists.

three patients (6.3%) patients in the promethazine group experienced nausea within 24 and 48 hours after surgery, respectively; while in the saline group, the patient numbers were 16 (34.8%) and 11 (23.9%), respectively. The difference was statistically significant between the two groups (P=0.023 for 24 hours, and P=0.0016 for 48 hours). Within 72 hours after surgery, three patients (6.3%) patients in the promethazine group and five patients (10.9%) in the saline group developed nausea, with no statistical difference observed (P=0.422).

In terms of nausea severity, there was one patient with mild nausea and one with severe nausea in the promethazine group within 6 hours after surgery; while in the saline group, one patient had mild nausea, one had moderate nausea, and six had severe nausea, with a significant difference in severity between the two groups (P=0.036). Within 24 hours after surgery, there were three patients with mild nausea, one with moderate nausea, and three with severe nausea; while in the saline group, there were five patients with severe nausea, five with moderate nausea, and six with mild nausea, with a significant difference in severity between the two groups (P=0.016). Within 48 hours after surgery, two patients with mild nausea and one with moderate nausea were reported in the promethazine group, compared to seven with mild nausea, three with moderate nausea, and one with severe nausea in the saline group, also with a significant difference (P=0.017). Within 72 hours after surgery, three patients experienced mild nausea in the promethazine group, while three and two patients in the saline group had mild and moderate nausea, respectively, with no significant difference observed in severity (P=0.398).

The incidence of vomiting within 6 hours after surgery was 2.1% (1 out of 48) in the promethazine group compared to 13% (6 out of 46) in the saline group, with a significant difference (P=0.043). Similarly, within 24 hours after surgery, the incidence rates were 2.1% (1 out of 48) in the promethazine group and 17.4% (8 of 46) in the saline group, and this difference was also significant (P=0.012). In contrast, no statistically significant differences in the incidence of vomiting

were observed between the two groups within 48 and 72 hours after surgery, with 0% in the promethazine group versus 6.5% (3 out of 46) in the saline group within 48 hours (P=0.072), and 0% in both groups within 72 hours (P=1).

In the promethazine group, one patient experienced severe vomiting within 6 hours after surgery; while in the saline group, one patient with mild, moderate, and severe vomiting were reported in one, three, and two patients, respectively. The difference in severity between the two groups was significant (P=0.048). Within 24 hours after surgery, one each patient suffered from moderate and severe vomiting in the promethazine group, compared with four, three, and one patients in the saline group experiencing respective mild, moderate and severe vomiting, with a significant difference in severity between the two groups (P=0.046). No patients in the promethazine group experienced vomiting within 48 and 72 hours after surgery, and three patients in the saline group had mild vomiting within 48 hours while no vomiting occurred within 72 hours, both with no significant difference in severity between the two groups (P=0.074 for 48 hours and P=1 for 72 hours, respectively; Table 2 and Figure 2).

Post-Anesthesia Care Unit Situation

There were no statistically significant differences observed between the two groups in terms of time to extubation, duration of stay in the PACU, and Ramsay sedation scores (Table 3).

Postoperative Ward Situation

Within three days after the patients were admitted to the ward, no statistical differences were observed between the two groups regarding time to first getting out of bed, time to first deflation, VAS pain score at rest or during exercise, incidence of postoperative adverse effects, length of stay, and the use of remedial antiemetics. A statistically significant difference was noted in postoperative patient satisfaction between the two groups (p=0.004; Table 4).

