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Additional Peripheral Nerve Block to Periarticular Injection Has No Benefit for Patients Undergoing TKA. A Factorial Propensity Score–Matched Analysis Comparing Four Multimodal Analgesic Techniques

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ABSTRACT

Background: Controversy remains over what and how many analgesic techniques are required as the most effective multimodal pain regimen in total knee arthroplasty (TKA). This study aimed to evaluate the effect of additional analgesic methods combined with periarticular injection (PAI) analgesia for TKA.
Methods: Using retrospective cohort data, patients undergoing TKA with spinal anesthesia and PAI were divided into 4 groups. Group A (control) comprised 66 patients; group B (73 patients) had additional adductor canal block; group C (70 patients) obtained additional femoral nerve block, and group D (73 patients) received additional adductor canal block and intrathecal morphine. Propensity score matching was applied to compare visual analog scale (VAS) for pain intensity, cumulative morphine use (CMU), knee flexion angle, straight leg raise, length of hospital stay, and postoperative nausea and vomiting.
Results: There was no significant difference regarding VAS and morphine use, when either group B or C was compared with group A. Group D had significantly lower VAS than groups A, B, and C during the first 24 hours after surgery and required significantly less CMU than groups A and B. However, the pain score of group D increased afterward, with significantly longer length of hospital stay than groups A and B. There was no difference in straight leg raise among the groups.
Conclusion: Additional peripheral nerve block to PAI provides no benefit for patients undergoing TKA. Adjuvant intrathecal morphine could significantly reduce the VAS and CMU in the acute postoperative period; however, rebound pain with prolonged hospital stays was observed.

Multimodal pain management is widely used as effective opioid-sparing analgesia for total knee arthroplasty (TKA) [1,2]. This technique usually requires several procedures to target the various pain pathways and to act synergistically to promote more effective pain control and rapid recovery, while lessening associated adverse effects [1–3]. Neuraxial anesthesia may be considered as recommended anesthesia for TKA because it is associated with fewer complications and a lower mortality rate than general anesthesia [1,4]. Thus, spinal anesthesia with either periarticular injection (PAI) analgesia or peripheral nerve block (PNB) has been commonly incorporated into the multimodal regimen for controlling pain after contemporary TKA [5,6].

Although PAI may be a favorite option for some surgeons because it is effective, safe, and easy to perform directly at the surgical site [6,7], various PNBs are also now commonly

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administered, with the advent of ultrasound guidance, either in conjunction with the PAI or independently to augment the rapid recovery protocol in TKA [8,9]. Femoral nerve block (FNB) has been shown to reduce pain scores and opioid use after TKA, but with the known risk of quadriceps weakness [10]. Recently, adductor canal block (ACB) which is a motor-sparing nerve block, has been used more frequently to control pain after TKA [8–11]. Alternatively, the addition of intrathecal morphine (ITM) to spinal anesthesia has been shown to provide better control of acute postoperative pain than a placebo. However, increasing incidence of morphine-related side effects is still its concerning issue [12]. Although it is unclear whether one analgesic technique is superior to the others for controlling pain after TKA, previous studies demonstrated that either PAI or ACB could provide comparable analgesic effects with FNB [13], without increasing the risks of quadriceps weakness [2,10,11]. In addition, PAI yields comparable pain relief with ITM with fewer events of emesis and pruritus [14,15].

Theoretically, preemptive analgesia may prevent the hyperexcitability stage of peripheral and central nociceptors and thus may better mitigate an amplification of postoperative pain [16]. Therefore, either PNB or ITM which typically performed in the preoperative setting, could be an additional intervention to PAI for better achievement of pain relief and improved functional outcomes [17–19]. Nevertheless, because of the inconsistency of reported multimodal regimens across the globe, controversy remains over the additional benefits of these analgesic techniques [1,4,9,20]. Hence, the purpose of this study was to assess the effect of multiple analgesic methods which were added on PAI. We hypothesized that additional analgesic techniques may improve pain management and facilitate recovery after TKA better than using standard PAI alone.

