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Effects of preoperative, scheduled administration of antiemetics in reducing postoperative nausea and vomiting in patients undergoing total knee arthroplasty

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Abstract

There is no established protocol regarding the timing of administration of antiemetics in patients undergoing total knee arthroplasty (TKA). The purpose of this study was to determine whether preoperative, rather than postoperative administration of an antiemetic could reduce postoperative nausea and vomiting (PONV) in patients undergoing TKA, and whether there was a difference in postoperative pain, patient satisfaction and complications after TKA between the 2 different administration times.

The included patients (N = 101) either received intravenous administration of the ramosetron 1 hour before surgery (N = 50) or at the end of surgery (N = 51) consecutively order. The incidence of PONV and the frequency of rescue medicine use were recorded until 48 hours postoperatively. The severity of postoperative pain and patient satisfaction were assessed using the visual analogue scale. The incidence of complications associated with use of antiemetic was assessed.

Preoperative administration of ramosetron did not decrease PONV during the first 48 hours. There was no significant difference in the incidence of nausea and vomiting, use of rescue antiemetics, and the severity of nausea ($P > .05$). Postoperative pain, satisfaction scores, and the incidence of complications were not different between the 2 groups ($P > .05$).

Preoperative administration of ramosetron did not show clinical advantage in reducing POVN, postoperative pain and improving patient satisfaction. However, the outcomes of complications were not inferior to those of postoperative administration. Therefore, under the current protocol of multimodal therapies, timing of administration of pre-emptive antiemetic did not have significant effect on PONV.

Abbreviations: LOS = length of stay, PAI = periarticular injection, PCA = patient-controlled analgesia, PONV = postoperative nausea and vomiting, TKA = total knee arthroplasty, VAS = visual analogue scale.

Keywords: antiemetics, PONV, TKA

1. Introduction

Postoperative nausea and vomiting (PONV) is a relatively common yet disconcerting side effect in patients undergoing total knee arthroplasty (TKA).[1] The incidence of PONV after TKA has been reported to be between 20% and 83%.[2,3] Prolonged PONV after surgery causes poor oral intake, delayed patient recovery, and an increase in the length of hospital stay (LOS).[4] Furthermore, PONV is associated with patient dissatisfaction after TKA[5,6]. Therefore, it is important to understand the management of PONV in patients undergoing TKA. Traditionally, antiemetics have been used depending on the patients needs after surgery. However, post-surgical administration of antiemetics alone cannot effectively control PONV[7]. Thus, recently

Editor: Arjun Ballal.

This work was supported by the Bio & Medical Technology Development Program of the National Research Foundation (NRF) funded by the Korean government (MSIT) (2017M3A9D8063538).

The authors have no conflicts of interests to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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How to cite this article: Park HJ, Chang MJ, Kang SB, Hwang Iu, Kim JS, Chang CB. Effects of preoperative, scheduled administration of antiemetics in reducing postoperative nausea and vomiting in patients undergoing total knee arthroplasty. Medicine 2021;100:1(e24143).

Received: 21 October 2020 / Received in final form: 4 December 2020 / Accepted: 7 December 2020

http://dx.doi.org/10.1097/MD.0000000000024143

there has been an interest in preemptive, scheduled use of antiemetic drugs for the prevention of PONV[8].

A systematic review reported that the administration of antiemetic drugs significantly affected PONV regardless of the type of surgery[9]. However, consensus remains to be established regarding the timing of administration of antiemetic drugs in patients undergoing TKA. In previous studies, the pre-emptive antiemetics were usually administrated at the end of surgery or at the induction of anesthesia[7,10,11]. However, despite administration of the antiemetics before an emetic event, the patients were already exposed to the noxious stimuli such as stress, anesthesia, and the surgical procedure[12,13]. Additionally, not only some patients experienced motion sickness when being transported from the ward to the operating room and some people complained of nausea, which arose from the stress response of the autonomic nervous system ahead of surgery.[14] The maximum intravenous level of ramosetron (5-HT3 receptor antagonist) is reached within 2 hours of administration and decreased by half at 6 hours after the injection.[15] However, the efficacy of the drug was maintained at 48 hours.[16,17] The known surgical time for primary TKA is known from 89 to 107 minutes[7,10,18]. Considering these findings, we hypothesized that the administration of ramosetron 1 hour before surgery would result in maximal level of the drug at the end of surgery and its effectiveness might be maintained until 48 hours after TKA. One study reported that preoperative use of aprepitant (NK1 receptor antagonist) 2 hours before surgery reduced the incidence of PONV after total hip arthroplasty and TKA.[19] However, no study has reported the effectiveness of ramosetron administrated 1 hour before surgery on PONV when the events were not triggered by noxious stimuli.