Table 2 The Incidence and Severity of PONV

	Promethazine Group (n = 48)	Saline Group (n = 46)	Risk Difference,% (95% CI)	*P*-value
Incidence of nausea				
6h after surgery	2 (4.2%)	8 (17.4%)	−13.2% (−0.26, −0.01)	0.031
24h after surgery	7 (14.6%)	16 (34.8%)	−20.2% (−0.37, −0.03)	0.023
48h after surgery	3 (6.3%)	11 (23.9%)	−17.7% (−0.32, −0.04)	0.016
72h after surgery	3 (6.3%)	5 (10.9%)	−4.6% (−0.16, 0.07)	0.422
Overall	14.6%	37.0%	−22.4% (−0.40, −0.05)	0.013
Severity of nausea (none/mild/moderate/severe/intractable)				
6h after surgery	46/1/0/1/0	38/1/1/6/0		0.036
24h after surgery	41/3/1/3/0	30/6/5/5/0		0.02
48h after surgery	45/2/1/0/0	35/7/3/1/0		0.017
72h after surgery	45/3/0/0/0	41/3/2/0/0		0.398
Incidence of vomiting				
6h after surgery	1 (2.1%)	6 (13.0%)	−11.0% (−0.22, 0.00)	0.043
24h after surgery	1 (2.1%)	8 (17.4%)	−15.3% (−0.27, 0.04)	0.012
48h after surgery	0 (0%)	3 (6.5%)	−6.5% (−0.14, 0.01)	0.072
72h after surgery	0 (0%)	0 (0%)	0% (0.00, 0.00)	1
Overall	6.3%	21.7%	−15.4% (−0.29, −0.02)	0.03
Severity of vomiting (none/mild/moderate/severe/intractable)				
6h after surgery	47/0/0/1/0	40/1/3/2/0		0.048
24h after surgery	46/0/1/1/0	38/4/3/1/0		0.046
48h after surgery	48/0/0/0/0	43/3/0/0/0		0.074
72h after surgery	48/0/0/0/0	46/0/0/0/0		1

Note: Data are n (%), %, n or % (95% CI).
Abbreviations: CI, confidence interval; PACU, post-anesthesia care unit; PONV, postoperative nausea and vomiting.

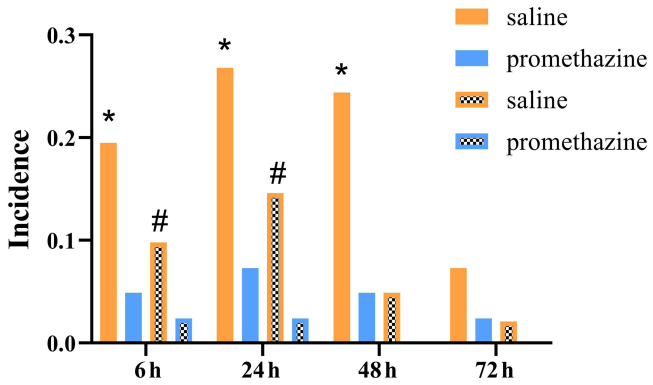

Figure 2 Incidence of PONV 72 h after surgery between two groups. * and # indicate a statistical difference between the two groups ($P < 0.05$).

Opioid Consumption

There were no statistical differences observed in the consumption of sufentanil and remifentanil between the two groups during surgery (P=0.305 and P=0.228, respectively). Similarly, no statistical difference was noted in the use of postoperative PCIA, including time to first press and the effective press times (P=0.138 and P=0.492, respectively; Table 5).

Discussion

This prospective, randomized controlled study showed that preoperative prophylactic intravenous administration of 6.25 mg promethazine significantly reduced the incidence and severity of PONV in patients with laparoscopic colorectal cancer within 48 hours after surgery.

Table 3 Post-Anesthesia Care Unit Situation

	Promethazine Group (n = 48)	Saline Group (n = 46)	*P*-value
Time-to-extubation, minutes	33.83±22.96	28.04±28.98	0.276
Duration of stay in the PACU, minutes	91.52±27.19	83.52±33.72	0.208
Ramsay scores	2.06±0.25	2.04±0.21	0.685

Note: Data are mean±standard deviation.
Abbreviation: PACU, post-anesthesia care unit.

Table 4 Postoperative Ward Situation

	Promethazine Group (n = 48)	Saline Group (n = 46)	*P*-value
Time to first getting out of bed, days	1.58±0.49	1.60±0.54	0.813
Time to first deflation, days	2.06±0.43	1.29±0.46	0.503
VAS score			
Rest pain	0.48±0.85	0.43±0.69	0.782
Motion pain	1.65±1.12	1.37±0.68	0.154
Patient satisfaction			
Poor / OK / Excellent / Satisfactory	0/2/2/44	1/10/1/34	0.004
Adverse effects	2 (4.2%)	1 (2.2%)	0.538
Length of stay, days	16.67±6.84	15.87±7.55	0.593
Remedial antiemetic administration	2 (4.2%)	2 (4.3%)	0.965

Note: Data are mean±standard deviation, n (%), or n.
Abbreviation: VAS, Visual Analog Scale.

