Original Article

Effect of total intravenous anesthesia and prophylactic 5-HT3 receptor antagonist on postoperative nausea and vomiting after gynecologic laparoscopic surgery: A prospective, randomized controlled study

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Objective: To evaluate the efficacy of palonosetron and ramosetron for the prevention of PONV in high risk patients undergoing gynecologic laparoscopic surgery.

Methodology: In this randomized, double-blind, placebo-controlled study, a total of 87 female patients who were undergoing elective gynecologic laparoscopic surgery under general anesthesia were included. Patients were randomly divided into the following three groups: palonosetron group (0.075 mg i.v. n=29), ramosetron group (0.3 mg i.v. n=29) and control group (0.9 % normal saline i.v. n=29). The occurrence of nausea and vomiting and the severity of nausea were evaluated using visual analogue scale. Administration of rescue anti-emetics was monitored during 48 hours after the end of surgery.

Results: The incidence of nausea was significantly lower in the palonosetron and ramosetron groups compared with the control group (34.5% vs 31.0% vs 65.5%, p=0.014) during 2 hours postoperatively, but not during 48 hours postoperatively. There were no significant differences in the incidence of vomiting and overall PONV, and the administration of rescue anti-emetics among the 3 groups.

Conclusion: Prophylaxis with ramosetron or palonosetron effectively decreased PONV during the early postoperative period. (Rawal Med J 201;42:73-77)

Key words: Postoperative nausea and vomiting, palonosetron, ramosetron.

INTRODUCTION

Postoperative nausea and vomiting (PONV) is one of the most common postoperative complication. The incidence is 20-30% in the normal population and approximately 70% in high risk patients.[1,2] Apfel et al.[3] suggested that the risk factors of PONV are female gender, non-smoking status, history of PONV and motion sickness, and perioperative opioid use. Also, laparoscopic surgery can increase the risk of PONV than open abdominal surgery.[4] The patients who are non-smokers, undergo gynecologic laparoscopic surgery and have a history of postoperative opioid use for pain control have three risk factors of PONV and these patients are classified in the high risk group for PONV. Total intravenous anesthesia is recommended in such high risk patients for PONV.

Palonosetron and ramosetron are recently developed selective serotonin receptor antagonists, which are widely used to prevent PONV. However, there is little research on the preventive effects of palonosetron and ramosetron in high risk patients for PONV who receive gynecologic laparoscopic surgery under total intravenous anesthesia (TIVA). We designed this study to evaluate the efficacy of palonosetron and ramosetron for preventing PONV in high risk patients who have more than 3 risk factors, including female gender, non-smoking status and history of perioperative opioid use.

METHODOLOGY

A total of 87 women were enrolled in this prospective, double-blind and randomized study. The study was conducted in patients with American Society of Anesthesiology (ASA) physical status 1-2, aged 20-49 years, and who were non-smokers,

who requested for intravenous patient-controlled analgesia (PCA) for pain control after gynecologic laparoscopic surgery. Exclusion criteria were patients who had an allergic reaction or hypersensitivity to selective serotonin receptor antagonists, were smokers, did not want PCA, and were ASA 3 or more.The study was approved by the Institutional Review Board and a Written Informed consent was obtained from all patients.

Patients were divided randomly into three groups. In all groups, the patients received non-invasive blood pressure monitoring, electrocardiogram, peripheral oxygen saturation and bispectral index (BIS). Anesthesia was induced with total intravenous anesthesia using propofol and remifentanil. Effect site target-controlled infusion (TCI) of propofol was set at 3.0 mcg/ml and TCI of remifentanil was set at 3.0 ng/ml. Rocuronium 0.6 mg/kg was administered intravenously for tracheal intubation. After tracheal intubation, the lungs were mechanically ventilated with oxygen and medical air mixture as a fraction of inspired oxygen 50%. TCI effect site concentrations of propofol were adjusted to achieve a BIS of 40-60, and TCI effect site concentrations of remifentanil were adjusted to maintain the mean arterial pressure within 20% of preinduction values.

In group A, patients received 3 ml of a mixture that contained palonosetron 0.075 mg and normal saline, immediately before induction of anesthesia, and they received 3 ml of normal saline 30 minutes before the end of surgery. In group B, patients received 3 ml of normal saline before induction of anesthesia and they received 3 ml of a mixture containing ramosetron 0.3 mg and normal saline 30 minutes before the end of surgery. In group C, patients received 3 ml of normal saline before induction of anesthesia and 30 minutes before the end of surgery. The medications were prepared by a nurse who was not involved in this study. Fentanyl 1 mcg/kg was administered 30 minutes before the end of surgery in all patients. PCA was started after surgery as a total volume of 100 ml that contained 20 mcg/kg of fentanyl and normal saline. The PCA devices were programed to deliver a basal infusion rate of 0.5 ml/hr and a bolus dose of 2 ml on demand, with 15 minute lock-out time.

