Original research

Randomized Double-Blind Controlled Trial Comparing 0.2 mg, 0.1 mg, and No Intrathecal Morphine Combined With Periarticular Injection for Unilateral Total Knee Arthroplasty

Chompunoot Pathonsamit, MD [a], Ittiwat Onklin, MD [b], Natthapong Hongku, MD [b], Pruk Chaiyakit, MD [b, *]

[a] Department of Anesthesiology, Faculty of Medicine, Vajira Hospital, Navamindradhiraj University, Bangkok, Thailand
[b] Department of Orthopedics, Faculty of Medicine, Vajira Hospital, Navamindradhiraj University, Bangkok, Thailand

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ABSTRACT

Background: The addition of intrathecal morphine (ITM) to neuraxial anesthesia during total knee arthroplasty (TKA) to achieve postoperative analgesia can elicit opioid-related side effects. The other methods of pain alleviation and side effect reduction, including multimodal analgesia, are challenging. This study aimed to determine the efficacy of various ITM dosages for primary unilateral TKA with periarticular injection (PI).

Methods: This randomized double-blind controlled trial was conducted at Vajira Hospital between April 2018 and March 2019. Patients undergoing TKA were randomized into 3 groups: no ITM (M_0), ITM 0.1 mg (M_1), and ITM 0.2 mg (M_2). All patients received PI. Postoperative pain scores, side effects of ITM, and orthopedic outcomes were compared.

Results: The trial enrolled 102 patients: M_0 (n = 32), M_1 (n = 35), and M_2 (n = 35). The postoperative pain scores and rescue analgesic consumption of groups M_1 and M_2 did not differ significantly within the first 24 hours and were significantly lower than those in group M_0. Nausea and vomiting were observed more frequently 4 hours postoperatively in M_2 than in groups M_1 and M_0 (77%, 51%, and 6%, respectively; $P < .05$), which required second-line antiemetic administration (29%, 9%, and 13%, respectively; $P = .09$).

Conclusion: Postoperative pain control achieved with PI combined with ITM 0.1 mg after primary unilateral TKA was comparable to that achieved with ITM 0.2 mg. PI without ITM resulted in higher pain scores and rescue analgesic consumption. The frequency and severity of nausea and vomiting 4 hours postoperatively were also lower in patients administered 0.1 mg of ITM than those in patients administered 0.2 mg of ITM.

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Introduction

Total knee arthroplasty (TKA) is a surgical procedure that can cause severe postoperative pain. Appropriate postoperative pain control is essential for achieving early ambulation, rapid recovery, and shortening the duration of hospitalization.

The International Consensus on Anaesthesia-Related Outcomes after Surgery group has recommended the use of neuraxial anesthesia during TKA [1]. Intrathecal morphine (ITM) has also been used to achieve postoperative pain control. The current standard dose for ITM is 0.2 mg [2,3]. However, even this dose elicits opioid-related side effects, such as postoperative nausea and vomiting, pruritus, and respiratory depression [4].

A previous study proposed that the ITM dose should be reduced, which resulted in inadequate postoperative pain control [5]. Multimodal analgesia administered by different routes, including the peripheral nerve block (PNB) and periarticular injection (PI) [6,7], has been used to increase the efficacy of postoperative pain control without inducing any systemic adverse effects. PNB has also been proposed as an alternative but with a variable reported efficacy. However, several studies have found that PNB may also cause

* Corresponding author. Department of Orthopedics, Faculty of Medicine, Vajira Hospital, Navamindradhiraj University, Bangkok, Thailand. Tel.: +6681-827-8238.
E-mail address: pruk@nmu.ac.th

adverse effects such as impairment of motor function and increased risk of catheter-related infection [8-14]. Previous studies reported that PI did not affect motor function significantly and provided variable pain control [5,15-18].

The aim of this study was to compare the efficacy of PI combined with different doses of ITM. The postoperative pain score was the primary outcome. The secondary outcomes included rescue analgesic (drug) consumption, opioid-related side effects, orthopedic outcome scores, and patient satisfaction.