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Table 5 Opioid Consumption

	Promethazine Group (n = 48)	Saline Group (n = 46)	*P*-value
PCIA effective press times	0.91±2.60	0.33±0.60	0.138
Time to PCIA first press	1.38±2.64	1.91±4.69	0.492
Intraoperative sufentanil, μg	39.69±2.80	38.91±4.33	0.305
Intraoperative remifentanil, μg	1615.73±325.04	1537.07±302.31	0.228

Note: Data are mean±standard deviation.
Abbreviation: PCIA, patient controlled intravenous analgesia.

Histamine is an important neurotransmitter in vomiting center. Promethazine emesis is associated with antihistamine, inhibition of emetic chemoreceptor in medulla oblongata, anti-dopamine and moderate anticholinergic effects.[13] Promethazine is one of the drugs recommended in the latest guidelines for the management of nausea and vomiting. Following intravenous administration, promethazine demonstrates a rapid onset of action, typically within 3–5 minutes, and antihistamine effects generally last for 6–12 hours, as well as the sedative effects persist for 2–8 hours.[18] Studies have shown that promethazine-related adverse effects are associated with its intravenous injection speed.[19] In this study, we injected promethazine slowly before the induction of anesthesia to reduce the occurrence of adverse effects. The etiology of PONV in laparoscopic colorectal surgery is still unclear, and may be related to pneumoperitoneum, long-term intestinal perfusion during surgery, which affects the recovery of postoperative intestinal function of patients, and the use of gas anesthetics and opioids during surgery.[20] In this study, both surgical and anesthetic factors involved were controlled, as all patients underwent laparoscopic surgery, and the surgical procedures and anesthesia methods were standardized. As predicted, the operation time, anesthesia time and anesthetic usage were similar between the two groups. Therefore, any observed differences could be attributed to the drugs studied.

Studies have shown that volatile anesthetics are an important contributor to the early onset of PONV within 6 hours after surgery.[21] In our study, both groups were anesthetized with sevoflurane. Within 6 hours after surgery, the incidence of PONV in the promethazine group was only 4.2%, while previous studies showed that the incidence of PONV in laparoscopic surgery was approximately 40%.[22] At present, studies on multimodal strategies for the prevention of PONV following laparoscopic surgery have focused on gynecologic procedures and gastrectomy;[23–25] however, little attention has been paid to the prevention of PONV after laparoscopic colorectal surgery. Talebpour et al[26] compared the effects of intramuscular injection of promethazine 50 mg plus dexamethasone and gastrine combined with dexamethasone 12 hours before surgery in the prevention and treatment of PONV after laparoscopic gastric sleeve resection, and found that the incidence of PONV in the promethazine group was 41% within 24 hours after surgery. Huang et al reported that in patients undergoing laparoscopic gastrointestinal surgery, the addition of fosaprepitant to dexamethasone and palonosetron during the first 24 postoperative hours resulted in the incidences of nausea and vomiting of 32.2% and 13.0%, respectively.[27] These findings appeared to be unsatisfactory. In our study, we explored an innovative strategy for the prevention and treatment of PONV through the intravenous injection of promethazine before the induction anesthesia and the continuous postoperative pump injection of metoclopramide. As a result, this regimen effectively reduced the incidences of nausea and vomiting within 24 hours after surgery to 14.6% and 2.1%, respectively, with a marked decrease in symptom severity. Furthermore, the incidence of PONV in the promethazine group within 48 hours after surgery was also lower than that in the saline group. These promising findings suggests that this novel strategy may be feasible for the early prevention of postoperative PONV.

Studies have shown that the occurrence of PONV may persist for up to 72 hours after surgery.[28] In our study, we observed a notably low incidence of nausea in the promethazine group among the two groups of patients who did not experience postoperative vomiting within 72 hours. First of all, the administration of preoperative preventive medicine resulted in a reduction of the incidence of PONV at an early stage. Secondly, both groups of patients received continuous treatment after surgery. In addition, each patient was treated with postoperative analgesia using PCIA, and the reduction in pain intensity could also alleviate the occurrence of PONV. Finally, PONV mainly occurs within 24 hours after surgery, suggesting the early management of PONV is associated with a reduced incidence of postoperative PONV after 24 hours.

