

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

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Research article

Keywords: antiemetics, postoperative nausea and vomiting (PONV), Total knee arthroplasty (TKA)

Posted Date: December 12th, 2019

DOI: <https://doi.org/10.21203/rs.2.18597/v1>

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Abstract

Background To date, there has been no established protocol regarding the timing of the scheduled administration of antiemetics in total knee arthroplasty (TKA). Previous prospective studies analyzing the scheduled use of antiemetics differed in the timing at which the drugs were administered. However, antiemetic drugs are not administered post-operatively until noxious stimuli caused by drugs used during anesthesia and operative procedures. The purpose of this study was 1) to determine whether preoperative scheduled administration of an antiemetic drug can reduce iatrogenic postoperative nausea and vomiting (PONV) in TKA compared to postoperative administration, and 2) to determine whether there was a difference in postoperative pain, patient satisfaction, and complications after TKA between pre- and postoperative administrations.

Methods This retrospective study included patients who were assigned to either intravenous administration of the antiemetic drug (ramosetron) 1 hour before surgery (pre-injection group: 50 patients) or at the end of surgery (post-injection group: 51 patients). The incidence of PONV and the frequency of rescue medicine use were recorded until 48 hours postoperation. Postoperative pain level and satisfaction were also assessed using the visual analogue scale (VAS). Possible complications associated with serotonin receptor antagonists; for example, headaches, dizziness, and drowsiness were also assessed.

Results The incidence of nausea events was lower in the pre-injection group than in the post-injection group. However, there was no difference between the two groups in terms of frequency of vomiting events and the use of rescue medicine for PONV. Also, postoperative pain, satisfaction scores, and incidence of complications were not different between the two groups.

Conclusions The patients with preoperative scheduled administration of antiemetics showed lower incidence of nausea events than those with postoperative administration. However, it is difficult to conclude that the extent of the effect was clinically significant. Further research is needed to determine the optimal timing and method for more effective antiemetic treatment.

Background

Postoperative nausea and vomiting (PONV) is a relatively common yet disconcerting problem for 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 (e.g. dehydration), delayed patient recovery, and an increase in 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 TKA. Traditionally, antiemetic drugs have been used according to patients' needs after surgery. However, the post-surgical administration of antiemetics alone was not able to effectively control PONV. Thus, recently there has been an interest in preemptive, scheduled use of antiemetic drugs for the prevention of PONV (7).

There has yet to be an established consensus regarding the timing of scheduled administration of an antiemetic drug in TKA. One previous study demonstrated that preemptive, scheduled use of ramosetron (5-HT₃ receptor antagonist) reduced postoperative emetic events after TKA; however, it was effective only during the 6- to 24-hour postoperative period (8). Even if the researchers administered the antiemetic drug before an emetic event, the drug was injected 1 hour after TKA. Antiemetic drugs are usually administered at the end of surgery, but postoperative administration is not performed until noxious stimuli caused by anesthetic and/or operative procedural drugs (e.g. periarticular injection).

The purposes of this study were 1) to determine whether preoperative scheduled administration of an antiemetic drug can reduce PONV in TKA compared to postoperative administration, and 2) to determine whether there was a difference in postoperative pain, patient satisfaction, and complications after TKA between pre- and postoperative administrations. We hypothesized that preoperative administration of an antiemetic drug would reduce PONV and postoperative pain. We also hypothesized that preoperative administration of an antiemetic drug would improve patient satisfaction without increased complications compared to postoperative administration.

Methods

This retrospective review of prospectively collected data included 101 patients who underwent primary TKA due to end-stage osteoarthritis. Before this study began, approval was obtained from the institutional review board of the authors' hospital. The study was designed according to the previous study regarding the effects of the ramosetron on reducing PONV in TKA (8). The patients who underwent TKA from July 2015 to January 2016 at our institution were checked for eligibility for study inclusion. 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 drugs use within 24 hours before surgery; and 6) history of cardiovascular or respiratory disease, alcohol or opioid dependence, and renal or hepatic failure. Informed consent was obtained from all participants in this study.

Eligible patients were assigned to either intravenous scheduled administration of 0.3 mg ramosetron 1 hour before surgery (pre-injection group) or at the end of surgery (post-injection group). The randomization was not carried out for this study. Instead of randomization, for the first 50 patients, the antiemetic drug was injected preoperatively, and the same antiemetic drug was injected postoperatively for subsequent TKAs for 51 patients. There were no differences between the two groups in terms of demographic data and the number of risk factors for PONV, which included female gender, history of PONV or motion sickness, nonsmoking status, and the use of postoperative opioids (Table 1). The four risk factors were described by Murphy et al.(9).