The postoperative pain, nausea, retching, and vomiting, the number of additional analgesics, and the rate of rescue anti-emetic use were recorded. Postoperative pain was estimated as a score using visual analogue scale (VAS) from 0 (no pain) to 10 (worst pain imaginable). When a patient experienced postoperative pain at a VAS score >4, ketorolac 30 mg was administered as an additional analgesic up to a maximal dose of 90 mg a day. Postoperative nausea was also estimated as a score using VAS from 0 (no nausea) to 10 (worst nausea imaginable). When a patient complained of nausea at a VAS score >4 with retching or vomiting, 4 mg of ondansetron was administered intravenously as a rescue antiemetic. When the symptom did not improve, 4 mg of ondansetron was administered again and if nausea persisted despite an additional dose of ondansetron, 0.3 mg of ramosetron was administered intravenously. Adverse effects were recorded. All assessments were done by anesthesiologists who were blinded to the study assignment at 30 min, 60 min, 90 min, 120 min, 6 hours, and 48 hours after the end of surgery.

Statistical Analysis: Sample size was estimated to show a 33% difference in the incidence of PONV, allowing an alpha error of 5%, a beta error of 20% and a dropout rate of 10%. The Chi square test was used to compare categorical variables among groups, while analysis of variance was used to compare continuous variables among groups.Two-way repeated measures analysis of variance (RM ANOVA) was used to compare repeated measurements among the three groups and within each group, and the Bonferroni procedure was applied in post-hoc analyses. The mean ± SE plots were also graphically presented. All statistical analyses were carried out using SPSS version 22.0.

RESULTS

A total of 87 female patients were included in the study. There were no differences in the demographic and basic operative data (Table 1). The overall incidence of PONV during postoperative 2 hours was 43.7%. The incidence of nausea after 2 hours was 34.5%, 31.0%, and 65.5% (p=0.014) in the palonosetron, ramosetron, and control groups, respectively (Table 2).

Table 1. Study patients' baseline characteristics.

Variable	Group A (n=29)	Group B (n=29)	Group C (n=29)	P value
Age (yrs)	40.00± 9.60	37.00± 8.65	37.97± 9.05	0.444
Height (cm)	159.02± 4.97	161.68± 5.94	160.52± 7.16	0.255
Weight (kg)	59.21± 9.54	58.53± 12.16	58.53± 7.62	0.874
BMI (kg/m^2)	23.40± 3.51	22.82± 4.00	22.87± 3.76	0.809
ASA				
1	19 (65.5)	19 (65.5)	20 (69.0)	0.950
2	10 (34.5)	10 (34.5)	9 (31.0)	
Apfel score				
3	19 (65.5)	18 (62.1)	16 (55.2)	0.713
4	10 (34.5)	11 (37.9)	13 (44.8)	
Anesthesia time (min)	111.03± 20.37	116.21± 25.97	106.21± 17.76	0.218
Surgery duration (min)	68.28± 21.06	73.97± 25.75	65.00± 16.48	0.278
Surgical type				
LAVH	16 (55.2)	13 (44.8)	12 (41.4)	0.549
Cystectomy	13 (44.8)	16 (55.2)	17 (58.6)	
Post-operative pain				
1 hrs	5.14± 2.15	4.86± 1.81	5.41± 1.88	0.562
24 hrs	3.00± 0.93 ab	2.83± 0.66 a	3.45± 1.06 b	0.028

Table 2. Incidence of nausea and vomiting.

Variable	Group A (n=29)	Group B (n=29)	Group C (n=29)	P-value
PONV				
Incidence				
120 min	**10 (34.5)**	**9 (31.0)**	**19 (65.5)**	**0.014**
48 hrs	16 (55.2)	9 (31.0)	16 (55.2)	0.104
Overlap*	8 (27.6)	6 (20.7)	14 (48.3)	0.065
Vomiting	1 (3.4)	3 (10.3)	1 (3.4)	0.428
Moderate				
120 min	5 (17.2)	4 (13.8)	7 (24.1)	0.585
48 hrs	5 (17.2)	4 (13.8)	8 (24.1)	0.585
Overlap*	2 (6.9)	2 (6.9)	3 (10.3)	0.856

*overlap: incidence of nausea and vomiting occurred at both 120 min and 48 hrs.

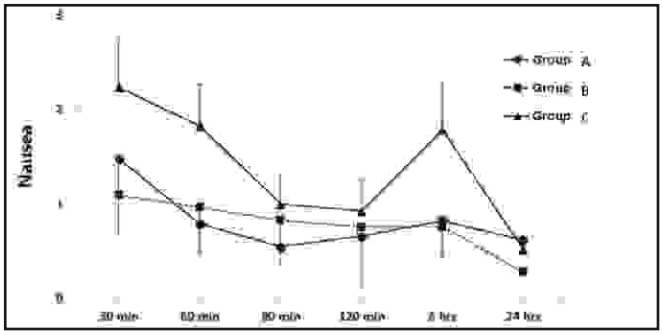
Table 3. Nausea scores at the six assessment time points, according to the treatment group.