In recent years, there have been few reports on the use of promethazine for the prevention of PONV. According to previous studies, promethazine-related adverse effects are the main reason for limiting its clinical application.[29] Promethazine has a wide range of anti-nausea and anti-vomiting mechanisms, demonstrating remarkable effects. According to the prescribing information of promethazine, the minimum dose is 12.5 mg for antiemetic purposes. Notably, studies have shown that there is no difference in anti-nausea and anti-vomiting effects between promethazine 6.25 mg and 12.5 mg, and the former is associated with fewer adverse effects. Considering that the sedative effect of promethazine lasts for 2–8 hours, we chose a prophylactic intravenous injection of a reduced 6.25 mg dose before surgery to avoid the adverse effects of postoperative sedation. This dosage also aligns with the latest guideline that endorse 6.25 mg as an effective dose of promethazine.[12] We observed the situation of all patients in the PACU, and there was no difference between the two groups in terms of sedation scores, time to endotracheal tube removal and duration stay in the PACU. We also analyzed the consumption of opioids in both groups, revealing no significant differences, thereby ruling out the influence of opioids on postoperative sedation. During the 72-hour postoperative period, two patients in the promethazine group had dizziness. Upon inquiry, one of them may have experienced dizziness due to prolonged water fasting, and the dizziness symptoms in both patients appeared after 12 hours after operation. This result could not be attributed to promethazine. On the other hand, promethazine has been included in National Basic Medical Insurance in China, substantially decreasing the associated treatment cost. Therefore, a single intravenous injection of promethazine before the induction of anesthesia may represent a cost-effective and safe alternative for the prevention of PONV. Nonetheless, future studies comparing the cost-effectiveness of promethazine with other antiemetic agents are warranted to further validate the advantages of this novel regimen.

Metoclopramide is a dopamine D2 receptor inhibitor, which acts on dopamine receptors in the medulla oblongata chemoreceptor trigger zone (CTZ) and chemoreceptors in the peripheral organs of the gastrointestinal tract.[30] This mechanism confers on metoclopramide unique advantage in the prevention and treatment of PONV in patients undergoing laparoscopic colorectal tumor surgery. Our previous research showed that metoclopramide 50 mg combined with PCIA after surgery was superior to tropisetron in reducing the occurrence of PONV and enhancing the recovery of gastrointestinal function in patients with colorectal cancer. In this study, no statistically significant differences were observed between the two groups in terms of time to first getting out of bed and time to first deflation, indicating that promethazine had no adverse effect on the recovery of gastrointestinal function.

Current studies have shown that the therapeutic mechanism of postoperative remedial antiemetic treatment should differ from that of prophylactic drugs. Therefore, we chose an intravenous injection of dexamethasone 8 mg as a remedial antiemetic agent,[30,31] and there was no difference in the use of this drug between the two groups. This may be related to the continued infusion of metoclopramide after surgery in both groups.

There are some limitations in this study. Firstly, as a pilot study with a relatively small sample size, these findings may not be generalizable and should therefore be interpreted with appropriate caution. And also, the small sample size was not possible to show that the simultaneous use of the two drugs before and after surgery would not yield adverse effects. Secondly, for ethical reasons, our study did not employ a placebo control group. Thirdly, the main observation indicators were subjective indicators, which may be introduce certain biases.

Conclusion

This pilot study preliminarily showed that intravenous injection of promethazine 6.25 mg before the induction of anesthesia combined with continuous postoperative pump injection of metoclopramide 50 mg had the potential to significantly reduced both the incidence and severity of PONV after laparoscopic colorectal surgery, with few postoperative adverse effects and high patient satisfaction. Larger, multicenter trials are needed to further validate these findings.

Data Sharing Statement

Deidentified data are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

This study was approved by the ethics committee of Gansu Provincial Hospital, and all patients provided written informed consent.

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Disclosure

The authors declare no competing interests in this work.

