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Impact of Dexmedetomidine on Analgesia and Inflammatory Response in Knee Surgery: A Study of IPACK and ACB Techniques

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: The interspace between the popliteal artery and posterior capsule of the knee block (IPACK) combined with adductor canal block (ACB) has short-term analgesic effect after arthroscopic knee surgery(AKS), and prolonging the duration of analgesia is very important for patients to recover quickly after surgery. The purpose of this study was to investigate whether perineural dexmedetomidine (DEX) or intravenous can prolong the analgesic time of IPACK and ACB, and ultimately promote the postoperative rehabilitation of patients undergoing AKS.

Material/Methods: In this randomized controlled trial, 102 eligible AKS patients were allocated to 3 groups: perineural DEX with ropivacaine for Group E (n=34), intravenous DEX for Group I (n=34), and standard IPACK-ACB (ropivacaine alone) for Group C (n=34). The outcomes included resting and active Visual Analog Scale (VAS) scores at 6 h, 12 h, 24 h, 48 h, 54 h, and 60 h postoperatively, inflammatory marker levels on the first postoperative day, and maximum walking distance at 24 and 48 hours after surgery.

Results: There were no significant demographic differences between the 3 groups. Resting and active VAS scores in Group E were significantly lower than those in Group C within 48 hours postoperatively ($P<0.05$), VAS at 48 h resting state ($P<0.001$, mean difference,-1.15; 95% CI, -1.65 to -0.65), VAS at 48 h active state ($P<0.001$, mean difference,-0.91; 95% CI, -1.32 to -0.50). On the first postoperative day, IL-1β levels in Groups E and I were significantly lower than in Group C ($P<0.05$). Group E had a significantly longer maximum walking distance at 24 and 48 hours after surgery compared to Groups I and C ($P<0.001$).

Conclusions: Perineural DEX prolongs IPACK-ACB analgesia to 48 hours, improves functional recovery, and attenuates IL-1β release, outperforming intravenous administration. These findings support the integration of route-specific DEX into enhanced recovery protocols for AKS.

Keywords: Analgesia • Inflammation Mediators • Nerve Block • Pain, Postoperative • Ultrasonography

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Introduction

Arthroscopic knee surgery (AKS) is a commonly performed orthopedic procedure known for its reduced tissue trauma and faster postoperative recovery. This minimally invasive technique encompasses a range of interventions, including joint examination, meniscal reshaping, and cruciate ligament reconstruction. However, despite its advantages, AKS is frequently associated with considerable postoperative pain due to factors such as surgical trauma, intraoperative tourniquet application, and inflammatory responses. Effective pain management is therefore essential to facilitate rapid patient recovery [1]. Recent evidence supports the use of ultrasound-guided adductor canal block (ACB) and interspace between the popliteal artery and posterior capsule of the knee (IPACK) block for controlling postoperative knee pain. These techniques selectively target sensory innervation of the anterior and posterior regions and preserving motor function, thereby reducing analgesic consumption and promoting quicker rehabilitation [2-4]. Our prior investigation evaluating the ACB-IPACK combination revealed significant reductions in 24-hour (h) postoperative Visual Analog Scale (VAS) scores and enhanced functional recovery. However, the inherent limitation of single-injection peripheral nerve blocks is their short analgesic duration. Nonetheless, the transient nature of single-shot peripheral nerve blocks necessitates strategies to prolong the effects of ACB and IPACK [5].

Dexmedetomidine (DEX), a highly selective alpha-2 adrenergic receptor (α2-AR) agonist, has sedative, analgesic, anxiolytic, and anti-inflammatory properties [6,7]. Preclinical and clinical studies suggest its ability to attenuate pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) implicated in postoperative pain pathogenesis. Notably, when used as a perineural adjuvant, DEX prolongs brachial plexus block duration and reduces rescue analgesia requirements [8-11]. However, the researchers suggested that the benefits and harms of prolonged nerve block duration should be weighed against adverse effects, and more studies are needed to confirm the safety of DEX as a local anesthetic adjuvant [12-14].