Variable		Group			P value	
		Group A (n=29)	Group B (n=29)	Group C (n=29)	Time	Time x Group
Nausea						
30 min		1.48± 0.51 a	1.10± 0.43 a	2.24± 0.50 a	.000	.393
60 min		0.79± 0.29 a	0.97± 0.50 a	1.83± 0.44 a		
90 min		0.55± 0.21 a	0.83± 0.45 a	1.00± 0.30 b		
120 min		0.66± 0.55 a	0.76± 0.42 a	0.93± 0.33 b		
6hrs		0.83± 0.33 a	0.76± 0.30 a	1.79±0. 53 ab		
48hrs		0.62± 0.22 a	0.28± 0.16 a	0.52± 0.21 bc		
	p value[2]		0.227			

[1]Values are expressed as mean±SE and Bonferroni's post-hoc test was used for multiple comparisons. Means with different scripts are different from each other in each group (P<0.05).
[2]P values are derived from the between-group effect.

Overall, the 48 hour incidence of vomiting was not different among the three groups (p=0.428). Table 3 demonstrates the nausea score using VAS at different time points. At the time points of 30, 60, 90, and 120 minutes after surgery, the nausea score in the palonosetron and ramosetron groups was lower than that in control group; however, the result did not reach statistical significance (Table 3). The nausea scores changed during the six assessment time points (p<0.001), but this change was not affected by the treatment group (p=0.227) (Figure 1).

Figure 1. The changes in nausea score according to the assessment time points.



An adverse effect such as mild headache and dizziness was observed in one patient in the ramosetron group; however, the result did not reach statistical significance.

DISCUSSION

In this study, the incidence of PONV and severity of nausea were not different between the palonosetron and ramosetron groups among high risk patients who had more than 3 risk factors including female gender, non-smoking status, and history of perioperative opioid use. However, the incidence of PONV was significantly decreased in both treatment groups than in the normal saline group.

The mechanism of PONV is complex and it is still unclear. The emetic center located in the medulla is triggered by various signals from the following multiple areas: chemoreceptor trigger zone (CTZ), higher cortical centers, cerebellum, vestibular apparatus, glossopharyngeal and vagal afferent nerves. 5-HT3, opioid, muscarinic and dopamine type 2 receptors have been known to play role in emesis.[5] Presence of various stimuli is the basis for combination therapy with anti-emetics that have different mechanisms.

PONV can cause many troublesome events, such as wound dehiscence, electrolyte imbalance, aspiration, and prolonged hospital stay.[1] The patient-specific risk factors of PONV in the postanesthetic care unit (PACU) were female gender, age less than 50 year, previous history of PONV, and non-smoking status. The reason for non-smoking status being a risk factor is that chronic exposure to toxic gas (tobacco) may desensitize a patient's reaction to anesthetic gas. As another possible etiology, one of the chemicals in cigarette smoke may have an anti-emetic effect.[6] Also, other anesthesia and surgery related risk factors were higher doses of perioperative opioids, surgery duration of more than 1 hourand laparoscopic surgery.[7]

The 5-HT3 receptor antagonists are highly specific and selective for PONV. Members of the family of serotonin receptor antagonists exert their effects by binding to the 5-HT3 receptor in the chemoreceptor trigger zone and on vagal afferents in the gastrointestinal tract.[8] The most recently developed 5-HT3 receptor antagonist, palonosetron, which has a half-life of approximately 40 hours and moderate (62%) plasma protein binding, may provide a clinical advantage over other 5-HT3 antagonists.[9,10] Ramosetron has a higher affinity than ondansetron and granisetron. The efficacy was well maintained during a 48-h period, so that efficacy was significantly higher with ramosetron in terms of nausea and vomiting 6-48 h after treatment.[11]

In a previous study by Chun et al., palonosetron 0.075 mg injection after induction reduced the incidence of PONV than that in the placebo group during 24 h and 72 h after surgery.[12] Lee et al. reported a randomized study which showed similar efficacy of palonosetron, granisetron, and ramosetron for the prevention of PONV.[13]

In comparison with the previous report, the incidence of PONV was slightly lower in the control group. Although we included the high risk group of patients, our results showed a decreased rate of PONV than that in the previous study (65.5% vs 80%).[3] The difference in results may be explained by the use of TIVA in our study. TIVA is known to decrease PONV incidence compared to other inhalational agents.

