Original Article

Ann Coloproctol 2018;34(1):36-41
https://doi.org/10.3393/ac.2018.34.1.36

Annals of Coloproctology
pISSN 2287-9714 eISSN 2287-9722
www.coloproctol.org

Efficacy and Safety of Ramosetron Injection for Nausea and Vomiting in Colorectal-Cancer Patients Undergoing a Laparoscopic Colectomy: A Randomized, Double-Blind, Comparative Study

Han Eol Park, Min Ki Kim, Won-Kyung Kang

Department of Surgery, College of Medicine, The Catholic University of Korea, Seoul, Korea

Purpose: A laparoscopic colectomy in colorectal-cancer patients is usually associated with a high risk of postoperative nausea and vomiting (PONV). The purpose of this study is to evaluate the efficacy of injection of long-acting 5-hydroxytryptamine type 3 (5-HT_3) receptor antagonist for the reduction of PONV in patients with colorectal cancer.

Methods: A total of 48 patients scheduled to undergo a laparoscopic colectomy for colorectal cancer were randomized in a double-blinded fashion. Patients were randomly allocated to 1 of 2 groups and assigned to receive either 0.3 mg of ramosetron intravenously (group A, n = 25) or 2 mL of normal saline (placebo) (group B, n = 22) immediately after the operation. The incidence of PONV, the nausea severity scale score, the visual analogue scale (VAS) score for pain, the total amount of patient-controlled analgesia used, the recovery of bowel function, and morbidities were assessed at 1 hour and at 24, 48, and 72 hours after surgery.

Results: The baseline and the operative characteristics were similar between the groups ($P > 0.05$). The number of cases without PONV (complete response) was higher for group A (ramosetron) than group B (normal saline): 24 hours after surgery, 92.0% (23 of 25) for group A versus 54.5% (12 of 22) for group B; 48 hours after surgery, 92% (23 of 25) for group A versus 81.8% (18 of 22) for group B (both $P < 0.05$). No serious adverse events occurred.

Conclusion: Postoperative ramosetron injection is effective for the prevention of PONV after a laparoscopic colectomy in colorectal-cancer patients.

Keywords: *Ramosetron; Postoperative nausea and vomiting; Laparoscopic colectomy*

INTRODUCTION

Postoperative nausea and vomiting (PONV) is a common complication after surgery and is related to the patient's quality of life and compliance with treatment [1, 2]. The preoperative nasogastric tube, patient-controlled anesthesia (PCA), and postoperative analgesics in the postanesthetic recovery room might be associated with PONV. Approximately 80% of postoperative patients have been reported to suffer distress from PONV [3, 4].

Major abdominal surgery is known to be associated with more severe postoperative bowel dysfunction, such as nausea, vomiting, and reinsertion of a nasogastric tube, compared with other surgeries. Even though some reports have stated that laparoscopic abdominal surgeries have better outcomes than open surgeries in terms of PONV [5], the patients still complain of postoperative bowel symptoms similar to those of open surgeries [6]. Based on

Received: June 28, 2017 • Accepted: October 30, 2017
Correspondence to: Won-Kyung Kang, M.D.
Department of Surgery, Yeouido St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 10 63 (yuksam)-ro, Yeongdeungpo-gu, Seoul 07345, Korea
Tel: +82-2-3779-1033, Fax: +82-2-780-9114
E-mail: wonkkang@catholic.ac.kr
ORCID code: https://orcid.org/0000-0002-3337-0644

This content was poster presented at the 2015 annual Scientific Meeting of the American Society of Colon and Rectal Surgeons (ASCRS).

the multiple factors mentioned above, patients who have undergone laparoscopic colorectal surgery can be classified as a high-risk group for PONV.

Several drugs and anesthetic methods have been studied over the last few years in order to reduce the symptoms of postoperative bowel dysfunction and PONV. Several reports have been published on the efficacy of metoclopramide, droperidol, and ondansetron regarding reductions in the incidence of PONV [7-9]. Although combination therapies involving more than two antiemetic drugs have been reported to be effective for prophylaxis of PONV [10, 11], single use of 5-hydroxytryptamine type 3 (5-HT_3) receptor antagonists has emerged as a better alternative therapy. Of several 5-HT_3 antagonists, ramosetron (Nasea, ODl Astellas Pharma Inc., Tokyo, Japan), which was developed to reduce gastrointestinal symptoms caused by chemotherapy [12] and irritable bowel syndrome, is a long-acting drug with high potency for 48 hours. The strong effects of ramosetron on abnormal bowel function and symptoms were proven in several studies [13, 14].

