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Ramosetron vs. ramosetron plus dexamethasone for the prevention of postoperative nausea and vomiting (PONV) after laparoscopic cholecystectomy: Prospective, randomized, and double-blind study

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ABSTRACT

Introduction: Up to 75% of the patients undergoing laparoscopic cholecystectomy develop postoperative nausea and vomiting (PONV). Both ramosetron, a serotonin subtype 3 (5-HT_3) antagonist, and dexamethasone are effective for PONV prophylaxis following laparoscopic cholecystectomy but their combined effect has not been investigated. We investigated the efficacy and tolerance of ramosetron alone and ramosetron with dexamethasone for PONV prophylaxis after laparoscopic cholecystectomy.

Methods: Seventy six patients scheduled for laparoscopic cholecystectomy were randomized to receive either intravenous (i.v.) 0.3 mg ramosetron (group R), or 8 mg dexamethasone plus 0.3 mg ramosetron (group D). Standardized anesthesia with desflurane and remifentanil was used in all patients. Postoperative nausea, retching, vomiting, rescue antiemetics, pain scores, rescue analgesics and side effects were assessed at 0–2, 2–24 and 24–48 h postoperatively.

Results: Seventy two patients were randomized. The overall incidence of PONV did not differ ($p = 0.31$) but fewer patients needed rescue antiemetics in group D than in groups R (3 vs. 13 patients, respectively; $p = 0.01$) during 0–48 h postoperatively. Additionally, pain scores were significantly lower in group D during the study period ($p < 0.01$) and rescue analgesics were required less often in group D during 2–48 h postoperatively ($p < 0.01$).

Conclusions: In patients undergoing laparoscopic cholecystectomy, the combined use of ramosetron and dexamethasone was more effective than ramosetron alone for reducing the need for rescue antiemetics and pain control following the procedure.

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1. Introduction

Laparoscopic cholecystectomy (LC) is frequently performed for gallbladder stones or polyps. Postoperative nausea and vomiting (PONV) is one of the most common adverse events after laparoscopic surgery with reported incidences of 40–75%.[1] This undesirable side effect may delay postoperative recovery and discharge, so the prophylactic use of antiemetics for high-risk patients is required to reduce hospital costs and increase patient satisfaction.[2]

In numerous investigations, PONV in patients scheduled for LC has been prevented and treated with a variety of antiemetics including anticholinergics,[3] antihistamines,[4] butyrophenones,[5] benzamide,[1,6] dexamethasone,[7-9] and 5-HT_3 antagonists.[1,3,4,6,7] Among the numerous antiemetic therapies, a combination of a serotonin receptor antagonist (*e.g.* ondansetron, granisetron, tropisetron, dolasetron, and ramosetron) with dexamethasone is considered to be highly effective for preventing PONV after LC. Ramosetron, a 5-HT_3 receptor antagonist, has prophylactic antiemetic effects after LC.[10] Dexamethasone, alone or in combination with other 5-HT_3 antagonists, is effective for preventing PONV, pain control and improving the recovery profile after LC.[7–9]

A Pubmed search using terms of “ramosetron” and “ dexamethason” revealed no studies of the combined effects of ramosetron plus dexamethasone for preventing PONV. We hypothesized that a combination of dexamethasone and ramosetron would be more effective for PONV prophylaxis and pain control than ramosetron alone after LC. Therefore, we designed and conducted a prospective, randomized, and double-blind study to compare the efficacy and tolerability of intravenous (i.v.) ramosetron plus dexamethasone and ramosetron alone for the prophylaxis of PONV in patients undergoing LC.

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2. Methods

This prospective, randomized, and double-blind investigation was registered with the Clinical Research information Service (CRiS, registration number KCT0000267) and the study protocol was approved by the Institutional Review Board of Seoul National University Bundang Hospital (No. B-1109-135-301). After then, informed consent from each patient, a total of 76 American Society of Anesthesiologist (ASA) physical status I–II subjects, aged 25–65 years, and scheduled for elective LC under general anesthesia from October 2011 to January 2012 were enrolled. Exclusion criteria included: gastrointestinal disease, obesity (more than 50% greater than their ideal body weight), pregnancy or menstruation, history of motion sickness and/or postoperative emesis, diabetes mellitus, use of steroids or antiemetics within 1 month of surgery and history of allergy to any study medication.