Material and methods

The study was approved by the institutional ethics committee (COA 161/60) and was registered with the Thai Clinical Trials Registry (TCTR no. 20180825003)

Patients

The inclusion criteria for this study were as follows: patients who were scheduled to undergo unilateral TKA for primary osteoarthritis of the knee, aged between 45 and 85 years, with an American Society of Anesthesiologists physical status I-III. The exclusion criteria were as follows: patients with contraindications to neuraxial anesthesia; allergies to ketorolac, bupivacaine, morphine; other inflammatory joint diseases or chronic knee joint pain unrelated to osteoarthritis; chronic opioid use before surgery (3 months or longer); preexisting neuropathy involving the operative site; major psychological problems; history of coronary artery bypass graft surgery; history of gastrointestinal ulcer or bleeding; pregnancy or breastfeeding; and impaired renal function (defined as a glomerular filtration rate <30 mL/min).

Sample size and statistical analysis

The sample size of this study was calculated assuming that a reduction of 2 points in the postoperative numerical pain scale would be clinically significant. We estimated that 35 patients were required per group, using an alpha value of 0.05 and beta value of 0.2 for an experimental design incorporating 3 groups of equal size.

All statistical analyses were conducted using Stata Statistical Software version SE 13 (StataCorp LP, College Station, TX). The 3 groups' data were compared using the one-way analysis of variance, Bonferroni multiple-comparison test, or Fisher's exact test, wherever appropriate. P values < 0.05 were considered statistically significant.

Randomization and blinding

Patients who met the inclusion criteria were informed about the study by a research assistant. Patients who agreed to participate in the study provided a written informed consent form before randomization. The participants were randomized into 3 groups (groups M_0, M_1, and M_2) using numbers that were electronically generated with Stata Statistical Software version SE 13 (StataCorp LP). Each number was placed in a well-sealed envelope by a research assistant, to be opened by the anesthesiologist responsible for intraoperative care on the day of surgery. All patients and outcome assessors were blinded to the assigned treatment group.

Surgery and anesthesia

All patients received spinal anesthesia using bupivacaine 15 mg (AstraZeneca, Bangkok, Thailand) in addition to ITM 0.1 mg (M_1), ITM 0.2 mg (M_2), or no ITM (M_0). Intraoperative sedation was administered at the anesthesiologist's discretion using short-acting drugs. Preoperative analgesic agents were not used.

The PI solution in this study was a mixture of levobupivacaine 150 mg (AbbVie Ltd., Maidenhead, UK) (0.5%, 30 mL), ketorolac 30 mg (Siu Guan Chemical Industrial, Chai Yi, Taiwan) (1 mL), and epinephrine 1 mg (1 mL) diluted up to 100 mL in a normal saline solution.

All surgeries were performed by 2 knee arthroplasty specialists (P.C. and N.H.). Standard TKA was performed with the conventional cemented knee prosthesis using the midvastus approach. A 50-mL PI solution was injected into the posterior capsule of the knee joint after the completion of bone preparation for prosthetic implantation. Subsequently, the remaining 50 mL of PI solution was injected into the anterior structure after complete implantation of the knee prosthesis. The location of injection was based on Guild's method [19].

Postoperative pain control protocol

Cold-pack compression and bandages were applied for 24 hours postoperatively. The patient-controlled analgesia (PCA) device was used for postoperative pain control. Fentanyl 30 mcg (20 mcg/mL) was delivered per bolus, with a 5-minute lockout interval, and 4-hour limit maximum dose of 300 mcg. Continuous baseline infusion was not performed. Fentanyl consumption was recorded 24 hours postoperatively by converting the total fentanyl dose to the morphine equivalent daily dose.

The fentanyl-PCA pain management protocol was replaced by intravenous morphine after the first 24 hours postsurgery. The morphine consumption dose was recorded for the 48- to 72-hour postoperative period.

Intravenous ketorolac was administered at an adjusted dose for 24 hours, in addition to PCA. The administered dosage of ketorolac was adjusted according to the patient's age, body weight, and renal function. Acetaminophen was also administered for 72 hours.