Material and Methods

This retrospective cohort analysis allocated patients with knee osteoarthritis who underwent primary unilateral TKA performed by a single surgeon during 2016-2019. We included the patients with age >50 years as the age might be a factor affecting pain and functional scores after TKA [21,22]. Patients with a history of any previous knee surgery, knee infection, diagnosis for secondary knee osteoarthritis, history of a bleeding disorder or thromboembolic event, and allergy or contraindication to the drugs being used in this protocol were excluded. The study protocol was approved by the institutional review board before data collection.

Surgical Procedure and Outcome Measurement

All patients received an identical preemptive medication including tranquilizer and gabapentinoid on the night before the index surgery. Spinal anesthesia was performed with bupivacaine (0.5% Marcaine, AstraZeneca, Sweden) in all patients. The adjunct multimodal approaches for pain management were categorized into 4 groups: group A, received only PAI during surgery (as a control group); group B, received a single shot of ACB before surgery and intraoperative PAI; group C, received a single shot of FNB before surgery and intraoperative PAI; and group D, received spinal anesthesia with intrathecal bupivacaine and 0.1-0.2 mg of morphine and ACB combined with intraoperative PAI. There were 8 anesthesiologists, two in each group, involving in this study cohort with their preferred anesthetic technique. All the ACBs and FNBs were conducted with 10 mL of bupivacaine diluted with normal saline solution to a total volume of 20 mL and by ultrasonography with a nerve stimulator–guided technique. A prophylactic antibiotic and a tourniquet control at the thigh for 250 mmHg were used in all TKA procedures.

All patients had identical protocols including surgical techniques, postoperative pain medication, physical therapy, and rehabilitation. A standard medial parapatellar arthrotomy was performed. The proximal tibia and distal femoral bone cut were prepared by using a conventional instrument via extramedullary and intramedullary reference guides, respectively. The bone plug was used to occlude the hole at the femoral medullary canal. The soft tissue was balanced to achieve the appropriate flexion and extension gap. PAI was performed in all knees before prosthetic implantation with a multimodal drug mixture consisting of bupivacaine (20 mL in group A and 10 mL in the remaining groups) and 30 mg ketorolac (Ketolac 1 mL, SiuGuan, Taiwan) which was diluted with a sterile normal saline solution to a total volume of 75 mL [23]. The cocktail mixture was administered at the anterior portion of the knee capsule (medial retinaculum, quadriceps muscle, pes anserinus, and retropatellar fat pad) and the posterior portion (posterior capsule, medial/lateral collateral ligament, and medial/lateral meniscal remnant) with a volume of 2:1 ratio [24]. Fixed-bearing, posterior stabilized TKA prosthesis was implanted with bone cement. Before the arthrotomy closure, a deep suction drain was applied and 15 mg/kg of intra-articular tranexamic acid was poured into the knee joint [25].

After surgical intervention, a compressive dressing was applied. The drainage tube was clamped for 3 hours and removed thereafter at 24 hours. Intravenous patient-controlled analgesia (PCA) with a 100-mL solution containing 50 mg of morphine sulfate was set to inject an on-demand bolus of 1 mL with a 5-minute lockout period, and intravenous 30 mg of ketorolac was given every 8 hours. After 48 hours, the PCA and ketorolac were discarded, and naproxen 250 mg twice a day, acetaminophen 500 mg three times a day, and tranquilizer were administered orally until discharge. Postoperative physical therapy and rehabilitation including a continuous passive motion device and early ambulation with a gait aid were conducted.