Patients were randomized to receive either intravenous ramosetron alone (group R, $n = 38$) or intravenous ramosetron plus dexamethasone (group D, $n = 38$) using a computer-generated randomization code (Random Allocation Software Version 1.0) with block size 4. Randomization was performed before the induction of anesthesia by an independent anesthesiologist who is responsible for patient allocation and not otherwise involved in this study. Study medications were prepared by an anesthetic nurse not involved in this study. Study medications consisted of (1) an identical syringe with 2 ml solution with normal saline for group R or 8 mg dexamethasone (Dexamethasone®; Daewon Pharm., Seoul, Korea) for group D, administered immediately after the induction of anesthesia and (2) a syringe with 2 ml solution with 0.3 mg ramosetron (Nasea® injectable; Astellas Pharma Inc., Tokyo, Japan) which was injected at the end of surgery. Syringes were labeled with the patient's inclusion number and passed to the anesthesiologist. Patients, anesthesiologists, and outcome assessors were blinded to group assignment.

Patient received IV 0.03 mg/kg midazolam as a pre-anaesthestic medication. On arrival in the operating room, standard monitors with continuous electrocardiogram, noninvasive blood pressure, pulse oximetry and capnography were applied to the patient. Anesthesia was induced with i.v. 2 mg kg^{-1} propofol and 3–4 ng ml^{-1} remifentanil target-controlled infusion; 0.6 mg kg^{-1} rocuronium was administered prior to endotracheal intubation. Immediately after the induction of anesthesia, study medication (normal saline or dexamethasone) was administered to the patient by the blinded anesthesiologist. Maintenance of anesthesia consisted of desflurane 4.0–6.0% (inspired concentration), medical air in oxygen ($FiO_2 = 0.5$) and IV remifentanil 2–3 ng ml^{-1}. Ventilation was mechanically controlled and an end-tidal concentration of carbon dioxide was maintained between 4.5 and 5.0 kPa throughout the surgery. Muscle relaxation was achieved with rocuronium, as required. Nasopharyngeal temperature was monitored and maintained at 36–37 °C throughout the surgery using a warming pad. Lactated Ringer's solution was infused at the rate of approximately 10 ml kg^{-1} h^{-1} during the surgery. At the end of the procedure, desflurane and remifentanil administration were discontinued and 0.3 mg ramosetron was administered intravenously. Muscle relaxation was reversed with i.v. 0.01 mg kg^{-1} glycopyrrolate and 0.04 mg kg^{-1} neostigmine. Extubation was done after spontaneous ventilation of the patient became adequate.

Patients' characteristics including age, gender, weight, height, non smoking status, Apfel simplified risk scores[11] and information on surgery and anesthesia were collected. All patients were transferred to the post-anesthesia recovery unit (PACU) until they fulfill discharge criteria and then moved to the ward. Episodes of nausea, retching and vomiting and the requirement of rescue antiemetics were recorded at three assessment periods, 0–2 h, 2–24 h, and 24–48 h, by a nursing staff blinded to treatment assignment. Nausea was defined as a subjectively unpleasant inclination to vomit; retching was defined as an involuntary effort to vomit without expulsion of gastric contents; vomiting was defined as actual expulsion of gastric contents from the mouth.[12] The degree of nausea (NRS; numerical rating scale, with 0 = none to 100 = most severe) was assessed verbally in order to guide the need of rescue antiemetics and this data was not part of analysis. The rescue antiemetic was i.v. metoclopramide (10 mg), which was administered to patients with an NRS for nausea > 30 or more than one episode of vomiting.

During the 0–48 h postoperative study period, patients were asked to evaluate their level of postoperative pain verbally, using NRS (0 = none to 100 = most severe). An i.v. bolus dose of 30 mg ketorolac was administered to the patient with an NRS >30. In addition, possible adverse effects related with ramosetron and dexamethasone, such as QTc interval prolongation, headache, dizziness, wound infection, stomach pain and increased appetite were also recorded.

