European Journal of Orthopaedic Surgery & Traumatology
https://doi.org/10.1007/s00590-022-03405-w

ORIGINAL ARTICLE

Effect of multiple analgesic pathways including local infiltration analgesia, peripheral nerve blocks, and intrathecal morphine for controlling pain after total knee arthroplasty

Siriluk Toolyodpun[1] · Artit Laoruengthana[2] · Inthiporn Kositanurit[1] · Surachart Podjanasupawun[1] · Chao Saenghirunvattana[3] · Krit Pongpirul[4,5]

Received: 7 June 2022 / Accepted: 28 September 2022

Abstract

Background We questioned whether the triple analgesic pathways procedure via local infiltration analgesia (LIA), peripheral nerve blocks, and intrathecal morphine (ITM) is superior to LIA only for controlling pain after Total Knee Arthroplasty (TKA).

Methods This retrospective study included 192 primary TKA patients. Group A (76 patients) received LIA only, Group B (61 patients) had ITM, adductor canal block and LIA, while Group C (55 patients) received ITM, femoral nerve block and LIA. A propensity score-matched analysis was used to compare visual analog scales (VAS) for pain intensity, total amount of morphine consumption (TMC), angle of knee flexion, and length of hospital stay (LHS).

Results Group A showed significantly higher VAS than Group B at 12 h (4.27 ± 2.70 vs 2.42 ± 2.35) and 18 h (4.24 ± 2.35 vs 2.18 ± 2.02), and significantly higher than Group C at 6 h (3.46 ± 3.07 vs 0.60 ± 1.50), 12 h (4.27 ± 2.70 vs 0.89 ± 1.48), and 18 h postoperative (4.24 ± 2.35 vs 1.82 ± 2.18). However, the VAS of Group C and B converged to equalize with Group A after 12 and 18 h, respectively. The TMC at 48 h postoperative of Group A was higher than that of Group B ($p < 0.01$). Nevertheless, there was no difference between groups in terms of knee flexion and LHS, except the LHS of Group B was longer than Group A ($p = 0.04$).

Conclusion Triple analgesic pathways could provide a better initial analgesic profile. However, the pain seems to be rebound after resolution of nerve block and ITM, with potentially longer LHS.

Keywords Total knee arthroplasty · Adductor canal block · Intrathecal morphine · Local infiltration analgesia · Femoral nerve block · Pain control

Introduction

Currently, pain control after total knee arthroplasty (TKA) is moving toward multimodal analgesia which includes neuraxial anesthesia (NA), peripheral nerve block (PNB), and local infiltration analgesia (LIA) [1]. NA has been reported to be associated with fewer complications such as deep vein thrombosis, pneumonia and pulmonary embolism, as well as a shorter length of hospital stay than is usual with general anesthesia (GA) [2]. Thus, NA may be considered as a preferred method to enhance rapid recovery after TKA. Additional intrathecal morphine (ITM) in spinal anesthesia is a simple and effective technique to reduce pain but opioid-related side effects such as respiratory depression, pruritus, and nausea and vomiting have been reported. However, using low-dose ITM will significantly reduce the

✉ Inthiporn Kositanurit
inthipornk@nu.ac.th

1 Department of Anesthesiology, Faculty of Medicine, Naresuan University, Phitsanulok, Thailand

2 Department of Orthopaedics, Faculty of Medicine, Naresuan University, Phitsanulok, Thailand

3 Department of Anesthesiology, Huachiew Hospital, Bangkok, Thailand

4 Department of Preventive and Social Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

5 Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

Published online: 19 October 2022

risk of those unpleasant effects [3, 4]. Over recent years, PNB, either femoral nerve block (FNB) or adductor canal block (ACB) has become increasingly incorporated into multimodal regimens to enhance patient recovery after TKA. Alternatively, surgeon-administered LIA has gained popularity due to its simplicity as an anesthetic infiltration method at the surgical site and its proven efficacy [5].