Record and measurement

The outcomes were assessed by the attending orthopedic staff and nursing research assistants. All outcome assessors were blinded to study and well-informed about the data scoring and evaluation methods.

The end of surgery was defined as 0 hour. All data were evaluated and recorded after the end of surgery, including the numerical pain scale scores, sedation scores, relevant side effects of ITM, and orthopedic outcomes.

Postoperative pain was assessed using the numerical rating scale (NRS). The NRS was graded from 0 to 10 points, which indicated no pain and extreme pain, respectively. Pain scores were recorded at rest and on knee flexion every 4 hours for 24 hours, followed by 48 hours and 72 hours after surgery. Pain induced by walking was also recorded 24 hours, 48 hours, and 72 hours postoperatively. The amount of rescue analgesic consumption was recorded: fentanyl use within the first 24 hours and subsequent morphine use between 24 and 72 hours postoperatively.

The incidence of any adverse effects of ITM, including nausea, vomiting, pruritus, and level of sedation, was recorded over the 72-hour postoperative period. The severity of nausea/vomiting and pruritus was scored on a scale ranging from 0 to 3, while the level of sedation was assessed using the Ramsay sedation scale ranging from 1 to 6 (Supplementary Data). The respiratory rate was monitored every hour over the first 12 hours and every 2 hours for 24 hours after the first 12 hours. Respiratory depression was defined as a respiratory rate below 10 breaths per minute. The provision of medications was administered and adjusted depending on the severity of symptoms and the patient's tolerance. For instance,
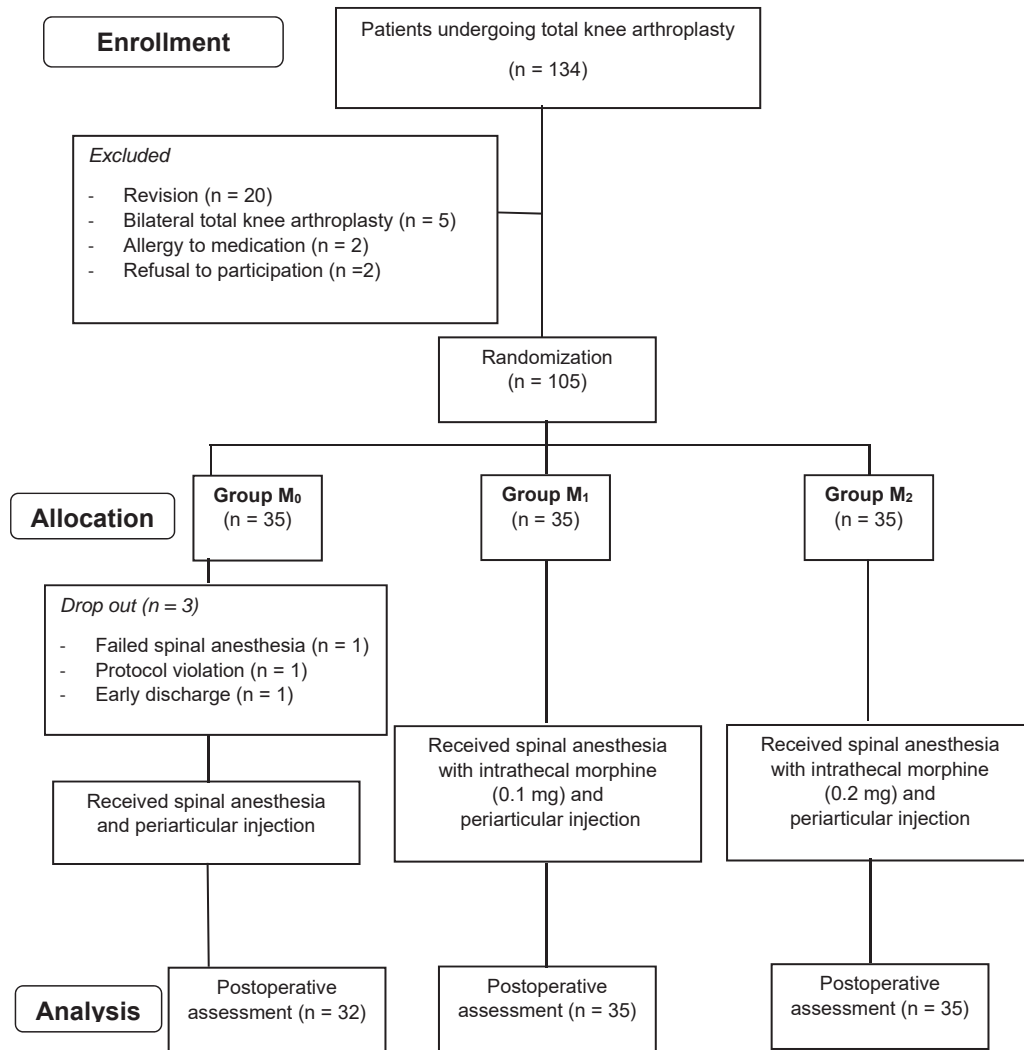
Figure 1. Flow chart of the study groups. Group M$_0$, no intrathecal morphine; group M$_1$, 0.1 mg of intrathecal morphine; group M$_2$, 0.2 mg of intrathecal morphine.