Previous studies have discussed the effects of ramosetron during breast surgery [15], a thyroidectomy [16], gynecologic surgery [17], cardiac surgery [18], a cholecystectomy [19], and other surgeries [20, 21]. However, not many of those studies were prospective and randomized, and few discussed the efficacy of ramosetron for the prophylaxis of PONV after laparoscopic colorectal surgeries, even though these patients are in a high-risk group for PONV. We, therefore, conducted a prospective, randomized, double-blinded, placebo-controlled trial to evaluate the efficacy of ramosetron injection after the completion of surgery.

METHODS

This study was approved by the Institutional Review Board of Seoul St. Mary's Hospital (approval number: KC12MISV0327). All patients who had been diagnosed with colon and rectal cancer by using colonoscopic biopsies, abdominal computed tomography scans, and other diagnostic tools were enrolled. All enrolled patients were planned for laparoscopic colorectal surgery, including a colectomy, under general anesthesia. Each patient signed informed consent to be enrolled in this study. Exclusion criteria were as follows: patients under 18 or over 80 years of age; patients requiring excision of other organs or another part of the colon due to synchronous/double primary cancers or other diseases; patients with American Society of Anesthesiologists (ASA) physical status classification greater than IV; patients unable to undergo radical surgery due to general medical condition; patients with a history of emergent surgery due to mechanical obstruction or intestinal bleeding; patients refusing to participate in the study or those unable to agree to participate by themselves; patients unable to participate in clinical trials due to legal reasons; patients that were definitely going to drop out from the trial and those unable to visit the hospital regularly; patients who were pregnant and lactating; patients with severe intra-abdominal adhesion due to previous abdominal surgery; patients with a previous history of intestinal inertia or severe constipation that might affect bowel motility after surgery; patients with a previous history of neoadjuvant chemotherapy or radiation therapy.

Patients were allocated into 2 groups by using a computer-generated randomizing method. The 2 groups were based on a placebo-controlled trial in a double-blind condition. At the completion of surgery and before the patient was fully awake from anesthesia, the patients in the ramosetron group (group A) received intravenously 0.3 mg of ramosetron and the patients in the placebo group (group B) received 2 mL intravenously of normal saline. The injected samples were kept in a sealed envelope.

All of the target patients were under standard general anesthesia. Anesthesia was maintained by sevoflurane 1.5%–2.5% (per volume), FiO_2 0.440% (without N_2O), and remifentanil 0.05–0.3 μg/kg/min. Remifentanil was the only opioid used during the whole operation. At the completion of surgery, the total volume (μg) of remifentanil administered was assessed. None of the target patients received any antiemetics at the completion of surgery.

All patients were under the same PCA device regimen. Using a PCA device (Ace Medical PCA, mechanic version), fentanyl, 25 μg/kg (total volume including normal saline 100 mL), was injected at a 2 mL/hr basal rate, 0.5 mL/hr of a bolus, and 15 minutes of lockout time. PCA devices were working under continuous infusion of fentanyl from the completion of surgery. The target patients did not receive any other analgesics. Postoperative patients that were distressed due to severe pain and that had a visual analogue scale (VAS) score greater than 5 were injected with 25-μg units of fentanyl in the postanesthetic recovery room. 5-HT_3 receptor antagonists, such as ramosetron were never used as antiemetics.

After 1 to 2 hours from the completion of surgery, patients were transferred from the postanesthesia recovery room to the general ward under appropriate conditions and were observed closely for 72 hours. All events of PONV were checked by medical staff. The nausea severity scale (NSS) score, vomiting, and VAS score for pain were recorded at a regular time of day (0–24 hours, 24–48 hours, and 48–72 hours after transfer) [22, 23]. The NSS was evaluated based on a 4-point scale (0 = none; 1 = mild; 2 = moderate; 3 = severe). The highest NSS scores that the patient reported were selected as meaningful scores. Vomiting was recorded as the number of occurrences and the time of each occurrence. Postoperative pain was assessed with an 11-point VAS from 0 (no pain) to 10 (worst pain imaginable). In addition to scores recorded within postoperative 72 hours, the total volume of PCA used and the total consumptions of additional metoclopramide for antiemetic effect and analgesics were precisely recorded. The times of return to diet and discharge from hospital were also recorded. The diet was decided by a medical attendant and depended on bowel sounds and gastrointestinal symptoms. Supplementary oxygen was given for 24 hours after surgery via a nasal prong at a rate of 2 L/min. Postoperative complications and remarkable find-

ings were also recorded in detail. Second-generation cephalosporin was used as a prophylactic antibiotic until 24 hours after surgery.