Meta-analyses suggested perineural DEX administration can extend postoperative analgesia duration compared to systemic delivery in peripheral nerve blocks; these conclusions are based on moderate-quality evidence with significant heterogeneity [15,16]. However, there have been no studies on the effects of perineural DEX to IPACK and intravenous DEX on postoperative analgesia and rehabilitation of patients with IPACK combined with ACB in AKS. Based on the above, we can assume that compared with intravenous DEX, perineural DEX has more advantages in prolongating IPACK and ACB block time and promoting postoperative rehabilitation. This study provides clinical evidence on the comparative effectiveness and safety of perineural versus intravenous DEX in enhancing and prolonging postoperative analgesia and functional recovery in AKS patients. Our findings can guide clinical practice by offering an efficient and safe analgesia regimen that can improve patient outcomes, reduce pain, and facilitate quicker rehabilitation. Improved pain management postoperatively can significantly enhance patient comfort, expedite recovery, and potentially reduce the length of hospital stays, thereby improving overall quality of life following AKS.

Material and Methods

The study was designed as a randomized, parallel-controlled, 3-arm trial conducted at Longgang Central Hospital of Shenzhen, Guangdong, China. The study period was from March 27, 2024, and August 27, 2024. The trial adhered to the CONSORT guidelines and was registered with the Chinese Clinical Trial Registry on February 28, 2024 (ChiCTR2400081326; http://www.chict.org.cn, principal investigator: Zeng Jian). Ethics approval was granted by the Ethics Committee of Longgang Central Hospital (Approval No. 2023ECPJ007). Written informed consent was voluntarily provided by all participants and their families before participation.

Randomization and Blinding

Preliminary experimental data on postoperative analgesic effects across the 3 study groups revealed mean 24-hour VAS scores of 2.6, 2.2, and 1.8, with standard deviations of 0.8, 0.9, and 0.6, respectively. Using a 2-tailed test with an α level of 0.05 and a test power (1-β) of 90%, sample size calculations were performed using PASS 15 software. To account for a possible 10% attrition rate, the minimum required sample size per group was determined to be 34 participants. This resulted in a total sample size of 102 subjects, ensuring adequate power to detect statistically significant differences among the groups [17,18].

$$n = \varphi^2(\sum s_i^2/g) / [\sum(\bar{X}_1 - \bar{X})^2 / (g - 1)]$$

In this equation, n represents the sample size per group, g denotes the number of groups, and si and x represent the standard deviation and mean, respectively.

Patients were randomly allocated into 3 groups of 34 patients each. Using a computer to generate random serial numbers, the generated serial numbers were randomly divided into 3 groups: perineural DEX adjuvant+IPACK+ACB for Group E, intravenous DEX+IPACK+ACB for Group I, and IPACK+ACB was Group C (the control group). The randomized sequences were hidden in opaque envelopes that were opened by the anesthesiologist performing the procedure, who was not aware of the study protocol and was not involved in postoperative

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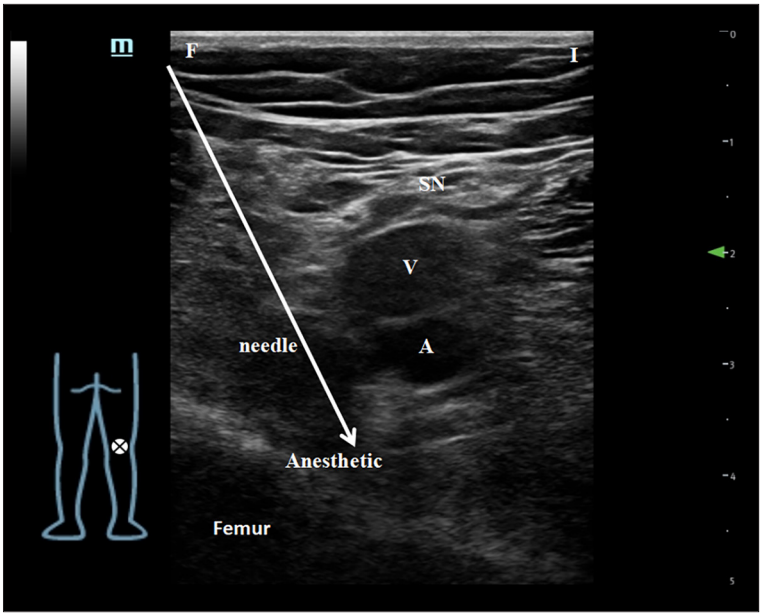

Figure 1. Ultrasound images demonstrating IPACK. SN – sciatic nerve; A – popliteal artery; V – popliteal vein. Arrows indicate the needle. F – distal left lower limb; I – inner thigh. Arrows indicate the needle; Anesthetic stands for injection target; ⊗ – ultrasonic probe placement position.

follow-up. The experimental drugs were dispensed by researchers who are completely unaware of the trials. The anesthesiologist who performed the procedure and the researchers who followed up and recorded the procedure were unaware of the drug configuration.

