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ORIGINAL ARTICLE

Effects of ramosetron and dexamethasone on postoperative nausea, vomiting, pain, and shivering in female patients undergoing thyroid surgery

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Abstract
Purpose Some antiemetics are effective in the treatment of postoperative pain and shivering, as well as for postoperative nausea and vomiting (PONV). The aim of this study was to investigate the effects of ramosetron and dexamethasone on PONV, pain, and shivering and to determine the correlations between nausea, pain, and shivering.
Methods For this study, 123 patients scheduled for thyroid surgery were randomly allocated to one of three groups: the control group (group C, $n = 41$), dexamethasone group (group D, $n = 41$), or the ramosetron group (group R, $n = 41$). The patients were treated intravenously with 2 mL of 0.9 % NaCl, 2 mL of 5 mg/mL dexamethasone, or 2 mL of 0.15 mg/mL ramosetron immediately after anesthesia.
Results The overall incidence and severity of postoperative nausea and the level of antiemetic consumption were significantly lower in group R compared with group D, and these parameters were significantly lower in groups R and D than in group C. There were significant differences in the incidence and severity of shivering, severity of pain, and analgesic consumption between group C and group R or D, but the incidence of shivering, pain severity, and analgesic consumption did not differ between groups R and D. The severity of shivering was significantly lower in group R than in group D. The correlation coefficients for shivering and pain, shivering and nausea, and pain and nausea were 0.210 ($P = 0.010$), 0.106 ($P = 0.198$), and 0.190 ($P = 0.035$), respectively, in group C.
Conclusions Two antiemetic drugs, ramosetron and dexamethasone, significantly reduced the incidence and severity of postoperative nausea and the need for administration of rescue antiemetic drugs. Furthermore, both drugs effectively decreased the severity of pain and shivering. Ramosetron was superior to dexamethasone for reducing nausea, antiemetic consumption, and the severity of nausea, but not for reducing the incidence of shivering. Further studies are required to elucidate the correlations between postoperative nausea, pain, and shivering, as a statistically significant but weak correlation was shown in the present study.

Keywords Antiemetics · Postoperative pain · Postanesthetic shivering · Postoperative nausea and vomiting

Introduction

Postoperative nausea and vomiting (PONV) and postoperative pain and shivering are common adverse side effects associated with surgery and are significantly troublesome conditions that occur during recovery from general anesthesia. It has been reported that the overall incidence of PONV ranges from 20 to 30 % in general surgery and is increased up to 80 % in high-risk surgical patients [1–3]. Postanesthetic shivering (PAS) has been reported to occur immediately after operation in 5–76 % of patients undergoing different kinds of surgeries [4]. Current multimodal approaches to manage PONV have led to treatments that can substantially reduce PONV. Some antiemetics have

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also been reported to decrease postoperative pain and shivering [5–7].

PONV and postoperative pain are separate outcomes, but anxiety, which can be associated with nausea, has been correlated with postoperative pain [8]. Postoperative pain facilitates nonthermoregulatory shivering, such as tremors [9].

The purpose of this study was to assess the effects of 2 antiemetics—ramosetron and dexamethasone—on PONV, pain, and shivering and to determine the correlations between nausea, pain, and shivering in female patients undergoing thyroid surgery.

Patients, materials, and methods

After obtaining approval from the Institutional Review Board at our institution and written informed consent from patients, 123 adult women (ages 20–65 years) with American Society of Anesthesiologists (ASA) classification I–II undergoing thyroid surgery were enrolled in this study.

Patients with a history of intolerance or allergy to any drugs used in the study, gastrointestinal disease, motion sickness, postoperative emesis, obesity (body mass index >35 kg/m^2), cardiovascular or respiratory disease, alcohol or opioid dependence, or renal or hepatic functional impairment, and those who were pregnant, menstruating, or had taken another antiemetic drug or a systemic steroid 24 h before surgery were excluded from the study.

A total of 123 patients scheduled for thyroid surgery were randomly (envelope randomization) allocated to one of three groups: the control group (group C, $n = 41$), dexamethasone group (group D, $n = 41$), or the ramosetron group (group R, $n = 41$). The patients were treated intravenously (i.v.) with 2 mL of 0.9 % NaCl, 2 mL of 5 mg/mL dexamethasone, or 2 mL of 0.15 mg/mL ramosetron immediately after anesthesia. The reasons we employed the doses mentioned above were as follows: (1) dexamethasone at a dose of 0.11–0.2 mg/kg is safe and effective as part of a multimodal pain strategy after surgical procedures [10]. (2) The manufacturer's recommended dose of ramosetron is 0.3 mg i.v. once a day.

