Metoclopramide, Versus Its Combination with Dexamethasone in the Prevention of Postoperative Nausea and Vomiting after Laparoscopic Cholecystectomy: A Double-Blind Randomized Controlled Trial

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Background: *Postoperative nausea and vomiting (PONV) are significant problems in laparoscopic surgery.*
Objective: *Compare the prophylactic use of metoclopramide and its combination with dexamethasone in the prevention of PONV in patients undergoing laparoscopic cholecystectomy (LC).*
Material and Method: *One hundred patients aged 18 to 75 with American Society of Anesthesiologists (ASA) class 1-2 who candidates for elective LC at Chiang Mai University Hospital, were included in this double-blind, randomized controlled trial (parallel design). Patients were randomly divided into two groups, by 'Block of four' randomization. Treatment group received 8 mg dexamethasone and 10 mg metoclopramide, and control group received 10 mg metoclopramide and normal saline solution 1.6 ml. These medications were administered intravenously when the gallbladder was removed from gallbladder bed. All of investigators, anesthetists, patients, care providers, and outcome assessor were blinded. Patients were asked to assess their nausea and vomiting at 2, 6, 12, and 24 hours postoperatively, and at discharge. The overall score of PONV in each patient based on a four-point whole number of nausea and vomiting by verbal rating scale 0-3 (0 = no nausea and vomiting, 1 = nausea, 2 = nausea with vomiting, and 3 = repeated vomiting ≥2 times).*
Results: *Fifty eligible patients were randomized to each group, and all were analyzed. There were no significant differences between baseline characteristics of patients in the two groups. The combination of dexamethasone and metoclopramide indicated a greater antiemetic effect with significant statistical analysis, odds ratio = 0.25 (95% confidence interval 0.11-0.55, p = 0.001). The postoperative hospital stay in the combined group and metoclopramide group were, 1 day = 47 (94%) and 37 (74%), >1 day = 3 (6%) and 13 (26%), respectively (p = 0.012). There were no postoperative complications occurred in both groups.*
Conclusion: *Intravenous administration of dexamethasone combined with metoclopramide had significant effects in prophylaxis of nausea and vomiting after LC and shorten the hospital stay.*
Clinical trials registration number: *TCTR20140128001*

Keywords: *Dexamethasone, Metoclopramide, Postoperative nausea and vomiting (PONV), Laparoscopic cholecystectomy (LC)*

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Since the first laparoscopic cholecystectomy (LC) has been reported in 1987, this operative technique has been widely accepted around the world due to the obvious advantages of less pain and faster recovery compared to standard open cholecystectomy (OC)[1-3]. Some centers have accommodated this operation as a day surgery case[2]. Nonetheless, postoperative nausea and vomiting (PONV) are common and troubled complications, and they are the primary concern of 37 to 72% of patients undergoing laparoscopic surgery[3-6].

Many types of drugs are used for the treatment of nausea and vomiting[4]. Commonly used antiemetic drugs include anticholinergic, antihistamines, butyrophenones, and benzamine. Common side effects

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such as sedation, dysphoria, and extrapyramidal events[7,8] may prolong recovery times.

Ondansetron, a 5-hydroxytryptamine subtype 3 (5HT3) receptor antagonist has been reported to be an effective antiemetic in preventing and treating PONV with few side effects[3]. Sandhu et al[9] compared ondansetron with metoclopramide in a study that showed ondansetron to be more effective in reducing the incidence of vomiting compared to metoclopramide (2.5% vs. 20%, $p = 0.02$). The incidence of nausea in the ondansetron-treated group was also only about 20% compared to 45% in the metoclopramide-treated group, the difference was statistically insignificant ($p = 0.05$). However, the high cost of ondansetron may limit its clinical use, especially in developing countries.

Dexamethasone is as effective as ondansetron 4 mg and granisetron 3 mg, and it provides a simple, safe, inexpensive, and effective prevention method for PONV[10].

In spite of the many drugs available for PONV, there is no single drug that can be effective enough for this problem. Combination drug therapy could be the answer. This is because the different pharmacological classes of drugs, with different mechanisms of action, in combination could be more effective than single drugs alone in inhibiting the complex emetic reflex[11]. This double-blind, randomized controlled trial compared the prophylactic use of metoclopramide and its combination with dexamethasone in the prevention of PONV in patients undergoing LC. The present study aimed to provide a simple, safe, inexpensive, and effective PONV prevention method in LC.