Participants

A total of 102 eligible patients were enrolled in this study, all of whom were scheduled for unilateral knee arthroscopic elective surgery (these include knee arthroscopy, knee arthroscopic meniscus dressing, and knee arthroscopic anterior fork ligament reconstruction) in the Department of Osteoarthrosis. Participants were classified with ASA grades I to II, aged 19-69 years, and included males and females. Their BMI ranged from 18 to 30 kg/m^2. Patients were required to have no contraindications to anesthesia, no history of narcotic dependence or abuse, no known allergies to local anesthetics, and no history of poorly controlled hypertension, diabetes, or cardiovascular disease. Exclusion criteria were the inability to speak or comprehend Mandarin, contraindications to anesthesia, a history of alcohol or drug abuse, allergic to any medication, poorly controlled hypertension, diabetes, heart disease, sinus bradycardia, coagulation dysfunction, pregnancy, and long-term glucocorticoid use. General anesthesia was provided during excision as a backup measure and to identify patients for whom the ACB or IPACK block was ineffective. The anesthesia procedures were performed by a board-certified attending anesthesiologist (Researcher A) specializing in perioperative anesthesia management and ultrasound-guided regional nerve blocks. Researcher A independently screened and enrolled eligible participants according to the predefined inclusion/exclusion criteria to ensure methodological rigor.

Procedures

Prior to surgery, all patients followed a standardized preoperative protocol, abstaining from fluids for 4 h and food for 8 h. Upon arrival in the operating room, patient identification was verified, peripheral venous access was established, and continuous non-invasive monitoring of blood pressure, electrocardiogram, and blood oxygen saturation was initiated. For the administration of lumbar anesthesia, all patients underwent ultrasound-guided ACB and IPACK block, using 20 ml of 0.25% ropivacaine. In Group E, 0.5 μg/kg of DEX, totaling 1 μg/kg, was added to the local anesthetic mixtures for both blocks. Group I received a 1 μg/kg intravenous infusion of DEX over a 15-minute period, while Group C, serving as the control group, received no DEX administration.

Ultrasound-Guided IPACK and ACB Block

The IPACK block was performed with the patient in the prone position. The ultrasound linear probe was placed transversely over the popliteal fossa, scanning parallel to identify the space between the high-echo line representing the femoral shaft and the popliteal artery. This identified the IPACK block target area, where the tibial nerve was located medially above the popliteal artery, and the common peroneal nerve was positioned laterally, both displaying a characteristic "honeycomb" appearance [5,19] (**Figure 1**).

Following the IPACK block, patients were repositioned supine for the ACB block, with the knee gently flexed and abducted. The ultrasound probe was positioned transversely over the inner thigh, targeting the middle and lower thirds of the line between the patella and inguinal region, identifying the femoral artery and femur. The ACB block area was characterized by a

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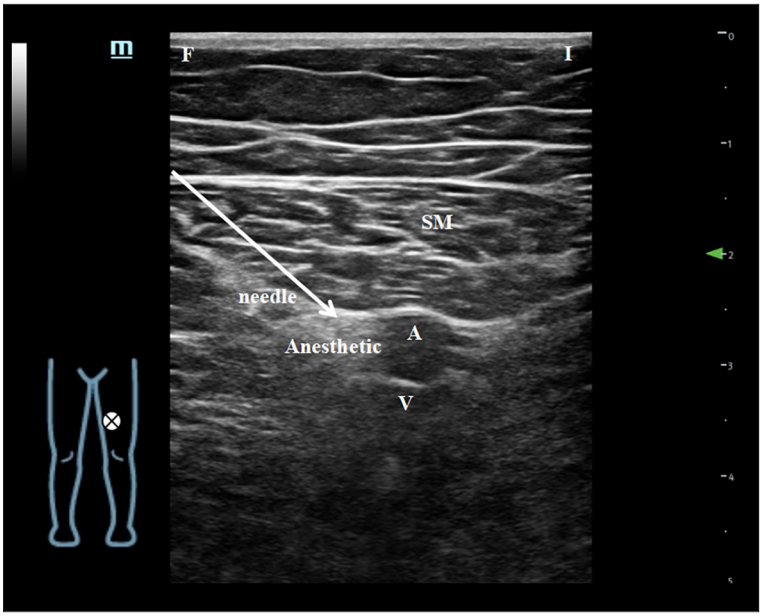

Figure 2. Ultrasound images demonstrating ACB. F – distal left lower limb; I – inner thigh; SM – sartorius; A – femoral artery; V – venae femoris. arrows indicate the needle. Anesthetic stands for injection target. ⊗ – ultrasonic probe placement position.