All patients were premedicated with midazolam 2–3 mg before arrival in the operating room. The patients were fitted with routine monitors, including pulse oximeter, automated cuffed blood pressure (BP), electrocardiogram (EKG), and end-tidal CO_2 ($ETCO_2$). Tympanic temperature was measured immediately before induction of anesthesia and just before extubation.

Induction of anesthesia commenced with a slow (30–60 s) i.v. bolus dose of remifentanil 1 μg/kg, followed by propofol 1–2 mg/kg. Tracheal intubation was facilitated with rocuronium 0.9 mg/kg in all groups, desflurane at an initial end-tidal concentration of 1 minimum alveolar concentration (MAC), and an oxygen–air mixture (fraction of oxygen 50 %). A remifentanil infusion was titrated to maintain heart rate and arterial blood pressure within 20 % of the baseline values. The desflurane concentration was titrated in response to hemodynamic changes and then the remifentanil infusion was titrated as required.

At the end of the surgery, neuromuscular blockade was reversed with pyridostigmine 0.2 mg/kg and glycopyrrolate 0.008 mg/kg when the train-of-four (TOF) ratio had returned to 25 %. The remifentanil infusion was discontinued when the last surgical stitch was placed.

The primary outcome measures were the incidence and severity of nausea, the incidence of vomiting, and the amounts of rescue antiemetic administered at 5 postoperative time intervals (T1: 0–1 h, T6: 1–6 h, T12: 6–12 h, T24: 12–24 h, and T48: 24–48 h). Nausea was defined as a subjective, unpleasant sensation in the epigastrium and the throat, with the urge to vomit. Vomiting was defined as the forceful expulsion of gastric contents from the mouth. The severity of nausea was assessed via a visual analog scale (VAS), ranging from no symptoms (0 mm) to worst possible symptoms (100 mm). Nausea was also assessed with a verbal rating scale (VRS) divided into 4 grades: 0 mm, no symptoms; 10–30 mm, mild symptoms; 40–60 mm, moderate symptoms; and 70–100 mm, severe symptoms. We assessed nausea using both the VAS and VRS for the following reasons: (1) the VAS allows greater sensitivity for determining treatment effects than a categorical scale such as the VRS, as there is a greater range of possible scores, (2) the interpretation of statistically significant but small changes in a VAS can be difficult, (3) a VRS (4-grade scale) is usually reduced to a binary scale, which might be expected to further reduce its sensitivity compared with a continuous scale.

Metoclopramide 10 mg i.v. was given as a rescue antiemetic if more than 3 emetic episodes occurred or if the patient had severe nausea (greater than 30 mm on the 0- to 100-mm VAS).

Secondary outcome measures were severity of PAS, severity of postoperative pain 1 h after surgery, and total amount of rescue analgesic administered for 48 h postoperation. Time point 0 was defined as just after extubation. Postoperative pain scores for movement at 1 h after surgery were documented using a 100-mm linear VAS, which is a straight line with the left end of the line representing no pain and the right end of the line representing the worst pain. Patients were asked to mark the point on the line corresponding to the level of pain they were experiencing. In patients complaining of pain corresponding to 40 mm or more on the VAS, the pain was treated with ketorolac 30 mg i.v. PAS in the recovery room was graded (G) between 0 and 3 (G0, no shivering; G1, mild fasciculations of the face or neck; G2, visible tremors involving more than 1 muscle group; and G3, gross muscular activity

involving the entire body). PAS was treated with a forced air-warming blanket if the shivering grade was 2 or more. Pethidine was not administered to treat shivering because it could have affected PONV.

Calculation of sample size was performed using power analysis and sample size calculation software for Windows 2008 (Kaysville, Utah, USA). Degrees of freedom and effect size were 3 and 0.3, respectively. A sample size of 41 patients per group was needed to demonstrate a significant difference with a power of 80 % and an α-coefficient of 0.05. The results are presented as means ± SD or the number of patients (%). Comparisons of age, body weight, height, duration of surgery, tympanic membrane temperature, VAS for nausea and pain during movement at 1 h after surgery, and analgesic consumption (ketorolac) during the study period among groups were conducted using one-way analysis of variance (ANOVA). Post-hoc comparisons were performed by applying the Bonferroni correction to the significance level. The χ^2 test or Fisher's exact test was used to analyze categorical data, such as smoking status, type of surgery, severity of PONV, number of occasions rescue antiemetic drugs were administered, and severity of shivering. Correlations between PAS and pain intensity using VAS and correlations between PAS and nausea intensity using VAS were analyzed using Kendall's tau correlation analysis. In group C, the correlation between pain and nausea intensity was analyzed using Pearson correlation analysis. A P value of less than 0.05 was considered statistically significant.