Table 1
Demographics and the risk factors for PONV.

	Preoperative injection (N = 50)	Postoperative injection (N = 51)	P-value
Demographic data			
Proportion of female*	43 (86%)	47 (92%)	0.321
Laterality (Right : left)	22 : 28	24 : 27	
Age [†]	71.5 (6.9)	71.1 (5.9)	
Risk factors identified			
With one factor	6	2	0.133
With two factors	1	2	0.579
With three factors	36	41	0.322
With four factors	7	6	0.737
Data are presented as numbers of patients; * data are presented as number of female patients and their percentages in parentheses. [†] Data are presented as means with standard deviations in parentheses. Abbreviations = PONV, postoperative nausea and vomiting.			

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. As was used in the previous study, we chose to utilize ramosetron due to its more potent and longer-acting properties than other serotonin receptor antagonists (8). 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, 650 mg acetaminophen. Intravenous 5 mg dexamethasone was also used to reduce postoperative PONV.

All surgical procedures were performed by one senior surgeon using the standard medial parapatellar arthrotomy with a tourniquet. Before prosthesis insertion with cement, 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 with a 10-minute lockout interval for 72 hours. An intramuscular injection of ketoprofen was administered for acute pain rescue when the patient-reported severity of pain level was 6 or higher on a pain visual analogue scale (VAS).

Patients were monitored for PONV every hour for the first 6 hours, then every 6 hours until 24 hours, and 24–48 hours postoperatively by the same clinical investigator without any information on which 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 occurrence of vomiting was recorded. Rescue antiemetics were given to patients if they had a VAS for nausea > 4, an episode of vomiting, or upon their request. An intravenous injection of 10 mg metoclopramide was used as a first-line rescue antiemetic treatment, and if severe nausea persisted after two 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. Common adverse drug reactions associated with serotonin receptor antagonists such as headaches, dizziness, and drowsiness were also assessed and reported.

All analyses were performed with SPSS for Windows version 16.0 (SPSS Inc, Chicago, IL). A P value of < 0.05 was considered statistically significant. It was estimated that the sample size of this study would be adequate to achieve a statistical power of 80% with less than a 5% probability of a type-I error. Continuous variables between two groups such as VAS scores were analyzed by student t-test. Chi-square or Fisher exact tests were used for categorical variables such as incidence of emetic events and frequency of antiemetic rescue medicine use.

Results

During the first 48 hours, the incidence of nausea events was lower in the pre-injection group than the post-injection group ($p = 0.02$). However, there was no significant difference between pre- and post-injection groups in terms of incidence of vomiting events. Furthermore, in terms of the frequency of rescue antiemetics use, there was no significant difference between the pre- and post-injection groups (Table 2).

Table 2
Incidence of emetic events and use of rescue antiemetics

	Preoperative injection (N = 50)	Postoperative injection (N = 51)	P-value
Nausea			
For 48 hours	32 (64%)	43 (86%)	0.020
0–6 hours	11	10	
6–24 hours	14	21	
24–48 hours	7	12	
Vomiting			
For 48 hours	7 (14%)	9 (18%)	0.616
0–6 hours	1	3	
6–24 hours	4	5	
24–48 hours	2	1	
Rescue antiemetics			
For 48 hours	8 (16%)	6 (12%)	0.538
0–6 hours	1	3	
6–24 hours	3	2	
24–48 hours	4	1	
Data are presented as the numbers of incidence and the percentage in the parentheses.			

Postoperative pain and satisfaction scores did not differ between the pre- and post-injection groups. Also, there was no significant difference between pre- and post-injection groups in terms of the incidence of complications including headaches, dizziness, and drowsiness (Table 3).

Table 3
Pain score, satisfaction score and the incidence of complications

	Preoperative injection (n = 50)	Postoperative injection (n = 51)	P-value
Pain score (VAS)			
For 48 hours	3.48	3.58	0.592
0–6 hours	3.22	3.41	
6–24 hours	3.52	3.57	
24–48 hours	3.70	3.65	
Satisfaction score (VAS)	1.68	1.94	0.561
Headache			
For 48 hours	17 (34%)	15 (30%)	0.620
0–6 hours	9	7	
6–24 hours	5	7	
24–48 hours	3	1	
Dizziness			
For 48 hours	22 (44%)	22 (44%)	0.930
0–6 hours	10	11	
6–24 hours	7	11	
24–48 hours	5	0	
Drowsiness			
For 48 hour	7 (14%)	12 (24%)	0.220
0–6 hours	4	5	
6–24 hours	2	4	
24–48 hours	1	3	
Data are presented as the numbers of incidence and the percentage in the parentheses. Abbreviations = VAS, visual analogue scale			