Material and Method

This double-blind, randomized controlled trial (parallel design) was approved by Research Ethics Committee 1, Faculty of Medicine, Chiang Mai University. Informed consent from patients was obtained at least 24 hours before the operation. Patients of the American Society of Anaesthesiologists (ASA) class 1-2, aged 18-75 years who required elective LC were enrolled by the investigators to participate in the study. The exclusion criteria were patients with pregnancy, breast feeding, more than 100 kg in weight, history of motion sickness, nausea/vomiting with the use of antiemetic drugs within 24 hours prior to surgery, insulin-dependent diabetes mellitus[4], allergy to any protocol medication, contraindication for metoclopramide such as epilepsy, pheochromocytoma and antipsychotic (haloperidol, chlorpromazine) treated patients, contraindication for dexamethasone such as tuberculosis and herpes simplex virus of ophthalmic, and procedure conversion to open cholecystectomy.

On the day of surgery, eligible patients were randomized to receive the study drug. Sampling technique was done by permuted block randomization. Ratio between treatment group (combination of metoclopramide and dexamethasone) and control group (metoclopramide) was 1:1. 'A' represented treatment group, and 'B' represented control group. Then 'Block of four' randomization was performed by a hospital pharmacist who prepared the drugs. This pharmacist was not involve in patient care or data collection. Accordingly, the 'Block of four' could be distributed into six blocks including 1) AABB, 2) ABAB, 3) ABBA, 4) BBAA, 5) BABA, and 6) BAAB respectively. The labeled numbers 1 to 6 were chosen at random until the full amount of the sample size. The orders in each number represented the orders of treatment that the patient received. The chosen numbers were converted into code A and B, as defined in each block. Concealment was performed by putting the card of assignment in an opaque envelope, and opened it before the end of surgery. Group A (treatment group) received intravenous 8 mg dexamethasone and 10 mg metoclopramide. Group B (control group) received intravenous 10 mg metoclopramide and normal saline solution 1.6 ml. The pharmacist assigned patients to interventions, and supplied syringes in a blinded fashion, so that the investigators, anesthetists, patients, care providers, and outcome assessor were unaware of which of the two drugs was being administered.

All patients fasted from midnight before surgery, and premedication with oral diazepam (0.2 mg/kg body weight) was administered approximately two hours before surgery. Anesthesia was delivered in a uniform fashion, balanced general analgesia with endotracheal intubation. Intravenous induction was performed using thiopental (5 mg/kg body weight), and intravenous fentanyl (1 µg/kg body weight) was given as an analgesic. Before the end of surgery, the study drugs in both groups were intravenously administered by the anesthesiologist when the gallbladder was removed from gallbladder bed.

Standard LC was performed by the set of surgeons. The abdominal cavity was inflated with carbon dioxide at a pressure between 12 and 14 mmHg. Possible intraoperative complications such as

gallbladder perforation, visceral damage, bowel injury, or bleeding[12] also were recorded without exclusion from the study. Then, all patients were extubated and transferred to the recovery room.

Patients were asked to assess their nausea and vomiting at 2, 6, 12, 24 hours, and at discharge by research nurse who was blinded to the study. Incidence of nausea, number of vomiting episodes, and antiemetic drugs requirements were recorded. The overall score of PONV in each patient based on a four-point whole number of nausea and vomiting by verbal rating scale 0-3 (0 = no nausea and vomiting, 1 = nausea, 2 = nausea with vomiting, 3 = repeated vomiting ≥2 times)[12]. An overall score was used to compare groups. In case of nausea or vomiting, intravenous metoclopramide 10 mg was given as a rescue drug. Any adverse events were recorded. Patients were given soft diet and then regular diet when they arrived at the ward and prescribed postoperative analgesics; intravenous morphine (0.05 mg/kg body weight) every four hours as needed when numeric rating score (NRS) ≥6, and combined paracetamol with codeine was the analgesic used for minor pain (NRS 3-5).

Statistical analysis

A standard statistical software package (STATA version 11.0) was used for data analysis and to calculate the sample size in the study based on the assumption that: 1) incidence of PONV in control group (metoclopramide) would be 45%[9]; 2) incidence of PONV in treatment group (dexamethasone and metoclopramide) would be 13%[13]; and 3) $\alpha = 0.05$ (two-sided) and for a power (1-β) of 90%, based on these assumptions would require 50 patients per group.