Results

The 3 groups did not differ in terms of distribution of age, weight, height, smoking status, history of PONV, duration of surgery, the amount of intravenous fluid administered, type of surgery, or tympanic temperature immediately before induction or just before extubation. The VAS values for pain and ketorolac consumption were significantly lower in groups D and R than those in group C ($P < 0.05$), but the values were not significantly different between groups D and R (Table 1).

The overall incidence and severity of postoperative nausea and rescue antiemetic consumption were significantly lower in group R than in group D, and these parameters in groups R and D were significantly lower than those in group C during the 48 h post-surgery. At different time intervals, both group D and group R exhibited significant reductions in the incidence of nausea and use of rescue antiemetic drugs compared with group C. However, group R exhibited significant decreases in the severity and incidence of nausea and use of rescue antiemetic drugs compared with these parameters in group D. There were no differences in the incidence and severity of vomiting among the groups (Tables 2, 3).

Table 1 Demographic data in three treatment groups

	Group C ($N = 41$)	Group D ($N = 41$)	Group R ($N = 41$)
Age (years)	52.3 ± 7.5	54.2 ± 7.7	55.1 ± 7.5
Weight (kg)	60.3 ± 6.6	58.44 ± 6.7	60.6 ± 5.9
Height (cm)	159.2 ± 3.8	158.4 ± 3.4	160.0 ± 3.7
Smoking status	4 (9.8)	3 (7.3)	3 (7.3)
History of PONV	2 (4.9)	2 (4.9)	3 (7.3)
Duration of surgery (min)	139.8 ± 45.4	144.0 ± 48.6	142.2 ± 43.6
Intravenous fluid administered (ml)	1,106 ± 21	1015 ± 22	1120 ± 20
Type of thyroid surgery			
Lobectomy	8 (19.5)	6 (14.6)	7 (17.1)
Subtotal thyroidectomy	14 (34.1)	12 (29.3)	13 (31.7)
Total thyroidectomy	19 (46.3)	23 (56.1)	21 (51.2)
VAS pain score at 1 h after surgery	39.5 ± 9.5	32.0 ± 8.7*	34.2 ± 9.2*
Ketorolac consumption (mg)	36.6 ± 29.6	16.8 ± 23.3*	19.8 ± 26.5*
Tympanic temperature (°C)			
Immediately before induction	36.5 ± 0.1	36.6 ± 0.1	36.6 ± 0.1
Just before extubation	36.5 ± 0.1	36.5 ± 0.1	36.5 ± 0.1

Values are means ± SD or numbers (%)

PONV postoperative nausea and vomiting, *VAS* visual analog scale

* $P < 0.05$ versus group C

The overall incidence and severity of PAS for 1 h in the post-anesthesia care unit (PACU) were significantly lower in groups D and R than in group C. There was no significant difference in the overall incidence of shivering between groups D and R. However, group R treatment was more efficacious than group D treatment in reducing the severity of shivering (Table 4).

The correlation coefficients between shivering and pain, shivering and nausea, and pain and nausea were 0.210 ($P = 0.010$), 0.106 ($P = 0.198$), and 0.190 ($P = 0.035$) in group C. There were significant correlations between pain and nausea and between pain and shivering, but not between nausea and shivering (Table 5).

No side effects of the study drugs were observed (data not shown).