The primary outcome of this study was the intensity of postoperative pain at rest which was assessed by the 10-cm visual analog scale (VAS). The patients were evaluated for the maximum pain in the laying down position on the bed after physical therapy. Another primary outcome was the cumulative morphine use (CMU) that was measured via the PCA pump. The secondary outcomes included knee function which was evaluated by the angle of maximum knee flexion and degrees of straight leg raise (SLR). The measurement was determined by a long-arm universal goniometer. The patients were assessed in the supine position and requested to flex the evaluated knee actively. The center of the goniometer was placed at the lateral femoral epicondyle. One arm was positioned toward the axis of the femur (between the lateral femoral epicondyle and the center of the greater trochanter), and the other arm was located on the axis of the tibia (between the lateral femoral epicondyle and the center of the lateral malleolus) [26]. After measurement of the maximum knee flexion angle, the patients were asked to raise the leg actively with full extension of the knee, and the goniometer was placed similarly to measure the degrees of SLR. In addition, length of hospital stay (LHS), incidence of patient-reported postoperative nausea and vomiting (PONV), and other complications were also collected. All the following outcomes were routinely recorded by the group of assessors who were blinded to the analgesic modalities.

Statistical Analysis

All characteristics and measured outcomes were demonstrated as mean and standard deviation for continuous variables and as numbers and percentages for categorical variables. The demographic variables consisted of age, gender, body mass index, and American Society of Anesthesiologists physical status classification, all of which were incorporated to a propensity score and matched among 4

Table 1
Demographic Characteristics of Total Participants and Propensity Score–Matched Patients Among Four Groups of Multimodal Analgesic Techniques.

Clinical Variables	Total Participants (N = 327)					Propensity-Matched Patients (n = 282)				
	Group A (n = 89)	Group B (n = 73)	Group C (n = 84)	Group D (n = 81)	*P*-Value	Group A (n = 66)	Group B (n = 73)	Group C (n = 70)	Group D (n = 73)	*P*-Value
Age (y)[a]	65.8 ± 7.8	67.5 ± 8.8	65.6 ± 8.2	69.0 ± 7.9	.022	66.6 ± 7.9	67.5 ± 8.8	67.3 ± 7.6	68.1 ± 7.7	.752
Gender (%)					.021					.054
Female	75 (84.3)	53 (72.6)	68 (81.0)	74 (91.4)		53 (80.3)	53 (72.6)	57 (81.4)	66 (90.4)	
Male	14 (15.7)	20 (27.4)	16 (19.0)	7 (8.6)		13 (19.7)	20 (27.4)	13 (18.6)	7 (9.6)	
BMI (kg/m^2)[a]	26.8 ± 3.5	26.9 ± 3.5	27.0 ± 4.1	27.2 ± 5.3	.920	27.5 ± 3.6	26.9 ± 3.5	27.2 ± 4.2	27.4 ± 5.5	.848
ASA classification (%)					.005					.158
1	3 (3.4)	0 (0)	6 (7.1)	0 (0)		0 (0)	0 (0)	0 (0)	0 (0)	
2	57 (64.0)	36 (49.3)	53 (63.1)	44 (54.3)		42 (63.6)	36 (49.3)	45 (64.3)	38 (52.1)	
3	29 (32.6)	37 (50.7)	25 (29.8)	37 (45.7)		24 (36.4)	37 (50.7)	25 (35.7)	35 (47.9)	
Preoperative VAS score[a]	6.4 ± 1.8	6.8 ± 2.0	7.0 ± 1.4	7.2 ± 1.7	.352	6.8 ± 2.0	6.8 ± 1.9	7.2 ± 1.6	7.1 ± 1.6	.686
Preoperative range of knee motion (degrees)[a]	107.6 ± 10.2	108.6 ± 17.4	103.2 ± 15.8	105.9 ± 22.7	.416	108.3 ± 12.1	108.6 ± 17.4	106.7 ± 18.6	103.7 ± 21.9	.508

Group A: PAI; group B: ACB + PAI; group C: FNB + PAI; group D: ITM + ACB + PAI.
BMI, body mass index; ASA, American Society of Anesthesiologists; VAS, visual analog scale; PAI, periarticular injection; ACB, adductor canal block; FNB, femoral canal block; ITM, intrathecal morphine.
[a] Data are presented as mean ± standard deviation; a *P*-value <.05 indicates statistical significance.

groups of multimodal techniques. Normality of data was assessed with the Kolmogorov-Smirnov test. Comparison between groups was evaluated using analysis of variance for continuous variables and the chi-squared test for categorical variables. Post hoc pairwise comparisons by Student's *t*-test were performed after significant differences were found. The sample size of at least 50 patients in each arm would have 85.1% statistical power with a two-sided alpha value of 0.05 to detect a difference of 1.5 of VAS for the pain score [27] with a standard deviation of 2.5. Stata/MP 15.0 software (StataCorp LP, College Station, TX, USA) was used for all statistical analyses and statistical significance being defined as a *P*-value <.05.