Discussion

Reducing PONV after TKA is important to improve patient recovery and shorten the LOF(8). Additionally, it is important to increase patient satisfaction and optimize postoperative fluid management by starting oral intake as soon as possible after surgery. There are several methods used to decrease PONV after surgery including reduced use of opioids with multimodal pain management, systemic steroid use, and scheduled use of antiemetics (7). Among these, however, the effects of the timing of scheduled use of antiemetics are still controversial. The principal finding of this study was that the preoperative administration of antiemetics is more effective in decreasing the incidence of postoperative nausea events than postoperative administration. However, it was difficult to conclude to what extent the effect is clinically significant.

Our results partly support the hypothesis that preoperative scheduled administration of an antiemetic drug would reduce PONV in TKA. Recently, preemptive pain management for TKA is frequently used, with previous studies reporting preemptive pain management decreased the PONV due to reduced use of opioids after surgery (10). In contrast to the consistent results in the literature regarding the effects of preemptive pain management on reducing postoperative pain and PONV, the effects of scheduled administration of antiemetics in reducing PONV remains unclear (11–13). PONV was reported to be reduced through the scheduled use of antiemetics, but the effects were not clinically significant (14–16). Furthermore, there was no difference in terms of PONV and postoperative mobilization between patients who received scheduled antiemetic as opposed to an as-needed basis (7). In contrast to the consistent timing of administration of preemptive pain medication before surgery, there were differences among studies related to scheduled antiemetic use. For example, certain authors used antiemetic drugs before the induction of anesthesia (17); as compared to other authors who used antiemetic drugs at the end of surgery (18). A recent systematic review showed that the time at which antiemetic drugs were administered significantly affected the resulting PONV (19). Therefore, we initially thought that the timing of antiemetic drug administration could be the main causative factor for inconsistent results among studies. However, we also found only modest effects of preoperative scheduled administration of antiemetics in reducing PONV in TKA. Thus, more effective and comprehensive antiemetic drug measures to reduce emetic events after TKA are needed.

In terms of postoperative pain and complications, there were no significant differences between the two groups. Previously, it was revealed that PONV control reduced the pain VAS (20, 21). In this study, there were no significant differences in pain and satisfaction VAS scores. It is understandable because we did not observe a substantial difference between the two groups in terms of PONV. Furthermore, there are many factors related to postoperative pain level including preemptive pain regimen, periarticular injections, and systemic use of dexamethasone (22, 23).

Our study has several limitations. First, the patients included in this study were not randomly assigned between the two groups. However, we sequentially used the two different methods to use scheduled antiemetics for TKA patients with similar demographic characteristics. Thus, we think that the selection bias could be minimized. Second, intravenous dexamethasone injection was used in all patients. Dexamethasone has substantial effects on reducing PONV (24). Therefore, differences caused by varying

the injection timing of antiemetics could have been undetectable. Third, our study only compared antiemetic usage timings and did not use a placebo control group. Fourth, we only used ramosetron as the primary antiemetic. Pharmacological characteristics are different among antiemetic drugs. Therefore, our findings would not be applicable to other antiemetics with different pharmacological characteristics.

Conclusions

Patients with preoperative scheduled administration of antiemetics showed reduced incidence of iatrogenic nausea events than those with postoperative administration. However, it is difficult to conclude to what extent the effect is clinically significant. Further research is needed to determine an effective and comprehensive method for antiemetic drug delivery to reduce emetic events after TKA.

Abbreviations

TKA; total knee arthroplasty, PONA; postoperative nausea and vomiting, LOS; length of hospital stay, 5-HT₃; 5-hydroxy-tryptamine receptor 3, VAS; visual analogue scale, PCA; patient-controlled analgesia

Declarations

Ethics approval and consent to participate

The institutional review board of our hospital reviewed the protocol and approved the study (IRB #. 26-2015-16).

Consent for publication

Not applicable.

Availability of data and material

The dataset used and analysed during the current study is available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Authors' contributions

	Design	Data acquisition	Analysis	Interpretation of data	Drafting	Critical revision	Final approval
MJC	O	O	O	O	O	O	O
SBK	O	O	O	O	O	O	O
HJP	O	O	O	O	O	O	O
KMH	O	O	O	O	O	O	O
IUH		O		O	O	O	O
CBC	O	O	O	O	O	O	O

Acknowledgements

We would like to thank all the residents and clinical fellows who took part in the study voluntarily.

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