intravenous chlorpheniramine 10 mg was administered for pruritus, and metoclopramide 10 mg was administered for nausea and vomiting with or without ondansetron 0.1 mg/kg up to 8 mg maximum.

Orthopedic outcome evaluation was also performed for 72 hours postoperatively by assessing the maximum active flexion of the knee in the supine position and the straight leg raising and timed up and go (TUG) tests.

Table 1
Demographic data.

Baseline characteristics	Group M$_0$ (N = 32)	Group M$_1$ (N = 35)	Group M$_2$ (N = 35)
General data			
Age (y)	66 ± 8	66 ± 8	67 ± 7
Sex (female/male)	30/2	30/5	30/5
Height (cm)	155 ± 8	155 ± 7	156 ± 7
Weight (kg)	67 ± 16	65 ± 11	66 ± 13
Body mass index (kg/m^2)	28 ± 6	27 ± 4	27 ± 6
ASA classification (I/II/III)	0/20/12	0/28/7	1/24/10
Preoperative conditions			
NRS at rest	1.3 ± 2.1	1.5 ± 2.0	1.5 ± 2.1
NRS at flexion	2.0 ± 2.2	2.7 ± 2.2	2.4 ± 2.6
Maximum active knee flexion (°)	114 ± 19	117 ± 21	118 ± 22
Preoperative Timed Up and Go test (s)	25 ± 13	21 ± 8	21 ± 11
Operative data			
Anesthetic time (min)	172 ± 29	170 ± 29	175 ± 32
Operative time (min)	122 ± 26	118 ± 30	121 ± 28

ASA Classification, American Society of Anesthesiologists Classification; NRS, Numerical Rating Scale for pain; M$_0$, no intrathecal morphine, M$_1$, intrathecal morphine 0.1 mg, M$_2$, intrathecal morphine 0.2 mg.

Patients were asked to rate their satisfaction with the quality of analgesia (excellent = 4, good = 3, inadequate = 2, poor = 1) on the day of discharge. Other data collected included the hospital length of stay (LOS) and any adverse event during hospitalization.

Results

A total of 105 patients were stratified randomly into 3 groups (Fig. 1). Three patients were excluded from the final analysis: Failure of spinal anesthesia was observed in one patient, one patient had postoperative gastrointestinal bleeding and received pain management that differed from the study protocol, and one patient was discharged earlier from the hospital. Hence, 102 patients were included in the modified intention-to-treat analysis. No differences were observed among the demographic data, preoperative function of the affected knee, and operation times of the 3 groups (Table 1).

Groups M_1 and M_2 had significantly lower postoperative pain scores at rest and flexion than group M_0 during the first 24 hours after surgery. Statistically significant differences were not observed between the postoperative pain scores of groups M_1 and M_2 (Fig. 2). Analgesic drug consumption was lower in the ITM groups (M_1 and M_2) than in the PI-only group (M_0). On the other hand, no such difference was observed between the M_1 and M_2 groups. The requirement of intravenous morphine 24 hours after surgery did not differ for the 3 groups over the subsequent 24-48 hours and 48-72 hours. Table 2 demonstrates the analgesic consumption over the 72-hour postoperative period.