References

1. Singh P, Yoon SS, Kuo B. Nausea: a review of pathophysiology and therapeutics. *Therap Adv Gastroenterol*. 2016;9(1):98–112. doi:10.1177/1756283X15618131
2. Shaikh SI, Nagarekha D, Hegade G, Marutheesh M. Postoperative nausea and vomiting: a simple yet complex problem. *Anesth Essays Res*. 2016;10(3):388–396. doi:10.4103/0259-1162.179310
3. Darvall J, Handscombe M, Maat B, So K, Suganthirakumar A, Leslie K. Interpretation of the four risk factors for postoperative nausea and vomiting in the Apfel simplified risk score: an analysis of published studies. *Can J Anaesth*. 2021;68(7):1057–1063. doi:10.1007/s12630-021-01974-8
4. Som A, Bhattacharjee S, Maitra S, Arora MK, Baidya DK. Combination of 5-HT3 antagonist and dexamethasone is superior to 5-HT3 antagonist alone for PONV prophylaxis after laparoscopic surgeries: a meta-analysis. *Anesth Analg*. 2016;123(6):1418–1426. doi:10.1213/ANE.0000000000001617
5. Hill RP, Lubarsky DA, Phillips-Bute B, et al. Cost-effectiveness of prophylactic antiemetic therapy with ondansetron, droperidol, or placebo. *Anesthesiology*. 2000;92(4):958–967. doi:10.1097/00000542-200004000-00012
6. Apfel CC, Laara E, Koivuranta M, Greim CA, Roewer N. A simplified risk score for predicting postoperative nausea and vomiting: conclusions from cross-validations between two centers. *Anesthesiology*. 1999;91(3):693–700. doi:10.1097/00000542-199909000-00022
7. Chatterjee S, Rudra A, Sengupta S. Current concepts in the management of postoperative nausea and vomiting. *Anesthesiol Res Pract*. 2011;2011:748031. doi:10.1155/2011/748031
8. Gan TJ, Diemunsch P, Habib AS, et al. Consensus guidelines for the management of postoperative nausea and vomiting. *Anesth Analg*. 2014;118(1):85–113. doi:10.1213/ANE.0000000000000002
9. Bamgbade OA, Oluwole O, Khaw RR. Perioperative antiemetic therapy for fast-track laparoscopic bariatric surgery. *Obes Surg*. 2018;28(5):1296–1301. doi:10.1007/s11695-017-3009-7
10. Naeem Z, Chen IL, Pryor AD, Docimo S, Gan TJ, Spaniolas K. Antiemetic prophylaxis and anesthetic approaches to reduce postoperative nausea and vomiting in bariatric surgery patients: a systematic review. *Obes Surg*. 2020;30(8):3188–3200. doi:10.1007/s11695-020-04683-1
11. White PF, O'Hara JF, Roberson CR, Wender RH, Candiotti KA, Group P-OS. The impact of current antiemetic practices on patient outcomes: a prospective study on high-risk patients. *Anesth Analg*. 2008;107(2):452–458. doi:10.1213/ane.0b013e31817b842c
12. Gan TJ, Belani KG, Bergese S, et al. Fourth consensus guidelines for the management of postoperative nausea and vomiting. *Anesth Analg*. 2020;131(2):411–448. doi:10.1213/ANE.0000000000004833
13. Bergese SD, Puente EG, Antor MA, et al. A prospective, randomized, double-blinded, double-dummy pilot study to assess the preemptive effect of triple therapy with aprepitant, dexamethasone, and promethazine versus ondansetron, dexamethasone and promethazine on reducing the incidence of postoperative nausea and vomiting experienced by patients undergoing craniotomy under general anesthesia. *Front Med*. 2016;3:29. doi:10.3389/fmed.2016.00029
14. Ruiz JR, Ensor JE, Lim JW, Van meter A, Rahlfs TF. Phenothiazine vs 5HT3 antagonist prophylactic regimens to prevent POST-ANESTHESIA CARE Unit rescue antiemetic: an observational study. *Open J Anesthesiol*. 2015;5(2):27–32. doi:10.4236/ojanes.2015.52006
15. Macario A, Claybon L, Pergolizzi JV. Anesthesiologists' practice patterns for treatment of postoperative nausea and vomiting in the ambulatory post anesthesia care unit. *BMC Anesthesiol*. 2006;6:6. doi:10.1186/1471-2253-6-6
16. Isola S, Hussain A, Dua A, Singh K, Adams N. Metoclopramide. *StatPearls*. 2025.
17. Cho JS, Kim SW, Lee S, Yoo YC. Dose-ranging study of ramosetron for the prevention of nausea and vomiting after laparoscopic gynecological surgery: a prospective randomized study. *J Clin Med*. 2019;8(12):2188. doi:10.3390/jcm8122188
18. Page CB, Duffull SB, Whyte IM, Isbister GK. Promethazine overdose: clinical effects, predicting delirium and the effect of charcoal. *QJM*. 2009;102(2):123–131. doi:10.1093/qjmed/hcn153
19. Paparella S. The dangers of intravenous promethazine administration. *J Emerg Nurs*. 2007;33(1):53–56. doi:10.1016/j.jen.2006.09.009
20. Candiotti KA, Kranke P, Bergese SD, et al. Randomized, double-blind, placebo-controlled study of intravenous amisulpride as treatment of established postoperative nausea and vomiting in patients who have had no prior prophylaxis. *Anesth Analg*. 2019;128(6):1098–1105. doi:10.1213/ANE.0000000000003733
21. Schlesinger T, Weibel S, Kranke P. Postoperative/postdischarge nausea and vomiting: evidence-based prevention and treatment. *Curr Opin Anaesthesiol*. 2023;36(1):109–116. doi:10.1097/ACO.0000000000001200
22. Szachnowicz B, Pawasauskas J, Brothers T. An analysis of the management and incidence of postoperative nausea and vomiting. *J Perioper Pract*. 2021;31(10):366–372. doi:10.1177/1750458920950659
23. Pourfakhr P, Aghabagheri M, Zabihi Mahmoudabadi H, Najjari K, Talebpour M, Khajavi MR. Prophylactic administration of diphenhydramine/acetaminophen and ondansetron reduced postoperative nausea and vomiting and pain following laparoscopic sleeve gastrectomy: a randomized controlled trial. *Obes Surg*. 2021;31(10):4371–4375. doi:10.1007/s11695-021-05589-2
24. Dewinter G, Teunkens A, Vermeulen K, et al. Alizapride and ondansetron for the prevention of postoperative nausea and vomiting in patients undergoing laparoscopic gynaecological surgery: a double-blind, randomised, placebo-controlled noninferiority study. *Eur J Anaesthesiol*. 2016;33(2):96–103. doi:10.1097/EJA.0000000000000288