We used the Fisher exact test with a type I error of 0.05 to calculate that the inclusion of 24 patients per group would afford an 80% chance of detection of a 40% reduction in the incidence of PONV. Considering a dropout rate of 5%, we increased the sample size to 26 patients per group. Data were expressed as mean ± standard deviation or number (%). Statistical analyses were performed using IBM SPSS Statistics ver. 24.0 (IBM Co., Armonk, NY, USA). Continuous data were analyzed using the t-test. Discrete data were analyzed using the chi-square test or the Fisher exact test, and *post hoc* comparisons were made with Bonferroni correction. $P < 0.05$ was considered statistically significant.

RESULTS

Between February 2013 and August 2014, 52 patients were found to be eligible for the study. Among them, 5 patients declined to participate in the study for personal reasons, so a total of 47 patients were enrolled in the study. Target patients were randomly allocated into 2 groups (group A, 3 mg of ramosetron, n = 27; group B, 2 mL of normal saline, n = 22) (Fig. 1). There were no significant differences in patients' demographic data and intraoperative variables between the 2 groups (Table 1). With regard to postoperative recovery course, 2 patients in group A (ramosetron group) needed metoclopramide as a rescue antiemetic ($P < 0.05$). Other than that, no significant differences were found between the 2 groups (Table 2).

We defined an improvement in patient's subjective feeling of nausea with a corresponding decrease in the NSS score as a complete response. The complete response rates at 24 hours and 48 hours after surgery were 92.0% (23 of 25) for group A versus 54.5% (12 of 22) for group B and 96.0% (24 of 25) for group A versus 81.8% (18 of 22) for group B, respectively. No statistically significant differences in the NSS score between the 2 groups were observed immediately after the surgery and at 24 hours and 48 hours after surgery ($P = 0.635$, $P = 0.411$, and $P = 0.632$, respectively) (Table 3). In addition, no serious adverse events, such as headaches and dizziness, occurred during the study.

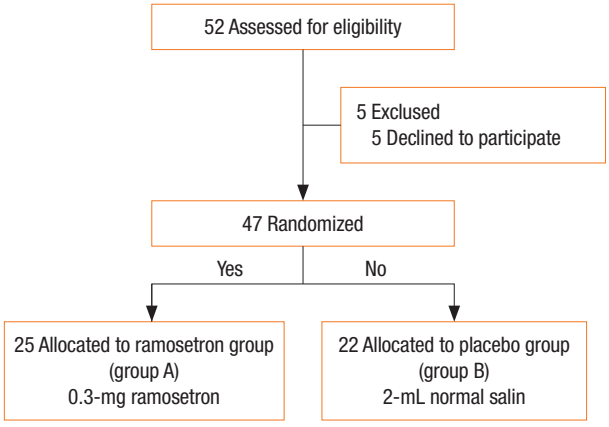

Fig. 1. Flow diagram showing the study design.

DISCUSSION

PONV is a significant concern for patients and physicians. Many trials have aimed to reduce postoperative bowel dysfunction and PONV, and several drugs and anesthetic methods have been stud-

Table 1. Baseline characteristics and information on surgery and anesthesia of the patients

Characteristic	Group A (n = 25)	Group B (n = 22)	P-value
Age (yr)	59.3 ± 10.6	63.4 ± 10.4	0.164
Sex			0.920
Male	14 (56.0)	12 (54.5)	
Female	11 (44.0)	10 (45.5)	
Height (cm)	162.4 ± 5.5	161.3 ± 5.4	0.642
Weight (kg)	64.24 ± 8.9	63.18 ± 8.6	0.794
ASA PS classification			0.125
I	11 (44.0)	5 (22.7)	
II	14 (56.0)	17 (77.3)	
III	0 (0)	0 (0)	
Body mass index (kg/cm^2)	23.86 ± 3.12	24.19 ± 2.62	0.179
History of smoking, yes/no	9/16 (36/64)	3/19 (13.6/86.4)	0.079
Pre-existing disease			
Hypertension, yes/no	10/15 (40/60)	9/13 (40.9/59.1)	0.949
Diabetes mellitus, yes/no	5/20 (20/80)	9/13 (40.9/59.1)	0.118
Liver disease, yes/no	0/25 (0/100)	1/21 (4.5/95.5)	0.365
History of previous abdominal surgery, yes/no	4/21 (16/84)	4/18 (18.2/81.8)	0.943
Operation			
RHC or ERHC	8 (32.0)	1 (4.0)	
T-colectomy	0 (0)	0 (0)	
LHC or ELHC	1 (4.0)	3 (13.0)	
AR	7 (28.0)	5 (23.0)	
LAR	9 (36.0)	13 (60.0)	
Conversion	0 (0)	0 (0)	
Operation time (min)	236.3 ± 21.4	237.3 ± 20.2	0.958
Anesthesia time (min)	276.7 ± 21.2	277.6 ± 21.1	0.967