The results from the two groups were compared using the t-test/Mann Whitney U test for comparing continuous data, and the Fisher's exact test for qualitative data. Ordinal logistic regression model was performed to compare the effects of metoclopramide, and its combination with dexamethasone in the prevention of PONV. A *p*-value of 0.05 was considered significant.

Results

One hundred patients underwent laparoscopic cholecystectomy at Chang Mai University Hospital between January 2012 and January 2014, and were randomized into the present study with no patients being excluded after randomization (Fig. 1). Baseline characteristics were not different in the two groups (Table 1). There was no significant difference between the two groups with the incidence of gallbladder perforation, 11 (22%) vs. 12 (24%) in the combined and metoclopramide group, respectively ($p = 1.000$). No major intraoperative complications such as visceral damage, bowel injury, and bile duct injury) occurred. There was no statistical significances in postoperative pain score, antiemetic and analgesic drug used. There was significant difference between groups, with postoperative hospital stay favoring the combined group. More patients in the metoclopramide group required longer hospital stay, (1 day: 47 (94%) vs. 37 (74%), >1 day: 3 (6%) vs. 13 (26%) in the combined and metoclopramide group, respectively), $p = 0.012$ (Table 2).

The incidence of PONV in the combined group and metoclopramide group were 13 (26%) vs. 20 (40%) at 2 hours ($p = 0.202$), 9 (18%) vs. 22 (44%) at 6 hours ($p = 0.009$), 5 (10%) vs. 13 (26%) at 12 hours

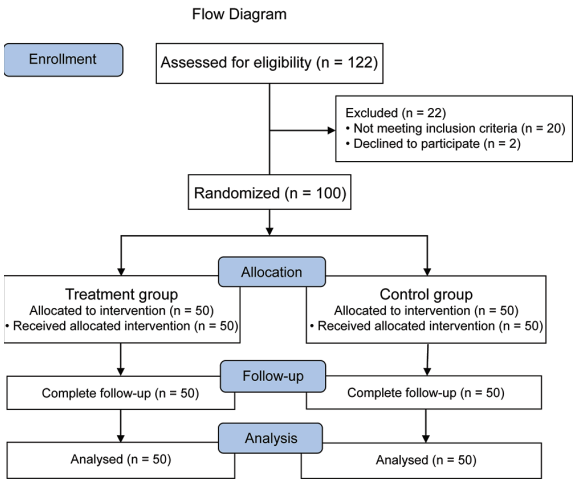

Fig. 1 Flow diagram of the whole study.

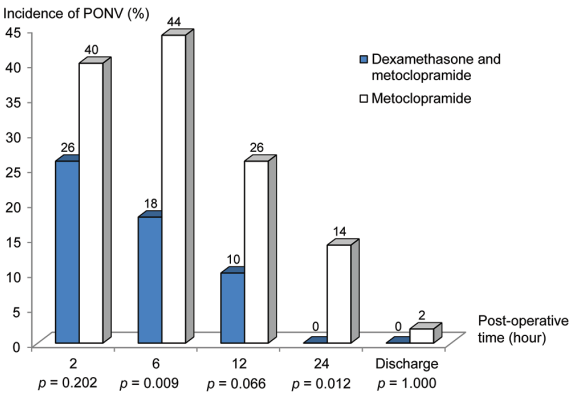

Fig. 2 Incidence of PONV in each group at 2, 6, 12, 24 hours and at discharge.

Table 1. Baseline characteristics

Characteristics	Dexamethasone & metoclopramide (n = 50)	Metoclopramide (n = 50)	*p*-value
Age, mean ± SD	52.5±34.0	50.9±12.7	0.536
Gender, n (%)			
Male	21 (42)	17 (34)	0.537
Female	29 (58)	33 (66)	
Body mass index (BMI), mean ± SD	23.9±3.5	23.7±2.8	0.721
ASA classification, n (%)			
Class 1	22 (44)	19 (38)	0.685
Class 2	28 (56)	31 (62)	
Previous upper intra-abdominal surgery, n (%)	3 (6)	5 (10)	0.715
Underlying disease, n (%)			
Diabetes mellitus	4 (8)	2 (4)	0.678
Hypertension	18 (36)	14 (28)	0.521
Cardiovascular disease	3 (6)	2 (4)	1.000
Cirrhosis	3 (6)	2 (4)	1.000
Dyslipidemia	7 (14)	11 (22)	0.436
Others (thalassemia, gout, etc.)	21 (42)	26 (52)	0.423
Indication for surgery, n (%)			
Symptomatic gallstones	46 (92)	45 (90)	1.000
History of cholangitis/pancreatitis	4 (8)	5 (10)	1.000
History of acute cholecystitis	7 (14)	10 (20)	0.595
Gallbladder polyp	4 (8)	1 (2)	0.362
Operative time (minute), mean ± SD	68.3±22.9	72.9±24.6	0.334