25. Zhao K, Gao Y, Zhang J, et al. Penehyclidine for prevention of postoperative nausea and vomiting in patients undergoing gynecological laparoscopic surgery under combined intravenous and inhalation anesthesia: a randomized, double-blind, placebo-controlled trial. *Drug Des Devel Ther*. 2024;18:685–697. doi:10.2147/DDDT.S453327
26. Talebpour M, Ghiasnejad Omrani N, Imani F, Shariat Moharari R, Pourfakhr P, Khajavi MR. Comparison effect of promethazine/dexamethasone and metoclopramide /dexamethasone on postoperative nausea and vomiting after laparascopic gastric placation: a randomized clinical trial. *Anesth Pain Med*. 2017;7(4):e57810. doi:10.5812/aapm.57810
27. Huang Q, Wang F, Liang C, et al. Fosaprepitant for postoperative nausea and vomiting in patients undergoing laparoscopic gastrointestinal surgery: a randomised trial. *Br J Anaesth*. 2023;131(4):673–681. doi:10.1016/j.bja.2023.06.029
28. Laiq N, Khan MN, Qureshi FA, Khan S, Jan AS. Dexamethasone as antiemetic during gynaecological laparoscopic surgery. *J Coll Physicians Surg Pak*. 2005;15(12):778–781.
29. Abeysundera H, Craig B, Pullich Z. Promethazine-induced delirium with perceptual abnormalities: are we thinking broadly when assessing patients? *BMJ Case Rep*. 2021;14(4):e241784. doi:10.1136/bcr-2021-241784
30. Al-Saffar A, Lennernas H, Hellstrom PM. Gastroparesis, metoclopramide, and tardive dyskinesia: risk revisited. *Neurogastroenterol Motil*. 2019;31(11):e13617. doi:10.1111/nmo.13617
31. Habib AS, Gan TJ. The effectiveness of rescue antiemetics after failure of prophylaxis with ondansetron or droperidol: a preliminary report. *J Clin Anesth*. 2005;17(1):62–65. doi:10.1016/j.jclinane.2004.04.004