"triangular" hyperechoic shadow formed by the adductor magnus, sartorius, and vastus medialis muscles [5,20] (**Figure 2**).

Ten minutes after both blocks were administered, their anesthetic efficacy was evaluated. Upon confirmation of successful blocks, single-shot lumbar anesthesia was performed. The patient was positioned laterally with their arms folded over the knees and the head bent forward. The L3-4 interspace was identified, and a 2.5-ml dose of 0.5% ropivacaine was injected to achieve lumbar anesthesia, ensuring that the anesthetic level did not exceed the T8 dermatome.

Postoperative Analgesia Management

Postoperatively, all patients received a standard analgesic regimen of intravenous flurbiprofen ester at 1.0 mg/kg, administered twice daily. If patients reported a VAS score above 4, an additional intravenous dose of 30 mg of pentazocine was provided for supplementary pain relief. After discharge, patients were advised to manage any residual pain with 200 mg oral celecoxib once daily if the VAS score was above 4.

Assessment of Postoperative Outcomes

Primary Outcome

Patients were instructed to self-report their resting and active VAS scores, with particular attention to instances where the joint curvature exceeded 45°, at designated intervals of 6 h, 12 h, 24 h, 48 h, 54 h, and 60 h postoperatively, as well as 1 week after discharge. Additionally, changes in serum levels of IL-1β, IL-6, and TNF-α on the first postoperative day were compared to baseline levels obtained prior to anesthesia administration.

Secondary Outcomes

The frequency of postoperative analgesic interventions in the ward and the amount of analgesics consumed during the week following discharge were meticulously recorded. Maximum ambulation distances at 24 h and 48 h after surgery were also assessed for the 3 patient groups, with family assistance provided for safety. Postoperative complication rates were carefully monitored and evaluated across all groups.

Postoperative Follow-Up

Three data records were designed for this study:

Record Table 1: Patient-reported outcomes were comprehensively logged by the postoperative follow-up personnel (Researcher B). Pain scores were measured according to VAS 0-10 (0 cm no pain and 10 cm worst pain). Data captured included resting and active VAS scores, particularly when the joint curvature exceeded 45°, as reported at 6, 12, 24, 48, 54, and 60 hours after surgery, and 1 week after discharge, adhering strictly to VAS scoring protocols. A measuring scale was installed at the entrance of adjacent wards to aid in data collection. With assistance from family members, patients recorded their maximum walking distances (in meters) at 24 and 48 hours after surgery. Analgesic consumption during the first week after discharge was also documented. After completing the records 1 week after discharge, patients were contacted by the data collector via WeChat to retrieve the completed forms.
Record Table 2: Postoperative complications such as nausea, vomiting, urinary retention, nerve damage, and foot drop were systematically documented by the designated investigator (Researcher B). The frequency of postoperative pain relief