Discussion

PONV, pain, and shivering are 3 of the major concerns in patients undergoing surgery. Inadequate management of

Table 2 Incidence of nausea, vomiting, and use of rescue antiemetics at different time intervals

	Group C ($N = 41$)	Group D ($N = 41$)	Group R ($N = 41$)
T1			
Nausea	25 (61.0)	13 (31.7)*	5 (12.2)†
Vomiting	3 (7.3)	0 (0)	0 (0)
Rescue antiemetic	23 (56.1)	12 (29.3)*	4 (9.8)†
T6			
Nausea	24 (58.5)	14 (34.1)	4 (9.8)†
Vomiting	2 (4.9)	1 (2.4)	0 (0)
Rescue antiemetic	23 (56.1)	10 (24.4)*	0 (0)†
T12			
Nausea	16 (39.5)	8 (18.2)*	2 (4.9)†
Vomiting	2 (4.9)	1 (2.4)	0 (0)
Rescue antiemetic	10 (24.4)	6 (14.6)	0 (0)*
T24			
Nausea	12 (29.3)	6 (14.6)	2 (4.9)*
Vomiting	0 (0)	1 (2.4)	0 (0)
Rescue antiemetic	7 (17.1)	1 (24.4)	0 (0)*
T48			
Nausea	4 (9.8)	1 (2.4)	1 (2.4)
Vomiting	0 (0)	0 (0)	0 (0)
Rescue antiemetic	2 (4.9)	0 (0)	0 (0)
T1–48			
Nausea	25 (61.0)	14 (34.1)*	5 (12.2)†
Vomiting	3	1	0 (0)
Rescue antiemetic	23 (56.1)	12 (29.3)*	5 (12.2)†

T1, T6, T12, T24, times, 1, 6, 12, and 24 h after surgery; *T1-48* time from surgery to 48 h post-surgery

Values are numbers (%)

* $P < 0.05$ versus group C

† $P < 0.05$ versus other groups

PONV, pain, and shivering after surgery is associated with patient dissatisfaction. Besides causing distress, PONV increases the risk of other adverse events, including dehydration, delayed oral intake, and electrolyte imbalance. Postoperative pain contributes to the sympathetic stress response and can cause dysregulation of hemodynamic, endocrine, and autonomic parameters, as well as feelings of helplessness, fear, anxiety, and depression, which result in delayed recovery and may be detrimental to postoperative outcomes [2, 3, 11–13]. PAS, which is a troublesome condition, especially in patients with coronary artery disease, increases oxygen consumption (100–600 %), cardiac output, carbon dioxide production, circulating catecholamines, intracranial pressure, and intraocular pressure [4].

Some antiemetics have been demonstrated to be effective in the management of postoperative pain, shivering, nausea, and vomiting [5–7]. In the present study, our results indicate that the antiemetics ramosetron 0.3 mg and dexamethasone 10 mg decreased PAS, pain, and postoperative nausea. A single dose of dexamethasone given preoperatively decreased the incidence and severity of nausea and the need for rescue antiemetic drugs after surgery. The mechanism through which dexamethasone exerts its antiemetic effects has not yet been elucidated, but it is thought to involve the central inhibition of prostaglandin synthesis, inhibition of endogenous opioid release, decreased serotonin turnover in the central nervous system, and changes in the permeability of the blood–brain barrier to serum proteins [14, 15]. Preoperative dexamethasone may also reduce postoperative swelling and pain after various types of surgery by modulating the systemic physiologic response in favor of anti-inflammatory mediators [10, 16]. PAS is common, and may be a result of intraoperative hypothermia. Another possible etiology is fever and chills secondary to activation of the inflammatory response and release of cytokines. Dexamethasone decreases the gradient between core and skin temperature and modifies the inflammatory response [17, 18]. Ramosetron is a newly developed 5-HT_3 antagonist that possesses more potent and longer-acting properties than those of previously developed 5-HT_3 antagonists at equivalent doses [19, 20]. 5-HT_3 antagonists are a class of medications that act as receptor antagonists of the 5-HT_3 receptor, a subtype of serotonin receptor found in terminals of the vagus nerve in the gastrointestinal tract and in the chemoreceptor trigger zone of the brain that inhibit emetic symptoms. It has been reported that the analgesic effects of 5-HT_3 receptor antagonists are mediated by nociceptive or facilitatory signal transmission [7, 21–23]. The inhibitory activity of 5-HT_3 antagonists may be the result of the 5-HT_3-mediated enhancement of gamma-aminobutyric acid-mediated (GABAergic) inhibitory signaling. Descending serotonergic neurons from the rostral ventromedial medulla facilitate nociceptive signaling in models of cancer-induced bone pain, inflammatory pain, and neuropathic pain. Although studies demonstrating the role of the 5-HT_3 receptor subtype in 5-HT-mediated thermoregulation are sparse, PAS is known to be attenuated by pretreatment with a 5-HT_3 antagonist. The mechanism of action of these antagonists could be related to the inhibition of serotonin re-uptake in the pre-optic anterior hypothalamic region. 5-HT_3 receptors may also influence both heat-production and heat-loss pathways. However, 5-HT_3 antagonists do not affect the shivering threshold [24]. It has been reported that ramosetron reduced shivering during spinal anesthesia [6]. Ramosetron 0.3 mg in the present study reduced PAS after remifentanil-based general anesthesia, although the core temperature was not significantly different from that in the control group.