In a preliminary study, 10 patients (with the same inclusion and exclusion criteria) undergoing LC were administered IV ramosetron at the end of surgery and the PONV incidence at postoperative 0–48 h was 40%. Reduction the incidence of PONV from 40% to 10% was considered to be clinically important. The analysis using sample size software (PASS 2005®, NCSS, USA) showed that 36 patients per group (power of 80% and type I error of 5%) would be sufficient to detect the antiemetic effect of ramosetron plus dexamethasone. Assuming a 5% dropout rate, the final sample size was set at 38 patients per group.

Analysis was performed using SPSS version 15.0 for Windows (SPSS, Chicago, IL, USA). Student's *t*-test (two-sided) was used to compare continuous variables (age, weight, height, anesthesia time, operation time, dose rate of remifentanil, and pain NRS). The *Chi-square* test was used to analyze categorical variables (gender, ASA class, nonsmoking status, Apfel score, nausea, retching, vomiting, rescue antiemetics, rescue analgesics and adverse effects). Data are presented as mean (SD) or as count (n). Two-sided *P*-values of <0.05 were considered statistically significant.

3. Results

Of the 76 patients enrolled in this study, 4 patients were excluded for conversion to open cholecystectomy (2 patients in group R, 1 patient in group D) and protocol violations (1 patient in group D, ondansetron as rescue antiemetic instead of metoclopramide). A total of 72 patients were randomized to 1 of 2 study groups (Fig. 1). Patient characteristics including age, weight, height, gender, non smoking status, ASA class, Apfel scores and information on surgery and anesthesia are presented in Table 1.

Cumulative results for the 0–48 h study period showed that there was no difference in the overall incidence of PONV ($p = 0.31$) but the requirements for rescue antiemetics were lower in group D than in groups R (13 patients for group R vs. 3 patients for group D; $p = 0.01$, Table 2).

The incidence of nausea of group D was comparable with that of group R during the first 24 h. However, the degree of nausea was less severe and therefore rescue antiemetics were less required in group D than in group R (8% [$n = 3$] in group D vs. 33% [$n = 12$] in group R during the first 2 h postoperatively [$p = 0.02$], and 3% [$n = 1$] group D vs. 22% [$n = 8$] in group R during the postoperative 2–24 h [$p = 0.03$]). No inter-group difference was observed during 24–48 h postoperatively in the incidence of nausea and the need for rescue antiemetics ($p = 1.0$) (Table 2). Retching, vomiting, and overall incidence of PONV were not different between the two groups during 0–2, 2–24 and 24–48 h postoperatively (Table 2).

Pain scores during 0–2, 2–24 and 24–48 h were significantly lower in group D than in group R ($p < 0.01$, Table 3) and rescue analgesics were required less frequently in group D than group R during 2–24 ($p < 0.01$) and 24–48 h ($p < 0.01$, Table 3) postoperatively.

No difference was observed in common adverse events related to ramosetron or dexamethasone treatment between the two groups. Headache (2 patients in group R and 1 patient in group D) and dizziness (3 patients in group R and 1 patient in group D) were the most common adverse effects (Table 3).

4. Discussion

The findings of this prospective, randomized, double-blind trial revealed that a combination of ramosetron and dexamethasone reduced the requirement for rescue aniemetics and postoperative pain compared with ramosetron alone and caused no adverse effects during the first 48 postoperative hours in patients undergoing LC.

No control group was included in this study because patients undergoing LC are at high risk of PONV with reported incidences ranging from 75 to 83%[8] and withholding prophylactic antiemetics from these patients would be unethical. Besides the general risk factors of PONV such as female gender, a history of motion sickness or PONV, nonsmoking status and the use of postoperative opioid,[11] prolonged carbon dioxide insufflations and increased intracranial pressure by cerebral vasodilation may contribute to the high incidence of PONV after LC.[13] The 5-HT_3 antagonists ramosetron has been administered as an antiemetic after LC[10] and combined antiemetic agents targeting different receptors are recommended for prophylactic use in groups at high risk of PONV.[2] The glucocorticoid, dexamethasone produces an antiemetic effect, possibly via the release of endorphin and inhibition of prostaglandin and serotonin production.[14] In this study, the incidence of PONV for 48 h postoperatively was 39% with ramosetron alone and 28% with ramosetron plus dexamethasone. The addition of dexamethasone to ramosetron did not reduce the overall incidence of PONV

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