Pain control after surgery is associated with PONV. There are consistent reports in the literature regarding the effects of preemptive pain management on reducing postoperative pain and PONV.[20,21] However, the effects of scheduled administration of antiemetics in reducing postoperative pain remains controversial.[7,22,23]

The aims of this study were to determine whether preoperative scheduled administration of an antiemetic could reduce PONV after TKA compared to postoperative administration, and to determine whether there was a difference in postoperative pain, patient satisfaction, and complications after TKA between the 2 administration times. We hypothesized that preoperative administration of an antiemetic would reduce PONV compared to postoperative administration. We also hypothesized that preoperative administration of an antiemetic would reduce postoperative pain and improve patient satisfaction without increased complications compared to postoperative administration.

2. Methods

A total of 101 patients who underwent primary TKA due to end-stage osteoarthritis from July 2015 to January 2016 at our institution were included in this study. The study was designed according to a previous study on the effects of the ramosetron in reducing PONV in patients undergoing TKA.[7] Patients who underwent TKA (N = 178) were assessed for eligibility for inclusion in the study. Seventy seven patients were excluded based on the proposed exclusion criteria. The inclusion criterion was the patients with primary osteoarthritis undergoing unilateral TKA. The exclusion criteria were as follows:

1. patients undergoing TKA, not due to osteoarthritis;
2. revision TKA;
3. patients undergoing bilateral TKA;
4. patients with an allergy to 5-HT3 receptor antagonists;
5. history of other antiemetic drug use within 24 hours before surgery; and
6. history of cardiovascular or respiratory disease, alcohol or opioid dependence, and renal or hepatic failure (Fig. 1).

Approval was obtained from the Institutional Review Board of the authors hospital (IRB No.: 26-2015-16, SMG-SNU BMC) before commencement of the study. The study protocol was registered in the Clinical Research Information Service (Register number: KCT0005080). Informed consent was obtained from all participants included in this study.

There were several risk factors for PONV.[24] Among them, 4 risk factors which included female sex, history of PONV or motion sickness, nonsmoking status, and the use of postoperative opioids, were selected to calculate the risk for PONV in the patients. The simplified risk assessment tool described by Apfel et al was used to evaluate the risk for PONV.[25]

Eligible patients either received intravenous scheduled administration of 0.3 mg ramosetron 1 hour before surgery (pre-injection group) at ward or the end of surgery (post-injection group) at operating room by registered nurses in consecutive order. The antiemetic drug was injected preoperatively in the first 50 patients, and the same drug was injected postoperatively in the subsequent 51 patients undergoing TKA. All patients received the same anesthetic and multimodal pain management protocol, excluding the timing of antiemetic drug administration. Among the antiemetic drugs currently used, 5-hydroxy-tryptamine receptor 3 (5-HT3) antagonist (e.g., ondansetron, granisetron, and ramosetron) are most commonly used to prevent PONV. We chose ramosetron, as used in a previous study, due to its increased potency and longer-acting properties than other serotonin receptor antagonists.[7] Preemptive medication for multimodal pain management was given 1 hour preoperatively to all patients on a call basis and consisted of 200 mg celecoxib, 75 mg pregabalin, and 650 mg acetaminophen. Intravenous 5 mg dexamethasone was also used to reduce postoperative PONV. There were no differences between the 2 groups in terms of demographic data, duration of surgery, level of spinal anesthesia, the number of risk factors, and calculated mean risk for PONV (Table 1).