Values are presented as mean ± standard deviation or number (%).
Group A, ramosetron group; group B, placebo group; APA PS, American Society of Anesthesiologists physical status; RHC, right hemicolectomy; ERHC, extended right hemicolectomy; T-colectomy, transverse colon colectomy; LHC, left hemicolectomy; ELHC, extended left hemicolectomy; AR, anterior resection; LAR, low anterior resection.

Table 2. Recovery course of the patients

Variable	Group A (n = 25)	Group B (n = 22)	P-value
Time to flatus (hr)	11.7 ± 4.2	11.0 ± 4.6	0.599
Time to defecation (hr)	13.7 ± 5.6	11.5 ± 6.2	0.275
Time to diet (hr)			
Sips of water	50.2 ± 4.1	45.5 ± 4.4	0.384
Liquid diet	65.6 ± 3.7	65.5 ± 3.5	0.679
Soft diet	86.7 ± 3.4	82.9 ± 3.4	0.324
VAS score for pain			
Recovery room to ward	5.4 ± 2.1	5.3 ± 2.4	0.875
Ward to 24 hr	4.5 ± 2.2	4.3 ± 2.5	0.662
24–48 hr	2.9 ± 1.3	2.8 ± 1.2	0.796
48–72 hr	1.8 ± 0.7	1.3 ± 0.5	0.142
Used amount of PCA (μg)	85.7 ± 10.6	100.0 ± 9.8	0.081
Used amount of fentanyl (μg)	128.9 ± 11.3	76.1 ± 14.5	0.135
Used amount of metochlopropamide (mg)	2	0	0.005
Postoperative hospital stay (day)	7.1 ± 2.4	7.2 ± 2.1	0.885

Values are presented as mean ± standard deviation or number.
Group A, ramosetron group; group B, placebo group; VAS, visual analogue scale; PCA, patient-controlled analgesia.

Table 3. Comparison of nausea and vomiting scales

Variable	Group A (n = 25)	Group B (n = 22)	P-value
Complete response			
24 Hours			0.0045
Response	23 (92.0)	15 (54.5)	
No response	2 (8.0)	10 (45.5)	
48 Hours			0.015
Response	23 (92.0)	18 (81.8)	
No response	2 (8.0)	4 (18.2)	
Vomiting			
Recovery room to ward	0 (0)	0 (0)	
Ward to 24 hr	0 (0)	0 (0)	
24–48 hr	0 (0)	0 (0)	
48–72 hr	0 (0)	0 (0)	
NSS score			
Recovery room to ward			0.635
None	18 (72.0)	17 (77.3)	
Mild	6 (24.0)	4 (18.2)	
Moderate	0 (0)	1 (4.5)	
Severe	1 (4.0)	0 (0)	
Ward to 24 hr			0.258
None	18 (72.0)	18 (81.8)	
Mild	4 (16.0)	3 (13.6)	
Moderate	1 (4.0)	1 (4.5)	
Severe	2 (8.0)	0 (0)	
24–48 hr			0.411
None	23 (92.0)	21 (95.5)	
Mild	1 (4.0)	1 (4.5)	
Moderate	1 (4.0)	0 (0)	
Severe	0 (0)	0 (0)	
48–72 hr			0.632
None	23 (92.0)	21 (95.5)	
Mild	2 (8.0)	1 (4.5)	
Moderate	0 (0)	0 (0)	
Severe	0 (0)	0 (0)	

Values are presented as number (%).
Group A, ramosetron group; group B, placebo group; NSS, nausea severity scale.

ied over the last few years; however, which method or drug is most effective in reducing PONV is controversial. The etiology of PONV remains unclear, but is probably multifactorial. Independent PONV risk factors include female sex, nonsmoking status, history of PONV and/or motion sickness, and perioperative opioid use; the frequency of PONV is 10% for patients with no risk factor, but increases to 60% to 80% for patients with more than three risk factors [24, 25]. In this study, these factors were well controlled. The characteristics of the patients (including a history of PONV, motion sickness, or both), the anesthetic used, and operative data were similar for both groups.