ASA = American Society of Anesthesiologists

Table 2. Postoperative data in the two groups

Postoperative data	Dexamethasone & metoclopramide (n = 50)	Metoclopramide (n = 50)	*p*-value
Antiemetic drug use, n (%)			
No	42 (84)	36 (72)	0.227
Use	8 (16)	14 (28)	
Antiemetic drug use (dose), median (range)	0 (0-2)	0 (0-2)	0.191
Pain score (NRS), mean ± SD	3.7±1.6	3.4±1.3	0.266
Analgesic drug use, n (%)			
Morphine	41 (82)	36 (72)	0.342
Oral analgesia	28 (56)	30 (60)	0.840
Analgesic drug use (dose), median (range)			
Morphine	1 (0-3)	1 (0-5)	0.800
Oral analgesia	1 (0-3)	1 (0-3)	0.611
Postoperative hospital stay (day), n (%)			
1 day	47 (94)	37 (74)	0.012
>1 day	3 (6)	13 (26)	

NRS = numeric rating score

($p = 0.066$), 0 vs. 7 (14%) at 24 hours ($p = 0.012$), 0 vs. 1 (2%) at discharge ($p = 1.000$), respectively (Fig. 2).

Summary of PONV in the combined and metoclopramide group were: 0 (no nausea/vomiting) = 35 (70%) vs. 18 (36%), 1 (nausea) = 5 (10%) vs. 9 (18%), 2 (nausea with vomiting) = 5 (10%) vs. 7 (14%), and 3 (repeated vomiting ≥2 times) = 5 (10%) vs. 16 (32%), respectively ($p = 0.005$) (Table 3).

Table 3. Overall score assessment of PONV

PONV, n (%)	Dexamethasone & metoclopramide (n = 50)	Metoclopramide (n = 50)	*p*-value
0: No nausea/vomiting	35 (70)	18 (36)	0.005
1: Nausea	5 (10)	9 (18)	
2: Nausea with vomiting	5 (10)	7 (14)	
3: Repeated vomiting ≥2 times	5 (10)	16 (32)	

PONV = postoperative nausea and vomiting

Table 4. Side effects of drugs in the two groups

Side effects, n (%)	Dexamethasone & metoclopramide (n = 50)	Metoclopramide (n = 50)	*p*-value
Sedation	9 (18)	29 (58)	<0.001
Dizziness	11 (22)	19 (38)	0.126
Cardiac dysrhythmia	0	5 (10)	0.056

Ordinal logistic regression analysis indicated that combination of dexamethasone and metoclopramide can reduce incidence of PONV more significantly than metoclopramide alone (odds ratio = 0.25, 95% confidence interval 0.11-0.55, $p = 0.001$).

Postoperative complications (such as wound infection or bowel obstruction) were not occurred in both groups. There was less tendency side effect in the combination group. Side effects of drugs, such as sedation 18% and 58% ($p<0.001$), dizziness 22% and 28% ($p = 0.126$), and cardiac dysrhythmia 0% and 10% ($p = 0.056$) in the combination group and metoclopramide group, respectively (Table 4). Other side effects such as dystonic extrapyramidal reactions (oculogyric crises, opisthotonus, trismus, or torticollis), and edema did not occurred in either groups.

Discussion

PONV are sometimes distressing and frequent adverse events of anesthesia and surgery, with a relatively high incidence (53%-72%) after LC[10]. These effects lead to longer recovery time, delayed discharge, and increased costs of hospital stay[14].

The origin of PONV after LC remains unclear, but it can be caused by several factors. The necessity of gas insufflation, which results in the extending of peritoneum and increased pressure in the abdominal cavity, is a very important factor stimulating PONV. The uses of nitrous oxide, slightly hypoxic mixtures during anesthesia and postoperative opioid have been proposed as other potential risk factors. The effectiveness of various antiemetic drugs has been studied for the prevention and treatment of PONV after LC[10].