Results

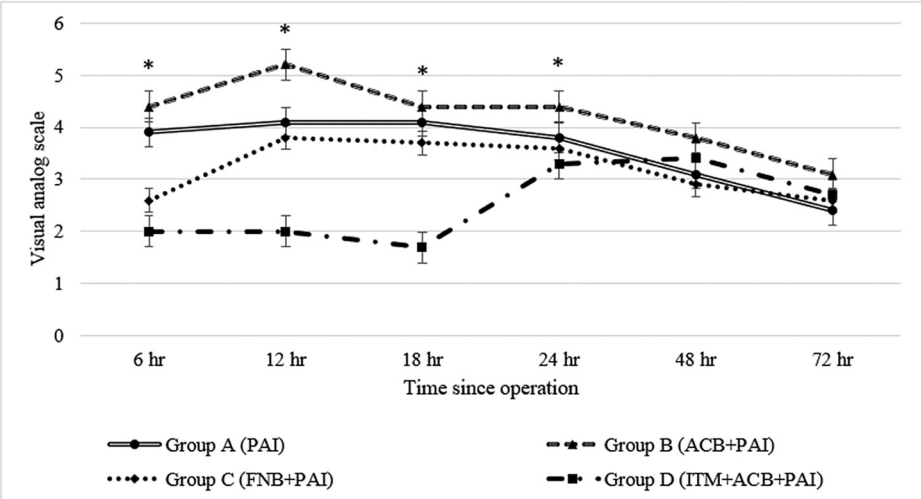
There were 327 patients included in this study and classified into 4 groups of multimodal techniques: 89 patients for group A (PAI), 73 patients for group B (ACB + PAI), 84 patients for group C (FNB + PAI), and 81 patients for group D (ITM + ACB + PAI). After propensity score matching, 282 patients (66, 73, 70, and 73 patients for groups A, B, C, and D, respectively) with no significant differences in demographic parameters were assessed. The overall mean age of patients was 67.4 ± 8.0 years, with the predominant female gender (81.2%). There was no significant difference in the preoperative VAS score and range of knee motion among the groups (Table 1).

There were statistically significant differences in postoperative VAS among the four groups during the first 24 hours (Table 2). Post hoc pairwise comparisons showed significantly lower VAS of group D than group A at 6-18 hours, group B at 6-24 hours, and group C at 12-18 hours after the surgery, whereas there was no statistically significant difference regarding VAS when either group B or C was compared with group A (Fig. 1). However, the pain score of group D increased from 18 hours onward, and the VAS equalized to the other three groups at 48 and 72 hours postoperatively.

Table 2
Comparison of All Measured Outcomes Among Four Groups of Multimodal Analgesic Techniques After Propensity Score matching.