All surgical procedures were performed by one senior surgeon using the standard medial parapatellar arthrotomy approach with a tourniquet. Before cementation of the prosthesis, a periarticular cocktail injection, comprising 300 mg ropivacaine, 10 mg morphine sulfate, 30 mg ketorolac, 300 μg 1:1000 epinephrine, and 1 g cefazolin, was injected entirely throughout the joint capsule and synovium. After surgery, patients received intravenous patient-controlled analgesia (PCA), which was programmed to deliver 1 ml of a 100 ml solution containing 2000 μg fentanyl for the patients younger than 70 years and 1500 μg fentanyl for those older than 70 years. The device was programmed to be locked for 10 minutes if the patient pressed the button of the pump. Intramuscular injection of ketoprofen was administered for acute pain relief in case where the patient-reported severity of pain level was 6 or higher on a pain visual analogue scale (VAS).

Patients were monitored for PONV for the first 6 hours, followed by every 6 hours until 24 hours, and 24 to 48 hours

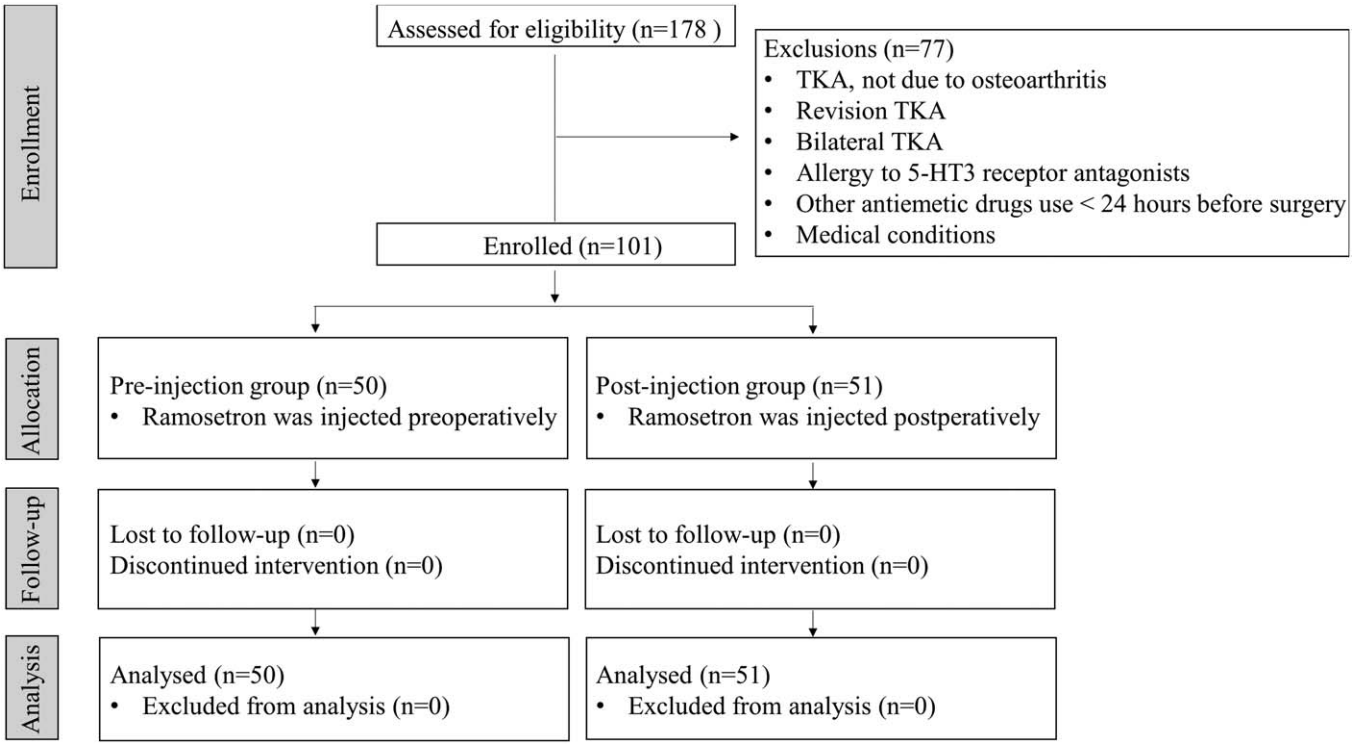

Figure 1. Flow chart for the study.