However, it is still inconclusive whether one analgesic technique is more effective than the other for managing post-TKA pain [4, 6]. Moreover, controversy remains over how many analgesic techniques and what combination is enough for enhancing recovery after TKA. Some studies reveal various multimodal regimens including combined local and regional anesthesia, and triple or quadruple nerve blocks, however, there is seldom a report on the efficacy of using a combination of triple analgesic pathways via LIA, PNB, and ITM [7–9]. Hence, the purpose of this study was to evaluate perioperative outcomes after TKA in patients who received this triple analgesic approach when compared to those who had LIA only. We hypothesized that this multimodal analgesia may improve perioperative pain control and rapid patient recovery than utilizing a single approach.

Methods

We conducted a retrospective analysis of patients who had undergone unilateral primary TKA, by a single surgeon, from January 2018 to July 2020. Cases where patients, before their surgery, had a history of knee infection, a previous knee surgery, or had been previously diagnosed with secondary osteoarthritis, were excluded. With these exclusions, the cases of 192 patients who had undergone TKA procedures were included. These TKAs procedures had been attended variously by seven anesthesiologists, applying their preferred anesthetic techniques.

The 192 patient cases were divided into three groups regarding preferred method of individual anesthesiologist: Group A, as the control group, consisted of 76 patients who had received spinal anesthesia (SA) only. Group B, 61 patients who had ITM and a single shot of adductor canal block (ACB), and Group C comprised 55 patients who had received ITM and a single shot of femoral nerve block (FNB). Three anesthesiologists had been involved with the patients in Group A, three in Group B, and one with Group C patients. All patients also received local infiltration analgesia (LIA) which was administered by surgeon. The study was approved by our Institutional Review Board (IRB) before data collection.

In the TKA procedures undertaken by the patients, all the patients had received preemptive medication that comprised gabapentin and anxiolytic drug on the night before the index surgery. For Group B, a single shot of ACB was administered prior to SA with 10 ml of 0.5% bupivacaine which was diluted with normal saline solution (NSS) to a total volume of 20 ml, by using ultrasonography guidance. For Group C, analgesic cocktails consisting of 2 ml of 0.5% bupivacaine, 6 ml of 2% lidocaine with epinephrine, 4 mg of dexamethasone, and 2 mg of morphine were used to perform a single shot of traditional FNB, by using landmark, prior to SA. The SA was performed at the L2-3 or L3-4 intervertebral space with bupivacaine (0.5% Heavy Marcaine, AstraZeneca, Sweden) for all patients, and 0.2 mg of morphine was added into the bupivacaine during the SA in Group B and C.

A prophylactic antibiotic had been administered before all the TKA procedures. A standard medial parapatellar arthrotomy with approximately 10 cm of skin incision was performed under tourniquet pressure of 250 mmHg. The proximal tibia bone cut was prepared by using conventional extramedullary reference guides, whereas the distal femoral bone was cut via intramedullary reference guides. The soft tissue was balanced to achieve appropriate flexion and extension gap. For Group A patients, analgesic cocktails consisting of 20 ml of 0.5% bupivacaine and 30 mg ketorolac (Ketolac 1 ml, SiuGuan, Taiwan), which were diluted with NSS to a total volume of 75 ml, were then applied as LIA. In Group B and C patients, LIA was administered using an analgesic cocktail consisting of 10 ml of 0.5% bupivacaine and 30 mg of ketorolac, which were diluted with NSS to a total volume of 75 ml. Fixed-bearing (FB), posterior stabilized (PS) TKA prostheses were implanted with bone cement in all patients. A suction drain was applied, and 15 mg/kg of intra-articular tranexamic acid was poured into the knee joint before the arthrotomy closure. A compressive dressing was applied while the drain was clamped for 3 h and was subsequently removed at 24 h.