Nausea and vomiting were the most commonly observed side effects of analgesic use. Nausea and vomiting were encountered most frequently in the M_2 group especially during the first 4 hours after surgery. The differences between the frequency of nausea and vomiting in the 3 groups during the first 4 hours after surgery were statistically significant: These differences were also statistically significant between groups M_1 and M_2 (77% in M_2 vs 51% in M_1 vs 6% in M_0 [$P < .05$]). The differences between the 3 groups remained significant during the 4- to 8-hour period after surgery, 46% in M_2 vs 31% in M_1 vs 9% in M_0 ($P < .05$), but were not significant between M_2 and M_1 ($P = .32$). The incidence of nausea and vomiting at different time points during the first 24 hours in the 3 groups is demonstrated in Figure 3.

The use of metoclopramide was significantly higher in group M_2 than that in groups M_1 and M_0 during the first 24 hours (consistent with the incidence of nausea and vomiting): 63% vs 49% vs 23%, respectively ($P < .05$). However, the difference was not significant between groups M_2 and M_1 ($P = .34$). Furthermore, patients in the M_2 group tended to require second-line antiemetic drugs for symptomatic relief during the 24-hour postoperative period (Table 2).

The pruritus-severity score was ≥ 1 only during the first 24 hours after surgery in all groups. The incidence of pruritus during the first 24 hours after surgery was higher in groups M_2 and M_1 than that in M_0 group (57%, 37%, and 3%, respectively; $P < .05$). The difference in antipruritic drug consumption of the 3 groups was not statistically significant.

Suppression of the level of sedation and respiratory depression were not observed in any participant in our study.

Patients in group M_0 had a significantly lower degree of maximum active knee flexion on the first day after surgery than those in the M_1 and M_2 groups with a median flexion of $38 \pm 21°$ in group M_0 compared with $50 \pm 21°$ and $54 \pm 27°$ in groups M_1 and M_2, respectively ($P < .05$). The difference between the maximum active knee flexion in groups M_2 and M_1 was not statistically significant. The maximum active knee flexion and TUG time on the second and the third postoperative days did not differ significantly among the 3 groups. Patient satisfaction did not differ among the groups, and 85% of patients graded their level of satisfaction as excellent. The hospital LOS did not differ in any group (Table 2).

Discussion

Adequate postoperative pain control plays a crucial role toward facilitating optimal recovery of the patient's ambulatory function (in addition to an effective surgical procedure for TKA). Systemic morphine administered via the intravenous or intrathecal routes was generally used to achieve postoperative analgesia. The postoperative analgesic efficacy of the 0.2-mg dose of ITM, which was reportedly comparable with that of higher doses of 0.3 mg [2,5,20], is commonly used in current practice. However, this dose (ie, 0.2 mg) of morphine still causes unfavorable side effects, which may negatively impact patients' postoperative recovery [3].

The efficacy of low-dose ITM alone, that is, 0.1 mg, is variable. Hassett et al. [5] reported that the postoperative analgesia afforded by 0.1 mg of ITM during TKA was inferior to that with ITM 0.2 and 0.3 mg. The potency of low-dose ITM alone is rarely comparable: A previous study by Frassanito et al. [10] reported a more efficient analgesic results for low-dose ITM than single-shot ultrasound-guided femoral nerve block.