Outcomes	Group A (n = 66)	Group B (n = 73)	Group C (n = 70)	Group D (n = 73)	*P*-Value
VAS score[a]					
6 h	3.9 ± 3.1	4.4 ± 3.2	2.6 ± 2.9	2.0 ± 2.6	<.001
12 h	4.1 ± 2.6	5.2 ± 3.0	3.8 ± 2.8	2.0 ± 2.2	<.001
18 h	4.1 ± 2.4	4.4 ± 2.4	3.7 ± 2.5	1.7 ± 1.9	<.001
24 h	3.8 ± 2.0	4.4 ± 2.2	3.6 ± 2.3	3.3 ± 2.4	.015
48 h	3.1 ± 1.8	3.8 ± 2.2	2.9 ± 2.1	3.4 ± 2.0	.062
72 h	2.4 ± 1.8	3.1 ± 1.8	2.6 ± 2.1	2.7 ± 2.1	.218
Knee flexion angle (degrees)[a]					
24 h	55.9 ± 17.7	57.5 ± 20.9	56.6 ± 17.3	53.6 ± 19.1	.649
48 h	75.2 ± 17.4	74.4 ± 18.3	71.6 ± 15.7	72.3 ± 17.5	.589
72 h	83.9 ± 14.0	88.1 ± 13.7	84.7 ± 13.8	79.6 ± 14.6	.005
SLR (degrees)[a]					
24 h	26.8 ± 31.4	36.0 ± 34.2	44.6 ± 33.5	38.9 ± 35.6	.064
48 h	34.0 ± 34.4	45.0 ± 35.2	51.1 ± 32.6	45.5 ± 38.2	.101
72 h	48.1 ± 37.5	57.6 ± 35.1	55.1 ± 37.3	49.6 ± 40.5	.430
CMU (mL)[a]	16.0 ± 13.2	17.1 ± 13.3	12.2 ± 13.3	6.2 ± 7.8	<.001
LHS (d)[a]	4.0 ± 1.0	3.9 ± 0.8	4.2 ± 0.9	4.6 ± 1.1	<.001
PONV (%)					
<24 h	41.5	31.8	15.9	56.3	<.001
≥24 h	3.8	1.5	1.6	0	.429

Group A: PAI; group B: ACB + PAI; group C: FNB + PAI; group D: ITM + ACB + PAI.
VAS, visual analog scale; SLR, straight leg raise; CMU, cumulative morphine use; LHS, length of hospital stay; PONV, postoperative nausea and vomiting; PAI, periarticular injection; ACB, adductor canal block; FNB, femoral canal block; ITM, intrathecal morphine.
[a] Data are presented as mean ± standard deviation; a *P*-value <.05 indicates statistical significance.



Time since operation	Post hoc pairwise comparisons *p*-value					
	Group A/B	Group A/C	Group A/D	Group B/C	Group B/D	Group C/D
6 hr	NS	NS	0.009	0.020	<0.001	NS
12 hr	NS	NS	0.001	NS	<0.001	0.003
18 hr	NS	NS	<0.001	NS	<0.001	0.001
24 hr	NS	NS	NS	NS	0.018	NS

Fig. 1. A graph showing mean postoperative VAS among four groups of multimodal analgesic techniques with post hoc pairwise comparisons of groups A/B/C/D. Asterisks (*) indicate the statistically significant differences among the groups (ANOVA). PAI, periarticular injection; ACB, adductor canal block; FNB, femoral canal block; ITM, intrathecal morphine; NS, nonsignificant.

Patients in group D also required the least morphine via the PCA pump in the 48 hours after the surgery, where post hoc pairwise comparisons demonstrated significantly less CMU in group D than group A and B patients ($P = .002$ and <.001, respectively) (Table 2; Fig. 2).

There were no significant differences among the groups in the postoperative angle of knee flexion and degrees of SLR along the study period, except the knee flexion angle at 72 hours after the surgery ($P = .005$) (Table 2). Post hoc pairwise comparisons demonstrated a greater angle of knee flexion in group B than group D patients (88.1 ± 13.7 and 79.6 ± 14.6, respectively, $P = .008$).

The average LHS was found to have a significant difference among the groups, in which the LHS of group D was significantly longer than that of groups A and B ($P = .005$ and .001, respectively) (Table 2; Fig. 3). The percentage of patients who experienced PONV in the first 24 hours after the surgery was significantly different among the groups (Table 2). The post hoc pairwise comparisons demonstrated that patients in group C had less emesis than groups A, B, and D ($P = .002$, .034, and <0.001, respectively). Nevertheless,