During the first 48 h postoperative, Group A and B had intravenous patient-controlled analgesia (PCA) morphine, which was set to inject an on-demand bolus of 1 of a 100 ml solution containing morphine sulfate 50 mg (0.5 mg/ml) with a 5 min lockout period, while patients in Group C did not receive any opioids during the first 24 h. Intravenous (IV) 30 mg of ketorolac was also given every 8 h to all groups. After 48 h, the morphine PCA and ketorolac were discarded, and thereby 2 mg (mg) of morphine were given intravenously every 8 h. Additionally, 250 mg of oral naproxen was administered twice a day, and an extra 2 mg of IV morphine was given on-demand as rescue analgesia until discharge. Postoperative physical therapy which included a continuous passive motion (CPM) device and early ambulation with gait aids were started on the next day after the index surgery in all groups.

The primary outcomes of this study are a comparison of 10 cm visual analog scales (VAS) for postoperative pain at rest and the total amount of morphine consumption (TMC)

during the first 48 h, between the three different pain regimes applied to the patients in Group A, B and C. The secondary outcomes included analysis of the angle of knee flexion, the incidence of postoperative nausea and vomiting (PONV), length of hospital stay (LHS), as well as any other complications experienced. In addition, the patients' total blood volume (TBV) was calculated using the equation of Nadler et al. [10]. The difference between preoperative and 24 h postoperative hemoglobin (Hb) was applied with the hemoglobin balance method to determine perioperative blood loss (PBL) [11]. Patients would have received a blood transfusion when serum Hb level dropped below 9.0 g/dl which is our institution transfusion trigger. All the aforementioned outcomes were routinely recorded by group of assessors who were blinded to the analgesic modalities.

Statistical analysis

A propensity score-matched analysis was used to reduce the confounding among the three groups of patients. These confounding adjustments included age, gender, body mass index (BMI), American Society of Anesthesiologists (ASA) physical status classification, and level of preoperative Hb which was determined as no-anemia (Hb ≥ 12 for female and ≥ 13 for male) vs anemia (Hb < 12 for female and < 13 for male). All measured characteristics and outcomes were summarized with descriptive statistics and were presented as means and standard deviation, frequencies and percentages as appropriate. All outcomes were compared between groups using ANOVA for continuous variables and Chi-square for categorical variables. According to a systemic review of minimal clinically important differences (MCID) for pain management following total hip and knee arthroplasty, the MCID of VAS at rest was 1.5 [12], the sample size of at least 55 patients in each arm provided 88.2% power with type I error of 5% to detect a difference of 1.5 of VAS with SD of 2.5. Stata/MP 15.0 software (StataCorp LP, College Station, TX, USA) was used for all statistical analyses. Statistical significance was defined as $p < 0.05$.

Results

After propensity score-matched method, there were remaining 182 patients with no significant differences in demographic parameters (Table 1).

While the mean preoperative VAS was comparable among three anesthetic groups. The mean VAS for pain scores at 6, 12, and 18 h after the surgery were significantly different between groups (Table 2). After post hoc pairwise comparisons, Group A showed significantly higher VAS than Group B at 12 ($p < 0.01$) and 18 h ($p < 0.01$), and higher than Group C at 6, 12, and 18 h after the surgery ($p < 0.01$, $p < 0.01$, and $p < 0.01$, respectively), while Group B had significantly higher VAS than Group C at 6 and 12 h postoperative ($p = 0.01$ and $p = 0.01$, respectively) (Fig. 1 and Table 3). However, the pain score of Group B increased from 18 h onward and for Group C it increased from 12 h onward, with the VAS of both groups were not significantly different from Group A at 24–96 h postoperative. The TMC at 24 and 48 h postoperative of Group A was significantly higher than that of Group B ($p < 0.01$), while Group C did

Table 1 Demographic characteristics of patients in three anesthetic groups after propensity score matching