PI, a part of the multimodal analgesic approach, is a conventional acute postoperative pain control technique used with TKA. The addition of PI to the multimodal analgesic approach tends to limit systemic opioid use [21]. However, there is a lack of sufficient evidence for defining the appropriate dose of ITM for postoperative
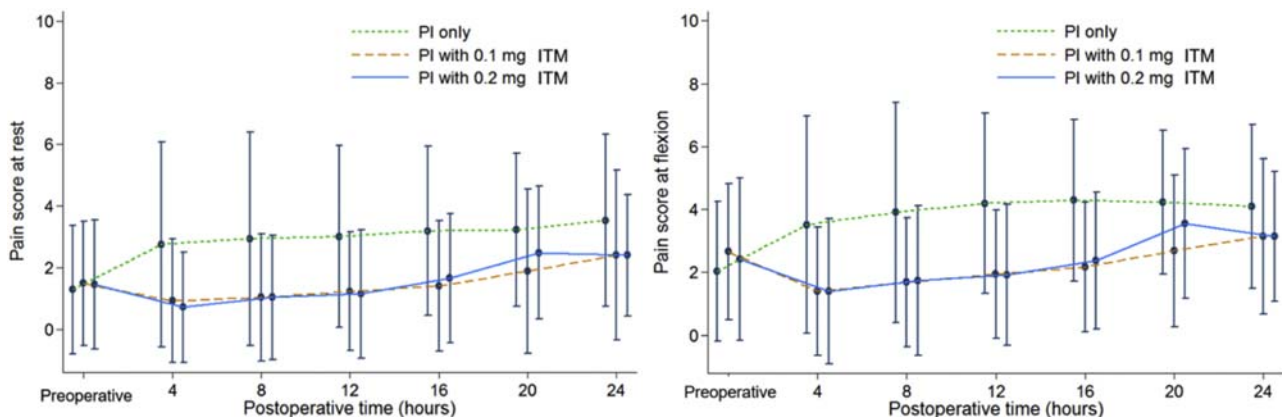

Figure 2. Postoperative pain scores at rest and during knee flexion. PI, periarticular injection; ITM, intrathecal morphine.

Table 2
Postoperative outcomes.

Variables	Group M_0 (N = 32)	Group M_1 (N = 35)	Group M_2 (N = 35)	P value[a]	P value[b]
Analgesic drug					
Fentanyl 0-24 h (mg MEDD)	43.1 ± 28.3	21.0 ± 23.6	17.9 ± 20.1	<.05	.56
Morphine 24-48 h (mg)	2.0 ± 3.0	2.0 ± 2.4	1.2 ± 1.8	.34	.16
Morphine 48-72 h (mg)	0.5 ± 1.6	0.2 ± 0.7	0.6 ± 1.2	.37	.11
Incidence of postoperative nausea and vomiting					
Postoperative time (h)					
0-4	2 (6%)	18 (51%)	27 (77%)	<.05	<.05
4-8	3 (9%)	11 (31%)	16 (46%)	<.05	.32
8-12	4 (13%)	6 (17%)	12 (35%)	.07	.11
12-16	4 (13%)	5 (14%)	3 (9%)	.80	.71
16-20	1 (3%)	2 (6%)	4 (11%)	.50	.67
20-24	1 (3%)	3 (9%)	2 (6%)	.87	1.00
Number of patients requiring antiemetic drugs					
Metoclopramide					
Postoperative time (h)					
0-24	7 (23%)	17 (49%)	22 (63%)	<.05	.34
24-48	3 (10%)	0 (0%)	3 (9%)	.16	.24
48-72	0 (0%)	1 (3%)	1 (3%)	1.00	1.00
Ondansetron					
Postoperative time (h)					
0-24	4 (13%)	3 (9%)	10 (29%)	.09	.06
24-48	1 (3%)	0 (0%)	0 (0%)	.30	NA
48-72	0 (0%)	0 (0%)	1 (3%)	1.00	1.00
Postoperative pruritus score (≥1)					
Postoperative time (h)					
0-24	1 (3%)	13 (37%)	20 (57%)	<.05	.15
24-48	0 (0%)	0 (0%)	0 (0%)	NA	NA
48-72	0 (0%)	0 (0%)	0 (0%)	NA	NA
Antipruritic drug					
Chlorpheniramine (mg)					
Postoperative time (h)					
0-24	1.0 ± 3.0	3.4 ± 7.3	4.6 ± 7.8	.08	.53
24-48	0 ± 0	0.3 ± 1.7	0 ± 0	.39	.32
48-72	0 ± 0	0 ± 0	0 ± 0	NA	NA
Respiratory depression	0 (0%)	0 (0%)	0 (0%)	NA	NA
Orthopedic outcome					
Postoperative maximum active knee flexion (°)					
Day 1	38 ± 21	50 ± 21	54 ± 27	<.05	.44
Day 2	58 ± 21	66 ± 19	66 ± 24	.21	.96
Day 3	73 ± 21	79 ± 18	79 ± 18	.28	1.00
Postoperative timed up and go test (s)					
Day 2	60 ± 11	57 ± 14	59 ± 16	.65	.71
Day 3	46 ± 10.78	45 ± 13	46 ± 12	.89	.72
Hospital length of stay (days)	2.8 ± 0.7	2.8 ± 0.7	2.9 ± 0.7	.80	.52

