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The Influence of Ramosetron on the Analgesic Effect of Tramadol

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Abstract

Background: The 5-hydroxytryptamine-3 antagonist antiemetics block the analgesic effect of tramadol. This prospective, randomized single-blinded study was designed to investigate the interaction between ramosetron and tramadol in females undergoing thyroidectomy.

Method: We randomized 128 patients into two groups to receive ramosetron-tramadol (group R) or normal saline-tramadol (group N). Intravenous ramosetron (0.3 mg) or normal saline was administered at the induction of anesthesia, and 50 mg tramadol were given intravenously for postoperative analgesia 30 min before extubation. The analgesic regimen in the post-anesthesia care unit included additional 50 mg doses of tramadol if pain scores were >40 at rest. Postoperative pain was evaluated using an 11-point visual analog scale at 1 and 24 h postoperatively. Pain and nausea scores, analgesic and antiemetic doses, side effects, patient satisfaction with pain management, and postoperative nausea and vomiting were recorded 1 and 24 h after surgery.

Results: The control group received 169.67 ± 46.80 mg tramadol vs. 168.33 ± 46.9 mg in the ramosetron group during the first 24 h after surgery (p=0.875). Total antiemetic dose was significantly lower in the ramosetron group than that in the control (p=0.012).

Conclusions: We found that 0.3 mg ramosetron administered at the induction of anesthesia did not reduce the antinociceptive properties of tramadol.

Keywords: Ramosetron; Thyroidectomy; Tramadol

Introduction

Tramadol is widely used to manage postoperative pain because it is associated with a low incidence of respiratory depression and sedation and is considered safe [1]. However, tramadol promotes a high rate of nausea and vomiting. High 5-hydroxytryptamine (5-HT) levels may affect emesis because tramadol exerts its analgesic activity by inhibiting reuptake of norepinephrine and 5-HT [2]. Thus, 5-HT3 antagonists, such as ondansetron and ramosetron, might be a treatment option for tramadol-associated emesis. However, Arcioni et al. reported that concomitant use of ondansetron, an antiemetic that acts on 5-HT3 receptors, increases the tramadol dosage needed and decreases its analgesic effect because both tramadol and ondansetron are metabolized by CYP2D6 [3]. Tramadol is metabolized to M1 metabolites by hepatic cytochrome CYP2D6; M1 metabolites have 200-fold greater affinity for μ-opioid receptors than that of the parent compound [4,5]. CYP2D6 plays a role in the metabolism of 5-HT3 receptor antagonists. Competition for CYP2D6 reduces metabolism of tramadol to M1 metabolites and reduces the analgesic effect of tramadol given with ondansetron.

Ramosetron is very effective at preventing postoperative nausea and vomiting (PONV) in patients undergoing general anesthesia. However, no interaction between ramosetron and tramadol has been reported [6]. Ramosetron may not share this problem because it is metabolized chiefly by CYP1A2, whereas ondansetron is also degraded by CYP2D6 [7]. Thus, we hypothesized that ramosetron would not affect postoperative tramadol activity when administered preoperatively to prevent PONV. The primary study outcome was the difference in tramadol consumption between the two groups. The secondary outcomes were pain score and incidence of nausea and vomiting. The aim of this study was to assess the analgesic effect of tramadol when given with ramosetron in females undergoing total thyroidectomy.

Method

This study design was approved by the Institutional Review Board of the National Cancer Center. After providing written informed consent, 128 female patients (age range, 18-64 years; ASA physical status I or II), who were planned for elective thyroid surgery, were enrolled. We excluded patients with a known allergy to tramadol or ramosetron, alcoholism, epilepsy, nausea or vomiting within 24 h preoperatively, and patients receiving antiemetics, antidepressants, anticholinergics, antihistamines, or steroids within 24 h preoperatively, a smoking history, and history of motion sickness or PONV.

This was a randomized, placebo-controlled study. Eligible patients were allocated into group R (ramosetron) or group N (normal saline) using computer generated randomization. The study drugs were administered in 5 mL syringes containing either 0.3 mg ramosetron or placebo (0.9% saline) in 2 mL. All patients were administered the study medication 1 min before inducing anesthesia with intravenous (IV) propofol and rocuronium to facilitate neuromuscular blockade.

Endotracheal intubation was conducted and intermittent positive ventilation was provided to maintain end-tidal CO_2 of 35-40 mmHg. Anesthesia was maintained with 50% oxygen and sevoflurane and was altered to maintain a bispectral index of 40-60. Continuous

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remifentanil infusion was used for intraoperative analgesia, and rocuronium was used for muscle paralysis. All patients were given 50 mg IV tramadol for postoperative analgesia 30 min before extubation. Sevoflurane and remifentanil were stopped during skin closure, and the neuromuscular blockade was reversed using pyridostigmine with 0.5 mg glycopyrrolate IV. The total volumes of remifentanil and fluid infused during anesthesia were recorded.