	Before propensity score matching ($N = 192$)				After propensity score matching ($N = 182$)			
	Group A	Group B	Group C	*p*-value	Group A	Group B	Group C	*p*-value
N	76	61	55		72	55	55	
Age	65.33 ± 7.50	68.10 ± 7.79	65.78 ± 8.16	0.10	65.17 ± 7.65	67.75 ± 7.98	65.78 ± 8.16	0.18
Gender								
Female	63 (82.9%)	55 (90.2%)	47 (85.5%)	0.47	59 (81.9%)	50 (90.9%)	47 (85.5%)	0.36
Male	13 (17.1%)	6 (9.8%)	8 (14.5%)		13 (18.1%)	5 (9.1%)	8 (14.5%)	
BMI	26.92 ± 3.62	27.30 ± 5.32	27.03 ± 4.33	0.88	27.04 ± 3.64	27.34 ± 5.56	27.03 ± 4.33	0.92
ASA								
1	3 (3.9%)	0 (0%)	2 (3.6%)	0.15	2 (2.8%)	0 (0%)	2 (3.6%)	0.46
2	52 (68.4%)	33 (54.1%)	32 (58.2%)		49 (68.1%)	33 (60%)	32 (58.2%)	
3	21 (27.6%)	28 (45.9%)	21 (38.2%)		21 (29.2%)	22 (40%)	21 (38.2%)	
Pre-op Hb								
No-anemia	55 (72.4%)	36 (59%)	35 (63.6%)	0.25	55 (76.4%)	36 (65.5%)	35 (63.6%)	0.23
Anemia	21 (27.6%)	25 (41%)	20 (36.4%)		17 (23.6%)	19 (34.5%)	20 (36.4%)	

PAI = periarticular anesthetic injection, ACB = adductor canal block, FB = femoral block, ITM = intrathecal morphine, No-anemia = preoperative Hb ≥ 12 in female, and ≥ 13 in male, Anemia = preoperative Hb < 12 in female, and < 13 in male ANOVA test and Chi-square test

Table 2 Comparison of all measured outcomes among three anesthetic groups after propensity score matching

	Group A ($N=72$)	Group B ($N=55$)	Group C ($N=55$)	p value
Visual analog scale for pain intensity				
Preoperative	6.68 ± 2.16	6.82 ± 2.08	6.94 ± 1.81	0.84
6 h	3.46 ± 3.07	2.48 ± 2.89	0.60 ± 1.50	< 0.01*
12 h	4.27 ± 2.70	2.42 ± 2.35	0.89 ± 1.48	< 0.01*
18 h	4.24 ± 2.35	2.18 ± 2.02	1.82 ± 2.18	< 0.01*
24 h	3.73 ± 2.02	3.50 ± 2.42	2.71 ± 2.41	0.05
48 h	3.13 ± 1.81	3.29 ± 2.12	3.26 ± 2.30	0.89
72 h	2.24 ± 1.87	2.53 ± 2.12	2.79 ± 1.98	0.32
96 h	1.46 ± 1.35	1.84 ± 1.53	1.48 ± 1.88	0.13
Angle of knee flexion				
Preoperative	111.24 ± 14.19	104.93 ± 18.51	103.36 ± 20.33	0.09
24 h	53.18 ± 16.66	51.89 ± 18.38	57.79 ± 16.75	0.18
48 h	74.27 ± 17.72	72.75 ± 16.40	76.02 ± 14.17	0.59
72 h	82.70 ± 13.37	81.36 ± 14.23	86.95 ± 10.88	0.13
96 h	90.43 ± 11.66	87.44 ± 13.16	91.06 ± 11.69	0.37
Total morphine consumption				
During the first 24 h	11.87 ± 10.27	4.17 ± 5.27	N/A	< 0.01*
During the first 48 h	16.05 ± 14.09	6.40 ± 8.22	N/A	< 0.01*
PBL at 24 h postoperative				
	447.19 ± 235.89	590.23 ± 269.42	641.24 ± 355.12	< 0.01*
Blood transfusion rate				
Blood transfusion rate	5.6% (4/72)	18.2% (10/55)	16.4% (9/55)	0.06
Postoperative nausea and vomit (PONV)				
During the first 24 h	41.7% (30/72)	61.8% (34/55)	65.5% (36/55)	0.07
After 24 h	4.2% (3/72)	0% (0/55)	3.6% (2/55)	0.40