Table 3 Comparisons of nausea severity in the three treatment groups

Time interval after surgery	Severity	Group C ($N = 41$)	Group D ($N = 41$)	Group R ($N = 41$)
0–1 h	Mild	2 (4.9)	1 (2.4)	4 (9.8)
	Moderate	14 (34.1)	11 (26.8)	1 (2.4)†
	Severe	9 (22.0)	1 (2.4)*	0 (0)*
1–6 h	Mild	1 (2.4)	2 (34.1)	3 (7.3)
	Moderate	21 (51.2)	12 (2.4)*	1 (2.4)†
	Severe	2 (56.1)	0 (0)	0 (0)
6–12 h	Mild	1 (2.4)	2 (34.1)	2 (4.9)
	Moderate	15 (36.6)	6 (14.6)*	0 (0)†
	Severe	0 (0)	0 (0)	0 (0)
12–24 h	Mild	5 (12.2)	5 (12.2)	2 (4.9)
	Moderate	7 (17.1)	1 (2.4)*	0 (0)*
	Severe	0 (0)	0 (0)	0 (0)
24–48 h	Mild	2 (4.9)	1 (2.4)	1 (2.4)
	Moderate	2 (4.9)	0 (0)	0 (0)
	Severe	0 (0)	0 (0)	0 (0)

Values are numbers (%)

* $P < 0.05$ versus group C

† $P < 0.05$ versus other groups

Table 4 Numbers of patients with different severities of shivering in the three treatment groups

Severity	Group C ($n = 41$)	Group D ($n = 41$)	Group R ($n = 41$)
G0	23 (56.1)	32 (78.0)	37 (90.2)
G1	0 (0)	1 (2.4)	4 (9.8)
G2	13 (31.7)	8	0 (0)†
G3	5 (12.2)	0 (0)*	0 (0)*

Values are numbers (%)

G0 no shivering, *G1* mild fasciculations of the face or neck, *G2* visible tremor involving more than one muscle group, *G3* gross muscular activity involving the entire body

* $P < 0.05$ versus group C

† $P < 0.05$ versus other groups

Table 5 Correlations among severity of postanesthetic shivering, intensity of pain, and nausea at 1 h after surgery

	Postanesthetic shivering	Pain	Nausea
Postanesthetic shivering			
Correlation coefficient	1	0.210	0.106
Significance (*P* value)		0.010	0.198
Pain			
Correlation coefficient	0.210	1	0.190
Significance (*P* value)	0.010		0.035
Nausea			
Correlation coefficient	0.106	0.190	1
Significance (*P* value)	0.198	0.035	

In our present study, the correlation coefficients between shivering and pain, shivering and nausea, and pain and nausea were 0.210 ($P = 0.010$), 0.106 ($P = 0.198$), and 0.190 ($P = 0.035$) in group C. Although the correlation coefficients were low, there were significant correlations between pain and nausea and between pain and shivering, indicating that each of these factors affects the other. Shivering may be facilitated by postoperative pain and appeared to be associated with hyperalgesia in patients who received high intraoperative doses of remifentanil [9, 25]. This suggests that a common mechanism, in part mediated through activation of the central glutamatergic system such as by the activation of N-methyl-D-aspartate (NMDA) receptors, underlies the two effects induced by high-dose remifentanil [25]. Postoperative pain can be influenced by anxiety [26], which is associated with PONV [27].

Further studies are required to elucidate the correlations between PONV, pain, and shivering, as these were shown to be statistically significant, but weak in the present study. Although dexamethasone and ramosetron showed similar efficacy in terms of reduction of pain severity in the present study, ramosetron was superior to dexamethasone in the reduction of nausea, rescue antiemetic consumption, and severity, but not in reducing the incidence of shivering.

In conclusion, our results showed that ramosetron 0.3 mg was more efficacious than dexamethasone 10 mg when monotherapy against PONV and shivering was implemented, although the difference in cost between these drugs may affect the use of ramosetron.

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