Dexamethasone is a corticosteroid with an anti-inflammatory effect that gives postoperative analgesia, and reduces PONV[13,15]. It has been used as an antiemetic drug for more than 20 years in patients treated with chemotherapy, with limited side effects, and has been reportedly reduced PONV when used in combination with other antiemetics[13,16]. Recently, a combination of ondansetron and dexamethasone has been revealed to be a highly effective prophylactic measure in patients scheduled for LC[16]. However, the higher cost of ondansetron has been a significant factor limiting its common use[13,17].

The mechanism of the antiemetic action of dexamethasone and the accurate site of action remain unclear[13]. Some studies have proposed that dexamethasone may antagonize prostaglandin[18] or release endorphins[19], resulting in elevating mood, feelings of well-being, and to stimulate appetite. The suggested dose in the prevention of PONV is 8 to 10 mg[13].

On the other side, the value of dexamethasone for other postoperative symptoms such as pain and fatigue has been controversial and not fully evaluated[16,20-24]. In the present study, the outcome of dexamethasone on postoperative pain was not demonstrated.

Metoclopramide is a central dopaminergic D_2 receptor antagonist and a prokinetic drug that increases gastric emptying and shortens bowel transit time[13]. The meta-analysis by Domino et al[25] showed that metoclopramide is not as effective as ondansetron

and droperidol in preventing postoperative vomiting. Nesek-Adam et al[13] found that metoclopramide justified to be a poor antiemetic agent at a dose of 10 mg and was associated with a high incidence of PONV (45%).

Nesek-Adam et al[13] evaluated the efficacy of intravenous dexamethasone 8 mg or metoclopramide 10 mg, and their combination to prevent PONV in patients undergoing LC. The total incidence of PONV was 60% with placebo, 45% with metoclopramide, 23% with dexamethasone, and 13% with the combination of dexamethasone plus metoclopramide[10].

Many combinations of antiemetic drugs have been used to test with different effects. However, it is difficult to verify which drug can be the gold standard in PONV prevention after LC. Due to many research centers have reported that the effects of various antiemetic drugs are not different, so it is appropriate to administer the least expensive and safest drugs[10].

In the present study, eligible patients had no statistical differences in baseline characteristics, which is probably due to 'block of four' randomization. Intraoperative complications also were not different. The study indicated that PONV prevention in the combined group was effective at 6, and 24 hours postoperatively. This effect was not significant in the first two hours, which was probably the result of anesthesia. The good result of 6 hours make the investigators can provide day surgery. Furthermore, the summary of PONV by a verbal rating scale 0-3 was statistically significant. Ordinal logistic regression also confirmed better results from the combined group. The combination of dexamethasone and metoclopramide was a simple, safe, inexpensive, and effective PONV prevention method. It will be useful in developing countries. In addition, the combination of these two drugs also results in shorter postoperative hospital stay than metoclopramide ($p = 0.012$).

Conclusion

Intravenous injection of dexamethasone combined with metoclopramide has significant effects in the prophylaxis of nausea and vomiting after LC. In additional, the hospital stay is also shorter in the combined group.

What is already known on this topic?

Many studies had been done providing information that prophylactic use of antiemetic drugs is effective in PONV prevention method.

What this study adds?

The present study provided more information that the combination of dexamethasone and metoclopramide is effective in the prevention of PONV after LC, and it is cost effective, especially in developing countries.

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Potential conflicts of interest

None.

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การใช้ยา metoclopramide เปรียบเทียบกับ metoclopramide ร่วมกับ dexamethasone ในการป้องกันการคลื่นไส้อาเจียนในผู้ป่วยที่ได้รับการผ่าตัดถุงน้ำดีผ่านกล้องส่อง: การศึกษาแบบสุ่มที่มีตัวควบคุม ปกปิดสองทาง

วาสนา โกเอี่ยม, ไตรจักร ซันดู, สหัทยา ไพบูลย์วรชาติ, ไพศาล พงศ์ชัยฤกษ์, สัณหวิชญ์ จันทร์รังสี, อานนท์ โชติรสนิรมิต, นเรนทร์ โชติรสนิรมิต, กำธน จันทร์แจ่ม, ธิดารัตน์ จิรพงศ์เจริญลาภ