Asterisks (*) indicate the statistically significant differences among the groups (ANOVA)

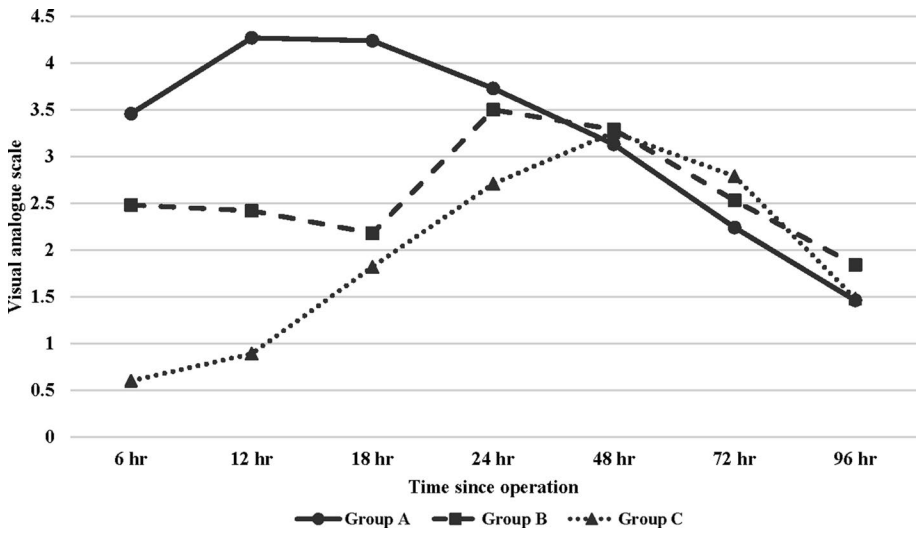

Fig. 1 Mean VAS at 6-96 hours postoperative among three anesthetic groups

not receive either morphine via PCA or equivalent opioids during the first 24 h (Table 2).

There was no difference in angle of knee flexion among the groups preoperative or postoperative during the study period. The incidence of PONV during the first 24 h and afterward was not significantly different among groups. Patients in Group A had significantly less mean PBL than those of Group B ($p=0.04$) and Group C ($p<0.01$), while

Table 3 Post hoc pairwise comparisons of postoperative VAS among groups A/B/C after propensity score matching

Time since operation	Post hoc pairwise comparisons *p*-value		
	Group A/B	Group A/C	Group B/C
6 h	0.18	< 0.01*	0.01*
12 h	< 0.01*	< 0.01*	0.01*
18 h	< 0.01*	< 0.01*	0.79
24 h	0.85	0.05	0.20

Asterisks (*) indicate the statistically significant differences among the groups

there was no difference between Group B and C. The blood transfusion rate of patients in Groups B and C tended to be higher than in Group A, but this was not statistically significant (Table 2). The average LHS of Group B was significantly longer than Group A ($p = 0.04$), while there was no difference between Group A and C, or between Group B and C (Fig. 2). Additionally, no acute complications were identified, such as infection, wound problem, venous thromboembolism, and adverse event related to analgesic procedures such as nerve injury and fall.

Discussion

Although the field of anesthesia has made substantial advances in pain control and recovery after TKA, the benefit of using multiple analgesic pathways which include neuraxial and peripheral regional anesthetic techniques and LIA has yet to be evaluated. In the present study, we found that Group C showed significantly lower mean VAS than Group A at 6, 12, 18 h postoperative, and significantly lower than Group B at 6 and 12 h after the surgery. Patients in Group B had significantly lower mean VAS than those who in Group A at 12 and 18 h after TKA, and thus required significantly less morphine via PCA at 24 and 48 h compared to Group A. By using low-dose ITM (0.2 mg), we found that the incidence of PONV was not significantly different among groups. These findings accorded with a study by Cheah et al. [13] who demonstrated that ITM could reduce initial pain scores and opioid consumption, without a higher incidence of PONV. The meta-analysis also showed that an ITM dose of less than 0.3 mg had a significantly lower risk of negative side effects such as PONV, pruritus and respiratory depression than a dose greater than 0.3 mg [3].