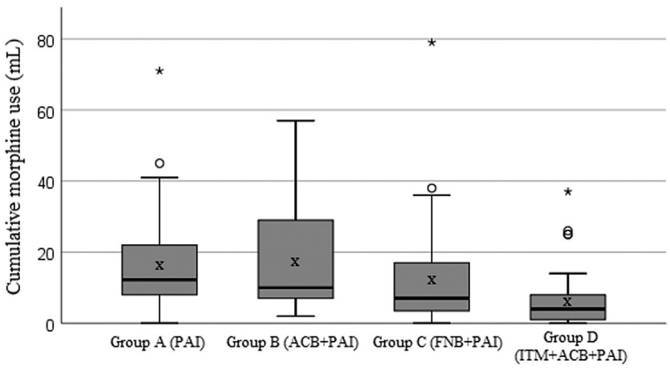


Fig. 2. A boxplot showing the distribution of CMU among four groups of multimodal analgesic techniques. The boxes represent the median, interquartile range, and the whiskers of data range. Cross marks (X) indicate the mean, circles (O) represent the potential outliers, and asterisks (*) display the extreme values. PAI, periarticular injection; ACB, adductor canal block; FNB, femoral canal block; ITM, intrathecal morphine.

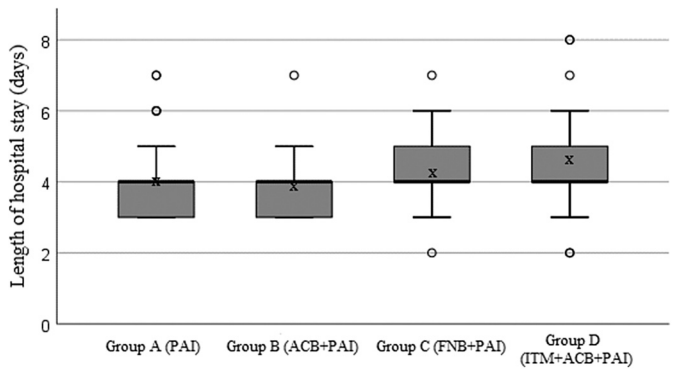


Fig. 3. A boxplot showing the distribution of LHS among four groups of multimodal analgesic techniques. The boxes represent the median, interquartile range, and the whiskers of data range. Cross marks (X) indicate the mean, and circles (O) represent the potential outliers. PAI, periarticular injection; ACB, adductor canal block; FNB, femoral canal block; ITM, intrathecal morphine.

the incidence of PONV after 24 hours declined in all groups, with no significant difference between groups (Table 2).

No complications related to analgesic procedures, such as infection, nerve injury, and fall, were identified.

Discussion

Adequate postoperative pain control after TKA could improve rehabilitation, functional recovery, and patient satisfaction, as well as being associated with better functional scores at 2 years of follow-up [28,29]. Although it is still controversial as to what is the most effective combination among multiple analgesic methods, we found that PAI + ACB and PAI + FNB groups showed comparable outcomes with the PAI group, regarding mean VAS pain score, CMU, knee flexion angle, SLR, LHS, and incidence of PONV. This accords with a meta-analysis study by Ma et al [17] in which they showed no differences in pain outcome, morphine requirement, and LHS between patients who received ACB + PAI compared with PAI alone. Recent randomized controlled trials have revealed that additional single-shot ACB to PAI could not significantly reduce pain intensity and opioid use after TKA when compared with the use of PAI only [30].

For additional FNB, Youm et al [18] demonstrated that preemptive FNB in adjunction to PAI could reduce the rebound pain and thus result in significantly lower VAS at 24 hours and less total opioid use in the first 72 hours after TKA than the PAI-only group, without differences in range of knee motion and time to walk. Furthermore, Marino et al [31] conducted a randomized controlled trial to compare the analgesic efficacy of continuous FNB + PAI with PAI with liposomal bupivacaine and found that patients who received additional FNB reported significantly lower pain scores during the maximum knee flexion at 24 hours. Nevertheless, as per our findings, there was no significant difference in primary outcomes whether FNB or ACB was used in conjunction with PAI, except significantly better pain reduction of the PAI + FNB than the PAI + ACB group at 6 hours postoperatively. This potentially lower pain score in the PAI + FNB group seemed to yield an opioid-sparing effect with slightly less morphine consumption postoperatively and significantly limited the subsequent events of PONV. Although other novel motor-sparing nerve blocks including lateral femoral cutaneous and obturator nerve block, as well as anesthetic infiltration into the interspace between the popliteal artery and the capsule of the posterior knee, have been introduced, there is also no sufficient evidence to support the routine use of combined analgesic methods as triple or quadruple nerve blocks in clinical practice [9,32,33].