The analgesic regimen in the postanesthesia care unit (PACU) included additional 50 mg doses of tramadol if pain scores were >40 at rest. Patients with a visual analog score (VAS) >40 after receiving 200 mg tramadol in total were administered fentanyl. If a patient experienced PONV, 10 mg metoclopramide was administered as a rescue antiemetic drug, and the total dose and nausea score were recorded (Table 1). A complete response was defined as no vomiting, a nausea score of zero, and no rescue therapy.

Pain intensity was evaluated 1 and 24 h postoperatively using a VAS in which pain was rated on a 0-10 cm scale (0=no pain and 10=the worst pain imaginable). Pain and nausea scores, analgesic and antiemetic doses, side effects, patient satisfaction with the pain therapy, and PONV during the first 24 h postoperatively were noted. These variables were evaluated by investigators blinded to the groups and were subdivided into two intervals of 0-1 h (at the PACU) and 1-24 h postoperatively. Nausea was defined as a subjectively unpleasant sensation associated with an awareness of the urge to vomit [8]. Nausea severity was evaluated using a 4-point scale (0=no nausea; 1=mild nausea not requesting pharmacological rescue; 2=moderate nausea requesting pharmacological rescue; 3=severe nausea resistant to pharmacological therapy) [9]. The patients were asked to rank their worst nausea over the time interval indicated. Vomiting was assessed as either present or absent. Adverse events were assessed and noted by the investigator during the first 24 h postoperatively. Patient satisfaction was ranked on a 5-point scale (very satisfied, satisfied, neutral, dissatisfied, and very dissatisfied) 24 h after surgery. Demographic data, including ASA physical status classification, age, and clinical data including duration of anesthesia and surgery, remifentanil and propofol doses during anesthesia, and VAS scores were analyzed.

A power analysis was performed using a power of 80% and α=0.05%. Based on our previous data, the respective consumption of tramadol would be 54.55 ± 21.85 (mean ± standard deviation) and 50 ± 40.31 mg in the ramosetron and saline groups, respectively. Sample size was calculated to be 58 patients/group; thus, 64 patients were included per group, assuming a 10% dropout rate. Statistical analyses were conducted with the χ^2 test for nonparametric data, such as the nausea and vomiting scores, pain scores, and patient demographic data, and parametric data were compared using the *t*-test. ASA physical status classification and the numbers of responders and non-responders were compared using the χ^2 test. A $p<0.05$ was considered significant.

Results

This study included 128 patients (64/group). Seven patients withdrew because they received a second antiemetic rescue (ramosetron) in the recovery room or they did not respond to the postoperative questionnaires. No significant differences in the demographic data, ASA class, anesthesia duration, duration of PACU stay, or total fluid volume infused were observed between the two groups (Table 2). The N group received 169.67 ± 46.80 mg tramadol *vs.* 168.33 ± 46.9 mg in R group ($p=0.875$) (Table 3) during the first 24 h after surgery. No difference was observed in the VAS score for nausea between the two groups. A complete response to antiemetic prophylaxis without nausea and vomiting during the first postoperative hour was accomplished in 59% and 78.3% of the N and R groups, respectively ($p>0.05$). The nausea scores (0/1/2/3) between 1 and 24 h postoperatively were (27.7/8.2/39.3/14.8%) and (50.0/16.7/20.0/13.3%) in the N and R groups, respectively. Twenty-nine patients (18 in group N, 11 in group R) were given antiemetic rescue medication in the recovery room, and 26 had their symptoms controlled after one dose. Three patients asked for additional treatment and were given a rescue antiemetic (one in group R and two in group N). Fifty patients (32 in group N and 18 in group R) were treated with rescue medication after transfer to the general ward; 40 patients (25/15) exhibited sufficient symptom control after one dose, whereas the symptoms were relieved after two doses in 10 patients (7/3). Nevertheless, the total antiemetic dose was significantly lower in the R group than that in the N group ($p=0.012$). The VAS scores for pain after 1 and 24 h did not differ between the groups. Satisfaction with the pain relief medication also did not differ between the groups. No major adverse effects were observed.

Discussion

Tramadol consumption did not differ significantly between the ramosetron and normal saline groups, confirming our hypothesis. We did not find an antagonistic antinociceptive interaction between tramadol and ramosetron. This confirmed our hypothesis that the analgesic efficacy of tramadol would not be reduced, as ramosetron has only minimal potential to cause clinically important CYP-mediated drug interactions *in vivo* [6].