MEDD, Morphine Equivalent Daily Dose; M_0, no intrathecal morphine; M_1, intrathecal morphine 0.1 mg; M_2, intrathecal morphine 0.2 mg.

[a] One-way ANOVA or Fisher's exact test for comparisons among groups M_0, M_1, and M_2.

[b] Student's t test or Fisher's exact test for comparison between groups M_1 and M_2.

pain control when combined with PI. Our study aimed to determine the optimum dose of ITM, which would provide adequate postoperative pain control and minimize the opioid-related side effects when coadministered with PI. We expected that the concomitant administration of ITM 0.1 mg and PI could possibly provide adequate postoperative pain control while lowering the opioid-related side effects. Therefore, we decided to include the 0.1-mg dose of ITM in this study.

This study found that the administration of PI alone resulted in higher postoperative pain scores and greater analgesic drug requirement during the first 24 hours after surgery. The use of ITM 0.1 mg or 0.2 mg with PI significantly improved postoperative pain control compared with PI alone. This study also illustrated that ITM 0.1 mg resulted in similar postoperative pain scores (NRS score: 2-3) as ITM 0.2 mg when combined with PI, with a lower incidence and severity of nausea and vomiting.

We found that a higher dose of ITM (0.2 mg) was associated with a higher incidence of nausea and vomiting, with a consequent higher requirement of antiemetic drugs than the lower dose (0.1 mg) and no-ITM regimens during the first 4 hours after surgery and
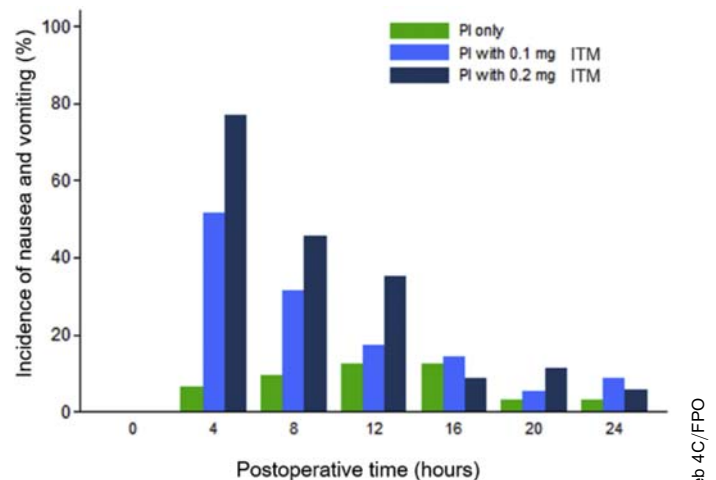
Figure 3. Incidence of nausea and vomiting. PI, periarticular injection; ITM, intrathecal morphine.

particularly lower than that with the no-ITM regimen during the subsequent 4- to 8-hour period (Fig. 3). This observation was buttressed by the lower observed consumption of antiemetic drugs in the ITM 0.1-mg group than that in the ITM 0.2-mg group during the initial 24-hour postoperative period: 49% vs 63% for metoclopramide ($P = .34$) and 9% vs 29% ($P = .06$) for ondansetron. Although the differences were not statistically significant, the clinical utility of the 15% to 20% reduction in the frequency of antiemetic drug administration with ITM 0.1 mg warrants debate. One observation was that patients who did not receive ITM at all also experienced nausea and vomiting (3% to 13%) during the first 24 hours, which may be caused by other factors besides morphine, such as hypotension or the effects of other medications.