Over the recent years, there was a question of whether ITM still plays a role in the era of modern multimodal analgesia in which PAI and regional analgesic techniques are commonly utilized. We found that the patients who received PAI combined with ACB + ITM showed lower VAS during the first 24 hours after the surgery than those receiving the other three methods and required significantly less CMU in 48 hours than patients who had either PAI alone or PAI + ACB. The additional benefit of ITM to PAI + PNB has also been demonstrated by other investigations [34,35]. One randomized double-blind trial revealed that patients who received combined analgesic methods including PAI, ACB, and low-dose (0.1 mg) ITM showed favorable outcomes as evidenced by lower pain scores at 12 hours and less CMU in the first 48 hours after TKA [30]. Sundarathiti et al [35] reported an improved analgesic profile which included significantly lower mean VAS, fewer patients experienced moderate-to-severe pain in the first 24 hours, and less intravenous tramadol request in 48 hours after TKA, when ITM (0.035 mg) was added to continuous FNB. However, approximately 40% of patients who received additional ITM had PONV at 6 hours postoperatively, where the incidence was significantly higher than those who were given only continuous FNB.

Despite early analgesic benefits, patients who received PAI + ACB + ITM in our study had rebound pain which began from 18 hours after the surgery and onward. In addition, the patients with PAI + ACB + ITM experienced significantly more PONV than PAI + FNB patients during the first 24 hours. They also had fewer degrees of the knee flexion angle at 72 hours postoperatively than patients with PAI + ACB and subsequently stayed in the hospital significantly longer than patients who received motor-sparing analgesic techniques, either PAI alone or PAI + ACB. A recent meta-analysis also found that ITM was associated with significantly more morphine-related complications and extended inpatient length of stay compared with PAI only [15]. Although the phenomenon of rebound pain has seldom been reported in ITM, it has been well recognized after PNB resolution and probably associated with undesirable responses and satisfaction from patients [36,37]. France et al [38] found that single injection of ITM during posterolateral lumbar fusion surgery tended to reduce the VAS pain score and significantly decreased the amount of morphine required during the first 24 hours after surgery. However, there were reversals in VAS and morphine consumption afterward, where lower VAS and less narcotic use were observed in the control group. Kaczocha et al [39] demonstrated a significant reduction of levels of circulating cortisol and endogenous cannabinoids which included anandamide, palmitoylethanolamide, and oleoylethanolamide in patients undergoing TKA with ITM when compared with the control group. Thus, they hypothesized that activation of the central opioid receptors could result in less stress response to surgical procedures and subsequently suppressed the biosynthesis of endogenous cannabinoids.

Nonetheless, there were some limitations in our study. The first limitation is related to the study design which was a retrospective cohort. However, we performed propensity score matching to reduce confounding among the control and study groups, and the sample size after the matching still had >80% power to differentiate the clinical significance of VAS. Second, our study consisted of predominantly female patients. Nevertheless, previous studies revealed that gender did not affect pain and functional recovery after TKA [40]. Third, we evaluated the severity of pain only at rest after the physical therapy session. Anyhow, the CMU may objectively reflect the overall pain intensity during 48 hours postoperatively. Finally, although there were many anesthesiologists involved in this study, all the procedures have been conducted with their preference and expertise. This situation would have prevented undue effects from an unfamiliar procedure, allowed for better external validity, and thus provided evidence that reflected real-life practice.

Conclusions

When PAI is administered to control post-TKA pain, the additional PNB could not improve the primary outcomes of VAS for pain and CMU. The adjuvant ITM to PAI and ACB may provide a better analgesic profile. However, the phenomenon of rebound pain, prolonged LHS, and potentially increased risk of PONV may be concerning drawbacks of the ITM adjuvant. Hence, risk-benefit based on the individual patient's condition and surgical environment should be carefully assessed.

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