Despite early analgesic benefits, we found the pain score of Group C increased from 12 h, while Group B began from 18 h onward. Additionally, patients in Group B stayed in the hospital significantly longer than Group A. This finding has been well recognized after PNB resolution which the nociceptive input from the site of injury could become apparent and the pain trajectory is converged [14]. Performing ACB with ultrasound guidance in Group B, which could reduce mechanical trauma to the nerve as opposed to landmarks or paresthesia-based approaches, may be the reason why rebound response occurs later than those of Group C [15]. Co-administration of dexamethasone, morphine and bupivacaine for FNB in Group C may provide an intense analgesic effect and that may be another explanation of early rebound response following FNB resolution [16, 17]. Otherwise, this rebound phenomenon may be a response following the initial analgesia effect of ITM which is often very obvious. Kaczocha et al. [18] demonstrated a significant reduction of levels of circulating cortisol and endogenous cannabinoids in patients undergoing TKA with ITM compared to those who received a placebo. They hypothesized that activation of the central opioid receptors will mitigate stress response to surgical procedures, and then suppress the biosynthesis of endogenous cannabinoids. Also, France et al. [19] revealed that a single injection of ITM could reduce pain score and

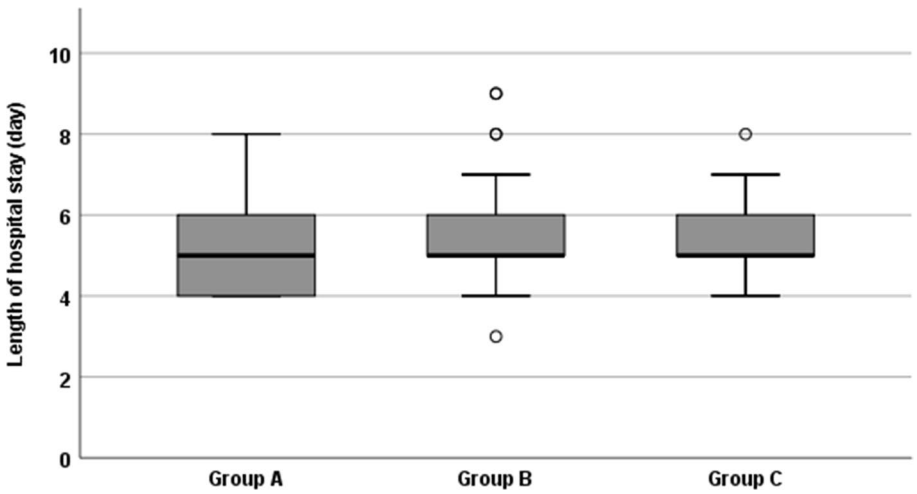

Fig. 2 Average LHS among three anesthetic groups

TMC during the first 24 h after posterolateral lumbar fusion surgery. Nevertheless, the pain scores and TMC required in ITM group was more than that of the control group afterward. Furthermore, a recent meta-analysis showed that additional ITM may contribute to poor mobilization and prolonged hospital stay in patients undergoing total knee and hip arthroplasty when compared to using PAI only [4]. Thus, patient education on appropriate expectations regarding PNB and ITM offset could help alleviate unsatisfactory responses.

In previous studies, inadequate pain control after TKA has been demonstrated to be possibly associated with higher perioperative blood loss and stress on the cardiovascular system [20, 21]. Interestingly, although the patients in Group B and C had significantly lower pain scores than those who received PAI only, they conversely had significantly more PBL than patients in Group A and also tended to require more blood transfusion. We hypothesized that the intrathecal morphine might decrease sympathetic nerve activity and thereby cause peripheral venodilation at the surgical site and increase blood loss [22].