Tramadol exerts its analgesic effect by inhibiting noradrenaline reuptake. It both increases the release and decreases reuptake of 5-HT in the spinal cord and has a weak effect on μ-opioid receptors [4,5]. The analgesic properties of tramadol are maintained by its active M1 metabolites, which are formed via the genetically polymorphic CYP2D6 iso-enzyme system [4]. However, CYP2D6 is also involved in forming the hydroxylated ondansetron metabolites [7]. Consequently, co-administering these drugs forces competition for CYP2D6 and influences the kinetics of ondansetron and tramadol, which may have been the cause for the significantly larger doses of tramadol needed. Two randomized controlled trials have shown increased tramadol consumption and reduced ondansetron efficacy upon co-administration [3,10]. Stammer explained that the P450 CYP2D6 isoenzyme reduces the analgesic effect of tramadol when it is co-administered with ondansetron [7].

Ramosetron is more potent and has a longer receptor-antagonizing effect than those of older 5-HT3 receptor antagonists [11]. In addition, the elimination half-life of ramosetron is longer than that of ondansetron or granisetron [12,13]. Ramosetron is metabolized chiefly by CYP1A2, whereas ondansetron is metabolized by multiple CYP isoforms [7]. Ramosetron was beneficial for reducing the use of rescue antiemetics 1 and 24 h postoperatively compared to that of placebo, although ramosetron failed to reduce rescue antiemetic use during the first hour. The recommended dose for preventing PONV is smaller; therefore, we used 0.3 mg ramosetron in this study. Smaller doses might be less effective in terms of blocking the analgesic effects of

	Grading criteria
Nausea	0 no nausea
	1 mild nausea not requesting pharmacological rescue
	2 moderate nausea requesting pharmacological rescue
	3 severe nausea resistant to pharmacological treatment

Table 1: The grades for nausea

Mean (SD)	Ramosetron (n=61)	Control (n=60)	P value
Age (years)	46.63 (10.4)	47.34 (9.3)	0.690
Weight(kg)	158.89 (5.65)	158.63 (5.0)	0.790
Duration of surgery (min)	68.36 (20.97)	70.89 (25.38)	0.549
Duration of anesthesia (min)	94.43 (24.85)	96.53 (25.71)	0.645
Amount of infused remifentanil	341.05 (150.83)	321.10 (143.46)	0.461
Amount of infused fluid	347.21 (188.39)	375.0 (187.47)	0.414
Duration of PACU stay	64.16 (11.5)	67.18 (14.07)	0.196

Table 2: Demographic and anesthesia data in ramosetron and control groups.

	Ramosetron (n=61)	Control (n=60)	P
VAS score 1 h postoperatively (mm)	3.15 (1.06)	3.38 (0.84)	0.192
VAS score 24 h postoperatively (mm)	1.88 (1.29)	2.33 (1.70)	0.109
Total dose of tramadol	168.33 (46.91)	169.67 (46.80)	0.091
Total dose of fentanyl	13.33 (24.12)	12.30 (25.26)	0.676
Number of patients to be needed rescue antiemetics (Postoperative 1 hour)	8(13.3%)	14(23%)	0.170
Number of patients to be needed rescue antiemetics (Postoperative between 1 hr and 24 hr)	18 (30%)	32 (52.5%)	0.012
Satisfaction (very satisfied /satisfied/neutral /dissatisfied/very dissatisfied)	10/39/10/0/0	11/36/12/0/0	0.962

Table 3: Postoperative responses

tramadol, making this interaction less important to prevent and treat PONV. Many clinical studies have investigated the impact of tramadol on postoperative pain. Tramadol has minimal effects on visceral function, gastrointestinal motility, and gastric emptying, [14] making tramadol suitable for ameliorating pain after abdominal surgery [15]. Tramadol (3 mg/kg) is as effective as morphine for pain management during the immediate postoperative period [16]. Therefore, Paola et al. reported that tramadol is a good alternative to morphine for treating postoperative pain [17]. However, tramadol use is associated with frequent PONV, limiting its usefulness [18]. Nausea and vomiting related to the initial tramadol dose can be almost completely avoided by administering the loading dose during surgery [18]. Therefore, we administered tramadol 30 min before extubation.

Our study had several limitations. First, no ondansetron prophylaxis group was included because ondansetron may cause widening of QRS and prolongation of QT waves by 5% [19]. Second, our study was conducted in a single-blinded manner. However, pain and nausea scores, analgesic and antiemetic doses, side effects, patient satisfaction with the pain therapy, and PONV during the first 24 h postoperatively were evaluated by investigators blinded to the groups. Third, no difference in satisfaction was observed between the ramosetron and control groups. We based the power analysis on tramadol consumption. The study sample size may have had limited power to evaluate patient satisfaction.

In conclusion, we found that 0.3 mg ramosetron administered at the induction of anesthesia did not reduce the antinociceptive properties of tramadol, and that a single 0.3 mg dose of ramosetron before induction of anesthesia reduced the total rescue antiemetics required, although it did not reduce the 24 h incidence of PONV. Therefore, we believe that ramosetron is the most efficacious choice when tramadol is used postoperatively.

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