Administration of anti-emetics is accompanied by the risk of side effects, which range from mild headache, dizziness to significant QTc prolongation.[14,15] Therefore, it is recommended to objectively evaluate the patient's baseline risk for PONV according to the validated risk score, which has reported a meaningful decrease in the incidence of PONV.[4,16,17] The Apfel simplified risk score is one of the most commonly used risk scoring system for PONV. It is based on 4 risk factors including female gender, history of PONV and/or motion sickness, non-smoking status, and postoperative opioid use. Presence of 3 or more risk factors has been considered to predispose the patient to high risk, and the incidence of PONV reaches 60-80%.[3]

The guidelines for the management of PONV published in 2014 by SAMBA recommended that PONV prophylaxis should be administered using 1 to 2 interventions in adult patients at moderate to high risk for PONV.[18]

The limitation of the study is that we compared ramosetron and palonosetron at the known optimal

doses instead of the equipotent doses. Despite prophylaxis using ramosetron and palonosetron, the incidence of PONV was found to be more than 30% in the high risk group. Therefore, further researches are needed to determine the combination prophylactic therapy for PONV including 5-HT3 receptor antagonists and other antiemetic drugs with different mechanisms of action.

CONCLUSION

Prophylactic therapy with ramosetron and palonosetron demonstrated equally preventive effect against PONV.

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REFERENCES

1. Gan TJ. Postoperative nausea and vomiting--can it be eliminated? JAMA 2002;287: 1233-6.
2. Watcha MF, White PF. Postoperative nausea and vomiting. Its etiology, treatment, and prevention. Anesthesiology 1992;77:162-84.
3. Apfel CC, Laara E, Koivuranta M, Greim CA, Roewer N. A simplified risk score for predicting postoperative nausea and vomiting: conclusions from cross-validations between two centers. Anesthesiology 1999;91:693-700.
4. 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.
5. Horn CC, Wallisch WJ, Homanics GE, Williams JP. Pathophysiological and neurochemical mechanisms of postoperative nausea and vomiting. Eur J Pharmacol 2014;722: 55-66.
6. Hough M, Sweeney B. The influence of smoking on postoperative nausea and vomiting. Anaesthesia 1998;53:932-3.
7. Apfel CC, Philip BK, Cakmakkaya OS, Shilling A, Shi YY, Leslie JB, et al. Who is at risk for postdischarge nausea and vomiting after ambulatory surgery? Anesthesiology 2012;117:475-86.
8. Habib AS, Gan TJ. Evidence-based management of postoperative nausea and vomiting: a review. Can J Anaesth 2004;51:326-41.
9. Siddiqui MA, Scott LJ. Palonosetron. Drugs 2004;64:1125-32; discussion 33-4.
10. Stoltz R, Cyong JC, Shah A, Parisi S. Pharmacokinetic and safety evaluation of palonosetron, a 5-hydroxytryptamine-3 receptor antagonist, in U.S. and Japanese healthy subjects. J Clin Pharmacol 2004; 44: 520-31.
11. Rabasseda X. Ramosetron, a 5-HT3 receptor antagonist for the control of nausea and vomiting. Drugs Today (Barc) 2002;38:75-89.
12. Chun HR, Jeon IS, Park SY, Lee SJ, Kang SH, Kim SI. Efficacy of palonosetron for the prevention of postoperative nausea and vomiting: a randomized, double-blinded, placebo-controlled trial. Br J Anaesth 2014;112:485-90.
13. Lee WS, Lee KB, Lim S, Chang YG. Comparison of palonosetron, granisetron, and ramosetron for the prevention of postoperative nausea and vomiting after laparoscopic gynecologic surgery: a prospective randomized trial. BMC Anesthesiol 2015;15:121. doi: 10.1186/s12871-015-0102-0
14. Charbit B, Albaladejo P, Funck-Brentano C, Legrand M, Samain E, Marty J. Prolongation of QTc interval after postoperative nausea and vomiting treatment by droperidol or ondansetron. Anesthesiology 2005;102:1094-1100.
15. Tricco AC, Soobiah C, Blondal E, Veroniki AA, Khan PA, Vafaei A, et al. Comparative safety of serotonin (5-HT3) receptor antagonists in patients undergoing surgery: a systematic review and network meta-analysis. BMC Med 2015;13:142. doi: 10.1186/s12916-015-0379-3
16. Pierre S, Benais H, Pouymayou J. Apfel's simplified score may favourably predict the risk of postoperative nausea and vomiting. Can J Anaesth 2002;49:237-42.
17. Pierre S, Corno G, Benais H, Apfel CC. A risk score-dependent antiemetic approach effectively reduces postoperative nausea and vomiting--a continuous quality improvement initiative. Can J Anaesth 2004;51:320-5.
18. Gan TJ, Diemunsch P, Habib AS, Kovac A, Kranke P, Meyer TA, et al. Consensus guidelines for the management of postoperative nausea and vomiting. Anesth Analg 2014;118:85-113.