Nevertheless, we are aware of some limitations in the present study. The first, inherent limitation is associated with a retrospective study of this type. Hence, the propensity score matching was applied to mitigate some confounding factors in the demographics of all groups. Second, there were seven anesthesiologists involved in our study. Nonetheless, this situation may allow for better external validity as well as better reflect real-life practice because all the anesthesiologists independently performed a preferred analgesic technique with their expertise.

Conclusion

Triple analgesic pathways could provide a better initial analgesic profile. However, the pain seems to be rebound after resolution of nerve block and ITM. Moreover, patient who received this triple analgesic approach had significantly more blood loss and tended to have longer LHS than those who received LIA only. Hence, the risk–benefit balanced when using this multimodal analgesia should be carefully assessed based on the individual patient's condition.

Acknowledgements The authors wish to thank Mr. Roy I. Morien of the Naresuan University Graduate School for his assistance in editing the English expression and grammar in this document. We also thank Atthakorn Jarusriwanna, MD, Piti Rattanaprichavej, MD, Kamonnop Sahasoonthorn, MD, Nopparat Santisathaporn, MD, Parin Samapath, MD, Passakorn Teekaweerakit, MD and Ms.Dollapas Punpanich for their technical of assistance.

Declarations

Conflicts of interest The authors declare no conflicts of interest.

References

1. Memtsoudis SG, Cozowicz C, Bekeris J et al (2019) Anaesthetic care of patients undergoing primary hip and knee arthroplasty: consensus recommendations from the international consensus on anaesthesia-related outcomes after surgery group (ICAROS) based on a systematic review and meta-analysis. Br J Anaesth 123(3):269–287. https://doi.org/10.1016/j.bja.2019.05.042
2. Hu S, Zhang ZY, Hua YQ, Li J, Cai ZD (2009) A comparison of regional and general anaesthesia for total replacement of the hip or knee: a meta-analysis. J Bone Joint Surg Br 91:935–942. https://doi.org/10.1302/0301-620X.91B7.21538
3. Gehling M, Tryba M (2009) Risks and side-effects of intrathecal morphine combined with spinal anaesthesia: a meta-analysis. Anaesthesia 64(6):643–651. https://doi.org/10.1111/j.1365-2044.2008.05817.x
4. Qi BC, Yu J, Qiao WS (2020) Comparison of intrathecal morphine versus local infiltration analgesia for pain control in total knee and hip arthroplasty: a meta-analysis. Medicine (Baltimore) 99(36):e21971. https://doi.org/10.1097/MD.0000000000021971
5. Seangleulur A, Vanasbodeekul P, Prapaitrakool S, Worathongchai S, Anothaisintawee T, McEvoy M, Vendittoli PA, Attia J, Thakkinstian A (2016) The efficacy of local infiltration analgesia in the early postoperative period after total knee arthroplasty: a systematic review and meta-analysis. Eur J Anaesthesiol 33(11):816–831. https://doi.org/10.1097/eja.0000000000000516
6. Fan L, Zhu C, Zan P, Yu X, Liu J, Sun Q et al (2015) The Comparison of local infiltration Analgesia with Peripheral nerve block following total knee arthroplasty (TKA): a systematic review with meta-analysis. J Arthroplasty 30(9):1664–1671. https://doi.org/10.1016/j.arth.2015.04.006
7. Qin L, You D, Zhao G, Li L, Zhao S (2021) A comparison of analgesic techniques for total knee arthroplasty: a network meta-analysis. J Clin Anesth 71:110257. https://doi.org/10.1016/j.jclinane.2021.110257
8. Wang Q, Hu J, Zeng Y, Li D, Yang J, Kang P (2021) Efficacy of two unique combinations of nerve blocks on postoperative pain and functional outcome after total knee arthroplasty: a prospective, double-blind, randomized controlled study. J Arthroplasty 36(10):3421–3431. https://doi.org/10.1016/j.arth.2021.05.014
9. Chinachoti T, Lungnateetape A, Raksakietisak M (2012) Periarticular infiltration of 0.25% bupivacaine on top of femoral nerve block and intrathecal morphine improves quality of pain control after total knee arthroplasty: a randomized double-blind placebo controlled clinical trial. J Med Assoc Thai 95(12):1536–42
10. Nadler SB, Hidalgo JH, Bloch T (1962) Prediction of blood volume in normal human adults. Surgery 51:224–232
11. Chen JY, Chin PL, Moo IH, Pang HN, Tay DKJ, Chia SL, Lo NN, Yeo SJ (2016) Intravenous versus intra-articular tranexamic acid in total knee arthroplasty: a double-blinded randomised controlled noninferiority trial. The Knee 23(1):152–156. https://doi.org/10.1016/j.knee.2015.09.004
12. Laigaard J, Pedersen C, Rønsbo TN, Mathiesen O, Karlsen APH (2021) Minimal clinically important differences in randomised clinical trials on pain management after total hip and knee arthroplasty: a systematic review. Br J Anaesth 126(5):1029–1037
13. Cheah JW, Sing DC, Hansen EN, Aleshi P, Vail TP (2018) Does intrathecal morphine in spinal anesthesia have a role in modern multimodal analgesia for primary total joint athroplasty? J