In addition to the general risk factors of PONV, the central action of carbon dioxide, stretching of the peritoneum, and increased blood pressure in the peritoneal cavity after gas insufflation during laparoscopic surgery all have been proposed to provoke nausea and vomiting [26] by reducing intestinal blood flow [27] and inducing the release of emetogenic substances, including serotonin [28]. A variety of pharmacologic approaches (antihistamines, butyrophenones, and dopamine receptor antagonists) have been investigated for the prevention and treatment of PONV. However, use of traditional antiemetics, such as droperidol and metoclopramide, has been limited due to undesirable adverse effects, including excessive sedation, hypotension, dry mouth, dysphoria, hallucinations, and extrapyramidal symptoms [7-9, 29]. Considering the etiopathogenetic mechanism of PONV after laparoscopic colorectal surgery, 5-HT_3 antagonists may be more effective than other antiemetics in preventing and treating PONV without these adverse effects. In this background, injection of the long-acting 5-HT_3 receptor antagonist ramosetron has emerged as an effective method for reducing PONV in patients who have undergone many different kinds of surgeries [10, 13, 15-21]. The most common adverse events caused by 5-HT_3 antagonists are headache and dizziness. The current study found no difference in

the incidence of these side effects between the groups, and no clinically important adverse events occurred. In the present study, treatment with ramosetron was more effective for preventing PONV than the placebo at 0–24 and 24–48 hours after surgery. This result was consistent with those of previous studies.