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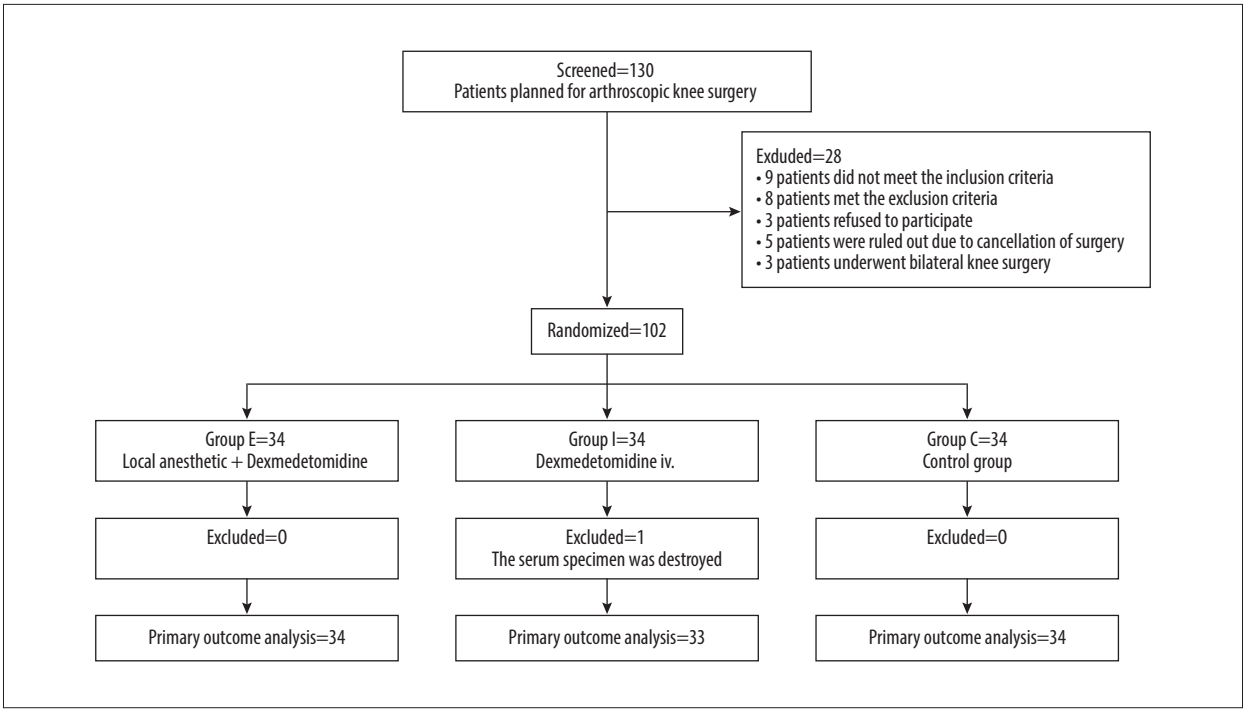

Figure 3. Patient enrollment, inclusion, and exclusion processes. Group E, perineural DEX adjuvant+IPACK+ACB. Group I, intravenous DEX+IPACK+ACB. Group C, (IPACK+ACB) control group.

interventions administered in the hospital was sourced from electronic medical records.

Record Table 3: Intraoperative complications, including nausea, vomiting, hypertension, and sinus bradycardia, were recorded by the primary anesthesiologist (Researcher A).

Records Form 1 and 2 were supervised by the follow-up staff (Researcher B), who fully communicated with the experimenter before filling in the form and explained the content to be filled in after the operation. Patients completed Record Table 1. Venous blood samples were drawn by a visiting nurse prior to anesthesia and by the ward nurse on the first postoperative day. The blood samples were sent to the laboratory within 1 hour of collection to measure serum levels of IL-1β, IL-6, and TNF-α using a Rejing Bio-C2000 automatic chemiluminescence immunoanalyzer. Upon completion of the study, the laboratory consolidated the final dataset and provided it to the data collection team for analysis.

Statistical Analysis

Data analysis was performed using SPSS version 29.0.1.0, whereas graphical representations were generated through GraphPad Prism 8.0, with statistical significance established at *P* values less than 0.05. Continuous variables were expressed as mean±standard deviation or median. Categorical variables were summarized using frequency and percentage. Continuous variables with normal distribution were analyzed utilizing one-way analysis of variance (ANOVA), followed by the Bonferroni correction for multiple tests. In cases of skewed continuous variables, the Kruskal-Wallis test was employed, accompanied by Bonferroni tests. Categorical variables were examined through chi-square or Fisher's exact tests, as appropriate.

Results

Summary of Participation

Between March 27, 2024, and August 27, 2024, a total of 130 patients scheduled for unilateral AKS were screened. Of these, 28 patients were excluded based on predefined criteria: 9 did not meet 1 or more of the inclusion criteria, 8 met the exclusion criteria, 3 declined to participate, 5 had their surgeries canceled, and 3 underwent bilateral AKS. The remaining 102 patients were randomly allocated into 3 groups: Group E (n=34) received 1 μg/kg perineural DEX, Group I (n=34) received a 1 μg/kg intravenous DEX injection, and Group C (n=34) served as the blank control. Following allocation, 1 patient in Group I was excluded due to postoperative serum sample degradation, resulting in a final total of 33 participants in Group I. Group E and Group C retained all 34 participants (**Figure 3**). The treatment compliance rate was 100%, the adherence rate was 100%, and the drop-out rate was 0.02%. A total of 14 subjects had adverse reactions, and the incidence of adverse events was 13.7%.