postoperatively by the same clinical investigator who did not have information on the injection method was used. Nausea was defined as the awareness of the urge to vomit or retch. The frequency and intensity of nausea were recorded. Nausea intensity was also assessed using a VAS (0–10; 0, no nausea and 10, most severe nausea). Vomiting was defined as the expulsion of the stomach contents through the mouth, and each episode of vomiting was recorded. Rescue antiemetics were administrated to patients with a VAS score of > 4 for nausea, an episode of vomiting, or upon their request. Intravenous injection of 10 mg metoclopramide was used as the first-line rescue antiemetic treatment, and if severe nausea persisted after 2 consecutive boluses of metoclopramide in a 30-minute interval; 4 mg ondansetron was administered intravenously as the second-line treatment. The VAS (0–10; 0, very dissatisfied, 10, very satisfied) was also used to assess patient satisfaction after 48 hours of surgery. Common adverse drug reactions associated with serotonin receptor antagonists such as headaches, dizziness, and drowsiness were also assessed and reported.

Table 1

Demographics and the risk factors for PONV.

	Preoperative injection (N = 50)	Postperative injection (N = 51)	*P* value
Demographic data			
Age (years)	71.3 ± 6.2	71.2 ± 5.9	.911
Proportion of female[a]	43 (86%)	47 (92%)	.321
Height (cm)	153.2 ± 6.7	153.7 ± 6.9	.666
Weight (kg)	61.4 ± 8.3	64.4 ± 10.6	.125
Body mass index (kg/m^2)	26.2 ± 3.2	27.3 ± 4.5	.171
Laterality (Right: Left)	22: 28	24: 27	.609
Duration of surgery (minutes)	95.9 ± 17.4	94.6 ± 12.8	.801
Level of spinal anesthesia	T5 (T1–T12)	T5 (T1–T10)	.553
Risk factors identified[b]			
With one factor	6	2	.133
With two factors	27	27	.915
With three factors	13	17	.420
With four factors	4	5	.750
Calculated mean risk[c]	2.3 ± 0.8	2.5 ± 0.7	.212

Data are presented as numbers of patients.

[a] Data are presented as number of female patients and their percentages in parentheses.

[b] The risk factors for PONV described by Murphy et al.

[c] Data are presented as calculated mean risk for PONV based on the risk scoring system described by Apfel et al.

PONV = postoperative nausea and vomiting.

The sample size was calculated based on the description in a previous study where the incidence of PONV was 54%.[7] Fifty patients were required in each group to determine a 50% reduction in the incidence of PONV. Continuous variables between 2 groups such as age, height, weight, body mass index, duration of surgery, calculated mean risk, VAS scores were analyzed by the Student *t* test. Chi-Squared or Fisher exact tests were used for categorical variables such as sex, risk factor for PONV, incidence of emetic events and frequency of antiemetic rescue medicine use. All analyses were performed with SPSS for Windows version 26.0 (SPSS Inc, Chicago, IL). *P* value of <.05 was considered statistically significant.

3. Results

Preoperative administration of ramosetron did not decrease PONV during the first 48 hours. Although there was a tendency of reduced incidence of nausea in the preoperative injection group compared to the postoperative injection group (62% vs 86%,

Table 2

Incidence of emetic events and use of rescue antiemetics in Preoperative injection and Postinjection group.