A limitation of this study was the differences in the types of operations that the patients underwent. In group A (ramosetron), 8 patients (32%) underwent a right hemicolectomy or an extended right hemicolectomy, compared with 1 patient (4.5%) in group B (placebo). Operations managing the right-side colon have more contact with the small intestines, which might result in dysfunction of bowel motility. The randomization protocol did not consider the types of operations that the patients were scheduled for. Future studies regarding the effect of ramosetron in reducing PONV after laparoscopic colorectal surgeries should consider the specific operation type.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Apfel CC, Korttila K, Abdalla M, Kerger H, Turan A, Vedder I, et al. A factorial trial of six interventions for the prevention of postoperative nausea and vomiting. N Engl J Med 2004;350:2441-51.
2. Tramèr MR. Strategies for postoperative nausea and vomiting. Best Pract Res Clin Anaesthesiol 2004;18:693-701.
3. Cohen MM, Duncan PG, DeBoer DP, Tweed WA. The postoperative interview: assessing risk factors for nausea and vomiting. Anesth Analg 1994;78:7-16.
4. Gan TJ, Ginsberg B, Grant AP, Glass PS. Double-blind, randomized comparison of ondansetron and intraoperative propofol to prevent postoperative nausea and vomiting. Anesthesiology 1996;85:1036-42.
5. Zmora O, Hashavia E, Munz Y, Khaikin M, Shabtai M, Ayalon A, et al. Laparoscopic colectomy is associated with decreased postoperative gastrointestinal dysfunction. Surg Endosc 2009;23:87-9.
6. Braga M, Vignali A, Zuliani W, Radaelli G, Gianotti L, Martani C, et al. Metabolic and functional results after laparoscopic colorectal surgery: a randomized, controlled trial. Dis Colon Rectum 2002;45:1070-7.
7. Alexander R, Lovell AT, Seingry D, Jones RM. Comparison of ondansetron and droperidol in reducing postoperative nausea and vomiting associated with patient-controlled analgesia. Anaesthesia 1995;50:1086-8.
8. Dresner M, Dean S, Lumb A, Bellamy M. High-dose ondansetron regimen vs droperidol for morphine patient-controlled analgesia. Br J Anaesth 1998;81:384-6.
9. Walder AD, Aitkenhead AR. Antiemetic efficacy of metoclopramide when included in a patient-controlled analgesia infusion. Anaesthesia 1994;49:804-6.
10. Gombar S, Kaur J, Kumar Gombar K, Dass A, Singh A. Superior anti-emetic efficacy of granisetron-dexamethasone combination in children undergoing middle ear surgery. Acta Anaesthesiol Scand 2007;51:621-4.
11. Paech MJ, Rucklidge MW, Lain J, Dodd PH, Bennett EJ, Doherty DA. Ondansetron and dexamethasone dose combinations for prophylaxis against postoperative nausea and vomiting. Anesth Analg 2007;104:808-14.
12. Rabasseda X. Ramosetron, a 5-HT3 receptor antagonist for the control of nausea and vomiting. Drugs Today (Barc) 2002;38:75-89.
13. Hirata T, Keto Y, Funatsu T, Akuzawa S, Sasamata M. Evaluation of the pharmacological profile of ramosetron, a novel therapeutic agent for irritable bowel syndrome. J Pharmacol Sci 2007;104:263-73.
14. Noda K, Ikeda M, Yoshida O, Yano S, Taguchi T, Shimoyama T, et al. Clinical evaluation of Ramosetron injections in the treatment of cisplatin-induced nausea and vomiting. J Int Med Res 2002;30:211-9.
15. Lee HJ, Kwon JY, Shin SW, Kim CH, Baek SH, Baik SW, et al. Preoperatively administered ramosetron oral disintegrating tablets for preventing nausea and vomiting associated with patient-controlled analgesia in breast cancer patients. Eur J Anaesthesiol 2008;25:756-62.
16. Fujii Y, Tanaka H. Comparison of granisetron and ramosetron for the prevention of nausea and vomiting after thyroidectomy. Clin Ther 2002;24:766-72.
17. Kim SI, Kim SC, Baek YH, Ok SY, Kim SH. Comparison of ramosetron with ondansetron for prevention of postoperative nausea and vomiting in patients undergoing gynaecological surgery. Br J Anaesth 2009;103:549-53.
18. Choi DK, Chin JH, Lee EH, Lim OB, Chung CH, Ro YJ, et al. Prophylactic control of post-operative nausea and vomiting using ondansetron and ramosetron after cardiac surgery. Acta Anaesthesiol Scand 2010;54:962-9.
19. Ryu J, So YM, Hwang J, Do SH. Ramosetron versus ondansetron for the prevention of postoperative nausea and vomiting after laparoscopic cholecystectomy. Surg Endosc 2010;24:812-7.
20. Choi YS, Shim JK, Yoon DH, Jeon DH, Lee JY, Kwak YL. Effect of ramosetron on patient-controlled analgesia related nausea and vomiting after spine surgery in highly susceptible patients: comparison with ondansetron. Spine (Phila Pa 1976) 2008;33:E602-6.
21. Hahm TS, Ko JS, Choi SJ, Gwak MS. Comparison of the prophylactic anti-emetic efficacy of ramosetron and ondansetron in patients at high-risk for postoperative nausea and vomiting after total knee replacement. Anaesthesia 2010;65:500-4.
22. Meek R, Egerton-Warburton D, Mee MJ, Braitberg G. Measurement and monitoring of nausea severity in emergency department patients: a comparison of scales and exploration of treatment efficacy outcome measures. Acad Emerg Med 2015;22:685-93.

23. Boogaerts JG, Vanacker E, Seidel L, Albert A, Bardiau FM. Assessment of postoperative nausea using a visual analogue scale. Acta Anaesthesiol Scand 2000;44:470-4.
24. Apfel CC, Roewer N. Risk assessment of postoperative nausea and vomiting. Int Anesthesiol Clin 2003;41:13-32.
25. Chatterjee S, Rudra A, Sengupta S. Current concepts in the management of postoperative nausea and vomiting. Anesthesiol Res Pract 2011;2011:748031.
26. Leksowski K, Peryga P, Szyca R. Ondansetron, metoclopramid, dexamethason, and their combinations compared for the prevention of postoperative nausea and vomiting in patients undergoing laparoscopic cholecystectomy: a prospective randomized study. Surg Endosc 2006;20:878-82.
27. Caldwell CB, Ricotta JJ. Changes in visceral blood flow with elevated intraabdominal pressure. J Surg Res 1987;43:14-20.
28. Diebel LN, Dulchavsky SA, Wilson RF. Effect of increased intraabdominal pressure on mesenteric arterial and intestinal mucosal blood flow. J Trauma 1992;33:45-8.
29. Watcha MF, White PF. Postoperative nausea and vomiting. Its etiology, treatment, and prevention. Anesthesiology 1992;77:162-84.