The benefits of ITM were also manifested by the significant improvement in maximum active knee flexion on the first postoperative day in the ITM 0.1-mg and ITM 0.2-mg groups compared with the group that did not receive ITM. The lack of a significant difference (although the maximum active knee flexion was slightly better in M_2 than that in M_1 [$54 \pm 27°$ vs $50 \pm 21°$]) should support the use of a lower dose of ITM. This study did not find any difference in the patient satisfaction and hospital LOS among patients who did not receive ITM and those who received low- or high-dose ITM. These findings may depend on the ethical issue that rescue analgesics were provided in case of any side effects, which may have obscured any possible differences.

Respiratory depression, which is one of the most serious opioid-related side effects, was not observed in our study. The incidence of respiratory depression with low-dose ITM was very low, consistent with other studies. Gehling and Tryba reported a lower incidence of respiratory depression with low-dose ITM than the standard dose [4], while Frassinato et al. [10] reported no respiratory depression with low-dose ITM.

The method used in this study has several advantages. First, this was the first study to combine PI with ITM 0.1 mg. Second, we used the 3-arm randomization double-blind method in our study. Finally, we used a single-shot PI, which is more practical and convenient to use, compared with the retained periarticular catheter.

Delayed-release drugs, such as liposomal bupivacaine, are currently being used in PI, to prolong pain control beyond 24 hours. A recent meta-analysis of randomized controlled trials found that PI with liposomal bupivacaine resulted in a lower consumption of morphine equivalents 24 to 72 hours postoperatively and reduced incidence of nausea and vomiting after TKA, compared with the traditional bupivacaine PI [22]. However, liposomal bupivacaine was not available at our institute.

This study has some limitations. First, the postoperative intravenous dose of ketorolac differed across the study sample, as it was adjusted according to each patient's renal function. However, this was balanced by the preplanned stratified randomization of the patients to each group. Second, one patient was excluded because of postoperative gastrointestinal bleeding, which could have been an adverse systemic effect of ketorolac or other undiscovered factors. Unfortunately, the main outcome of pain could not be assessed, so the patient was dropped out from our study. Nevertheless, this side effect requires cautious consideration in future trials or clinical practice, and the administration of proton pump inhibitors should be considered to prevent this adverse effect. Finally, we did not blind the anesthesiologist who administered spinal anesthesia to each patient. As the outcome assessors were not anesthesiologists, we assumed that this process did not influence the results.

Although we did not use PNB, which is quite commonly used in several studies, the combination of PI with ITM could be a reasonable substitute because it can be easily administered by any anesthesiologist compared with the PNB, which requires higher skill and experience. Our simple technique could be readily applied in any clinical setting, especially in hospitals with limited personnel. The combination of our technique with prophylactic antiemetic drugs could be used clinically during the early postoperative period.

Conclusions

PI combined with a lower dose of ITM (0.1 mg) provided postoperative pain control, which was comparable to the standard ITM dosage (0.2 mg) in primary unilateral TKA. The frequency and severity of nausea and vomiting 4 hours postoperatively were also lower in patients who received a low dose (0.1 mg) of ITM (and those who did not receive ITM) than those who received the standard ITM dose.

Conflicts of Interest

The authors have no conflict of interest to declare with respect to this study.

Acknowledgment

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Table S1

Ramsay sedation score (Ramsay MA, Br Med J. 1974).

Sedation level	Score
Anxious and agitated or restless, or both	1
Co-operative, oriented, and tranquil	2
Responds to commands only	3
Exhibits brisk response to light glabellar tap or loud auditory stimulus	4
Exhibits a sluggish response to light glabellar tap or loud auditory stimulus	5
Exhibits no response	6

Ramsay MA, Savege TM, Simpson BR, Goodwin R. Controlled sedation with alphaxalone-alphadolone. Br Med J. 1974;2(5920):656-9.