ภูมิหลัง: ภาวะคลื่นไส้อาเจียนหลังผ่าตัดเป็นปัญหาที่สำคัญในการผ่าตัดผ่านกล้องส่อง

วัตถุประสงค์: การศึกษานี้มีวัตถุประสงค์เพื่อเปรียบเทียบการใช้ยา metoclopramide และmetoclopramide ร่วมกับ dexamethasone ในการป้องกันอาการคลื่นไส้อาเจียนในผู้ป่วยที่ได้รับการผ่าตัดถุงน้ำดีผ่านกล้องส่อง

วัสดุและวิธีการ: ผู้ป่วยจำนวน 100 ราย อายุ 18-75 ปี ที่มี ASA ระดับ 1-2 ที่ได้รับการผ่าตัดถุงน้ำดีผ่านกล้องส่องในโรงพยาบาลมหาราชนครเชียงใหม่ จะได้รับคัดเลือกเข้าในการศึกษานี้ ซึ่งเป็นการศึกษาแบบสุ่มที่มีตัวควบคุม ปกปิดสองทาง (แบบคู่ขนาน) ผู้ป่วยดังกล่าวจะถูกแบ่งออกเป็น 2 กลุ่ม โดยวิธีสุ่มคัดเลือกแบบ block of four กลุ่มศึกษาจะได้รับ dexamethasone ขนาด 8 มิลลิกรัม และ metoclopramide ขนาด 10 มิลลิกรัม อย่างละ 1 syringe ส่วนกลุ่มควบคุมจะได้รับ metoclopramide ขนาด 10 มิลลิกรัม และน้ำกลั่นบริสุทธิ์ปริมาณ 1.6 มิลลิลิตร อย่างละ 1 syringe โดยยาทั้ง 2 กลุ่ม ฉีดเข้าหลอดเลือดดำในระหว่างการผ่าตัดขณะตัดถุงน้ำดีเสร็จ ทั้งผู้นิพนธ์ วิสัญญีแพทย์ผู้ให้ยา ผู้ป่วยที่ได้รับยา และผู้ประเมินผลของการใช้ยา ไม่มีผู้ใดทราบว่าผู้ป่วยได้รับยาชนิดใด จากนั้นประเมินการเกิดอาการคลื่นไส้และอาเจียนในช่วง 2, 4, 6, 12, 24 ชั่วโมงหลังผ่าตัด และขณะออกจากโรงพยาบาล โดยคะแนนของการคลื่นไส้อาเจียนมี 4 ระดับ คือ 0-3 (0 = ไม่มีคลื่นไส้หรืออาเจียนเลย, 1 = มีคลื่นไส้อย่างเดียว, 2 = มีคลื่นไส้และอาเจียน 1 ครั้ง, 3 = อาเจียนซ้ำตั้งแต่ 2 ครั้งขึ้นไป)

ผลการศึกษา: วิเคราะห์ข้อมูลจากผู้ป่วยที่ถูกสุ่มทั้งหมด กลุ่มละ 50 ราย ลักษณะพื้นฐานของผู้ป่วยทั้ง 2 กลุ่ม ไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ กลุ่มที่ได้รับ dexamethasone ร่วมกับ metoclopramide สามารถป้องกันการเกิดคลื่นไส้อาเจียนหลังผ่าตัดได้ดีกว่า (odds ratio 0.25, 95% CI 0.11-0.55, p = 0.001) การนอนโรงพยาบาลหลังผ่าตัดในกลุ่มที่ได้รับยาทั้ง 2 ชนิดร่วมกันและกลุ่มที่ได้รับ metoclopramide มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ คือ 1 วัน: 47 ราย (94%) และ 37 ราย (74%), มากกว่า 1 วัน: 3 ราย (6%) และ 13 ราย (26%) ตามลำดับ (p = 0.012) และไม่พบภาวะแทรกซ้อนหลังผ่าตัดในทั้ง 2 กลุ่ม

สรุป: การให้ยา dexamethasone ร่วมกับ metoclopramide ฉีดเข้าหลอดเลือดดำมีประสิทธิภาพในการป้องกันการเกิดคลื่นไส้อาเจียนหลังผ่าตัด รวมทั้งลดระยะเวลานอนโรงพยาบาลหลังผ่าตัด