	Preoperative injection (N = 50)	Postperative injection (N = 51)	*P* value
Nausea			
For 48 hours	31 (62%)	43 (86%)	.075
0–6 hours	11	10	.767
6–24 hours	14	21	.164
24–48 hours	6	12	.130
Vomiting			
For 48 hours	7 (14%)	9 (18%)	.846
0–6 hours	1	3	.317
6–24 hours	4	5	.750
24–48 hours	2	1	.546
Rescue antiemetics			
For 48 hours	8 (16%)	6 (12%)	.596
0–6 hours	1	3	.317
6–24 hours	3	2	.630
24–48 hours	4	1	.162

Data are presented as the numbers of incidence and the percentage in the parentheses.

respectively, $P = .075$), there was no significant difference between the 2 groups in terms of incidence of nausea and vomiting events, use of rescue antiemetics, and the severity of nausea ($P > .05$) (Tables 2 and 3).

Although there was no significant difference in the incidence of complications related to ramosetron based on the timing of administration, preoperative administration of ramosetron did not reduce postoperative pain or improve patient satisfaction. There was no difference in the consumption of fentanyl and the severity of postoperative pain between the 2 groups ($P > .05$ in all postoperative periods). Additionally, there was no significant difference in patient satisfaction (1.7 ± 2.3 vs 2.0 ± 2.2, respectively, $P > .05$) and the incidence of complications related to ramosetron between the 2 groups ($P > .05$) (Table 4).

4. Discussion

Reducing the incidence of PONV after TKA is important to improve patient recovery and shorten the LOS.[7] Additionally, it is important to increase patient satisfaction and optimize postoperative fluid management by initiating oral intake as soon as possible after surgery. Several methods have been used to decrease PONV, including reduced use of opioids with multimodal pain management, systemic steroid use, and scheduled use or continuative use of antiemetics.[8,26] However, among these, the effect of the timing of use of antiemetics remains controversial. The principal finding of this study was that preoperative administration of the antiemetic did not reduce postoperative nausea, vomiting, and pain compared to postoperative administration. In addition, preoperative use of the antiemetic was not associated with improvement in patient satisfaction.

Our findings negated the hypothesis that preoperative scheduled administration, rather than postoperative administration, of an antiemetic would reduce PONV after TKA. One study reported that ramosetron administrated 30 minutes before the end of surgery decreased the incidence of nausea in the 2- to 6-hour and the 6- to 24-hour postoperative period.[10] However, in our study, administration of ramosetron 1 hour before surgery did not reduce PONV in the patients until 48 hours after the surgery compared to those in the post-injection group. This could be attributed to the other medications used, such as celecoxib, pregabalin, acetaminophen, as well as dexamethasone, to control postoperative pain, nausea and vomiting. However, dexamethasone was not used in the previous study for controlling PONV and there was no description of multimodal pain management such as premedication and periarticular injection (PAI). Maximal blood levels of dexamethasone are achieved 1.6 to 2 hours after the injection. Therefore, patients who received dexamethasone were at lower risk of experiencing POVN compared to the patients who did not receive the drug.[27] This discrepancy could be partly explained by the difference in multimodal medication. Thus, although there was a tendency to reduce the incidence of nausea for 48 hours postoperatively, the effectiveness might not have been significant when the patients were managed with a different multimodal therapy for postoperative pain, nausea and vomiting.

Table 3

Comparison of the severity of nausea between Preoperative injection and Postinjection group.

	Preoperative injection (N = 50)	Postperative injection (N = 51)	*P* value
0–6 hours	0.9 ± 1.8	1.0 ± 2.4	.705
6–24 hours	1.4 ± 2.4	1.8 ± 2.7	.307
24–48 hours	0.7 ± 2.1	0.8 ± 1.6	.776

Data are presented as means with standard deviation using VAS. VAS = visual analogue scale

Table 4

Pain score, satisfaction score and the incidence of complications.