Arthroplasty 33(6):1693–1698. https://doi.org/10.1016/j.arth.2018.01.016
14. Joshi G, Gandhi K, Shah N, Gadsden J, Corman SL (2016) Peripheral nerve blocks in the management of postoperative pain: challenges and opportunities. J Clin Anesth 35:524–529. https://doi.org/10.1016/j.jclinane.2016.08.041
15. Koscielniak-Nielsen ZJ (2008) Ultrasound-guided peripheral nerve blocks: what are the benefits? Acta Anaesthesiol Scand J 52(6):727–737. https://doi.org/10.1111/j.1399-6576.2008.01666.x
16. Wiseskarn K (2021) The efficacy of different combination drugs in ultrasound-guided axillary brachial plexus nerve blockade. Thai J Anesthesiol 47(2):136–142
17. Heesen M, Klimek M, Imberger G, Hoeks SE, Rossaint R, Straube S (2018) Co-administration of dexamethasone with peripheral nerve block: intravenous vs perineural application: systematic review, meta-analysis, meta-regression and trial-sequential analysis. Br J Anaesth 120(2):212–227. https://doi.org/10.1016/j.bja.2017.11.062
18. Kaczocha M, Azim S, Nicholson J, Rebecchi MJ, Lu Y, Feng T, Romeiser JL, Reinsel R, Rizwan S, Shodhan S, Volkow ND, Benveniste H (2018) Intrathecal morphine administration reduces postoperative pain and peripheral endocannabinoid levels in total knee arthroplasty patients: a randomized clinical trial. BMC Anesthesiol 18:27. https://doi.org/10.1186/s12871-018-0489-5
19. France JC, Jorgenson SS, Lowe TG, Dwyer AP (1997) The use of intrathecal morphine for analgesia after posterolateral lumbar fusion: a prospective double-blind randomized study. Spaine 22(19):2272. https://doi.org/10.1097/00007632-199710010-00015
20. Guay J (2006) Postoperative pain significantly influences postoperative blood loss in patients undergoing total knee replacement. Pain Med 7(6):476–482. https://doi.org/10.1111/j.1526-4637.2006.00236.x
21. Laoruengthana A, Chaibhuddanugul N, Rattanaprichavej P, Malisorn S, Tangsripong P, Pongpirul K (2021) Perioperative outcomes of patients who were not candidates for additional nonsteroidal anti-inflammatory drugs in a multimodal pain control regimen for total knee arthroplasty. Clin Orthop Surg 13(2):160–167. https://doi.org/10.4055/cios20154
22. Mori T, Nishikawa K, Terai T, Yukioka H, Asada A (1998) The effects of epidural morphine on cardiac and renal sympathetic nerve activity in α-Chloralose-anesthetized cats. Anesthesiology 88:1558–1565. https://doi.org/10.1097/00000542-199806000-00020