	Preoperative injection (N = 50)	Postoperative injection (N = 51)	*P* value
Pain score (VAS)			
0–6 hours	5.7 ± 1.8	5.1 ± 1.8	.092
6–24 hours	6.8 ± 1.8	6.5 ± 2.1	.455
24–48 hours	6.2 ± 1.7	5.5 ± 2.1	.081
Fentanyl consumption (μg)			
For 48 hours	59.9 ± 14.1	51.0 ± 23.2	.066
0–6 hours	16.5 ± 6.1	14.0 ± 7.6	.335
6–24 hours	24.3 ± 10.7	21.2 ± 13.2	.346
24–48 hours	19.1 ± 9.2	15.8 ± 11.0	.182
Satisfaction score (VAS)	1.7 ± 2.3	2.0 ± 2.2	.561
Headache			
For 48 hours	15 (30%)	17 (33.3%)	.584
0–6 hours	9	7	.556
6–24 hours	6	9	.425
24–48 hours	0	1	1.000
Dizziness			
For 48 hours	17 (34%)	21 (41.2%)	.692
0–6 hours	9	9	.963
6–24 hours	7	11	.320
24–48 hours	1	1	1.000
Drowsiness			
For 48 hours	14 (28%)	11 (21.6%)	.376
0–6 hours	7	5	.515
6–24 hours	6	3	.318
24–48 hours	1	3	.617

Data are presented as the numbers of incidence and the percentage in the parentheses. VAS = visual analogue scale.

Our findings negated our hypothesis that preoperative administration of an antiemetic would reduce postoperative pain and improve patient satisfaction. In instances where the pain after surgery was not controlled, the patients required more pain medications including opioids, which caused nausea and vomiting. Therefore, postoperative pain control is important to manage the incidence of PONV. However, the effect of antiemetic on postoperative pain control has not been established.[7,22,23,28,29] One study reported that ramosetron reduced the severity of postoperative pain after thyroid surgery.[23] Another study reported that ramosetron was superior to ondansetron for postoperative pain control 24 to 48 hours after lumbar spine surgery[22]. On the other hand, Koh et al reported that ramosetron did not provide postoperative pain relief after TKA.[7] Hartrick et al reported that antiemetic (aprepitant) did not decrease the pain after TKA. The findings of our study were line with those reported by Koh et al and Hartrick et al Early use of ramosetron was not advantageous in reducing the severity of pain and consumption of fentanyl. Patients undergoing TKA, unlike those undergoing thyroid or spine surgery, generally receive premedication and PAIs for pain management. The type of surgery and pain control protocol, such as premedication and PAI might contribute to the effectiveness of ramosetron in postoperative pain control. Based on the similar rate of complications and absence of any benefit in controlling postoperative pain, nausea and vomiting, the lack of improvement in patient satisfaction was comprehensible after surgery in the pre-injection group. Preoperative administration of ramosetron did not present any clinical advantage, as there was no significant difference in the incidence of postoperative nausea, vomiting, pain, and complications. However, given the different circumstances of each hospital, preoperative administration of ramosetron might be one of the alternatives that could be considered to reduce the incidence of PONV.

Our study has several limitations. First, the proportion of female included in the study was high. Therefore, there is a possibility of different results when it applied to the population with different sex proportion. Second, the patients included in this study were not randomly assigned to each group. However, we sequentially used the 2 different methods for scheduled administration of the antiemetic in patients undergoing TKA with similar demographic characteristics. Thus, in our opinion, the selection bias was minimized. Third, all patients received an intravenous injection of dexamethasone. Dexamethasone has a substantial role in reducing PONV; thus, it could affect the incidence of PONV after TKA.[30] Fourth, our study compared the timing of antiemetic usage but did not include a placebo control group. Fifth, we used ramosetron alone as the primary antiemetic. Finally, multimodal therapies were used in all patients in our study to control PONV. However, the results obtained could differ after administration of ramosetron, in cases where multimodal therapies for controlling PONV was not given to patients. Pharmacological characteristics of different antiemetic drugs may vary. Therefore, our findings would not be applicable to other antiemetics with different pharmacological characteristics.

5. Conclusion

Preoperative scheduled administration of ramosetron showed a modest effect in reducing the incidence of postoperative nausea compared to postoperative administration of the drug. However, the difference observed was not clinically significant. Under the current protocol of multimodal therapies, timing of administration of preemptive antiemetics did not have significant effect on PONV.

Acknowledgments

We acknowledged So Hee Oh, Ph D for advice on statistical analysis.

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