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Table 1. Comparison of basic data among 3 groups.

Project	Group E (n=34)	Group I (n=33)	Group C (n=34)	*P* value[a,b]
Sociodemographic characteristics				
[a]Mean age (SD) in years	41.7 (11.4)	40.9 (11.9)	39.8 (11.2)	0.795
[b]Sex, n(%)				0.908
Male	18 (52.9)	19 (57.6)	18 (52.9)	
Female	16 (47.1)	14 (42.4)	16 (47.1)	
Surgical characteristics				
[a]Mean BMI (SD) in kg/m^2	24.8 (3.7)	23.8 (3.3)	23.7 (3.1)	0.331
[b]ASA classify, n				0.771
I	6 (17.6)	8 (24.2)	8 (23.5)	
II	28 (82.4)	25 (75.8)	26 (76.5)	
[a]Mean operative time (SD) in minutes	43.3 (18.3)	45.8 (24.1)	45.7 (24.1)	0.873
[a]Mean preoperative VAS pain score (SD)				
At rest	1.4 (0.8)	1.6 (0.8)	1.4 (0.8)	0.589
At activity	2.3 (0.8)	2.5 (0.8)	2.2 (0.8)	0.388

BMI – Body Mass Index; VAS – Visual Analog Scale. ASA – American Society of Anaesthesiologists. [a] single-factor ANOVA. [b] χ^2 tests. The *P* value is the comparison between groups. Group E, perineural DEX adjuvant+IPACK+ACB. Group I, intravenous DEX+IPACK+ACB. Group C, (IPACK+ACB) control group.

The primary surgical procedures conducted among the 101 cases included joint cavity exploration, meniscal sculpting, and cruciate ligament reconstruction. Comparative analysis of baseline characteristics across the 3 groups showed no statistically significant differences in terms of sex, age, BMI, ASA grade, surgery duration, resting period 24 h before surgery, and preoperative VAS scores during physical activity (*P*>0.05) (**Table 1**).

Primary Outcomes

Postoperative Resting and Active VAS Scores

Compared to Group C, Group E exhibited significantly lower resting VAS scores at 12 h (*P*=0.002, mean difference,-0.77; 95% CI, -1.30 to -0.23), 24 h (*P*<0.001, mean difference,-0.91; 95% CI, -1.42to -0.41), 48 h (*P*<0.001, mean difference -1.15; 95% CI, -1.65 to -0.65), and 54 h (*P* =0.015, mean difference -0.53; 95% CI, -0.98 to -0.08) after surgery, as well as lower active VAS scores at 12 h (*P*<0.001, mean difference 1.82; 95% CI, -2.30 to -1.35), 24 h (*P*=0.003, mean difference 0.71; 95% CI, -1.22 to -0.20), and 48 h (*P*<0.001, mean difference -0.91; 95% CI, -1.32 to -0.50). Group I demonstrated a significant reduction in active VAS scores at 12 h (*P*=0.007, mean difference -0.61; 95% CI, -1.09 to -0.13) after surgery. No significant differences were observed between the groups for resting and active VAS scores at other time points (*P* > 0.05). When comparing Group E to Group I, Group E showed significantly lower resting VAS scores at 12 h (*P*=0.029, mean difference -0.59; 95% CI, -1.13 to -0.05), 24 h (*P*=0.003, Mean difference -0.71; 95% CI, -1.22 to -0.20), and 48 h (*P*=0.005, Mean difference -0.67; 95% CI, -1.17 to -0.17), as well as lower active VAS scores at 12 h (*P*<0.001, mean difference -1.21; 95% CI, -1.69 to -0.73) and 24 h (*P*=0.035, mean difference -0.54; 95% CI, -1.06 to -0.03) (**Figure 4A, 4B; Table 2**).

Difference in Inflammatory Factors Between The First Day After Surgery and Before Anesthesia

In terms of inflammatory markers, Group E showed a significantly smaller difference in serum IL-1β levels on the first postoperative day and before anesthesia compared to Group I (*P*=0.04). Group I showed a significantly smaller difference in serum IL-1β levels on the first postoperative day and before anesthesia compared to Group C (*P*<0.001). However, no significant differences were observed in serum IL-6 levels across the groups at the same timepoint (*P*>0.05). Compared to Group C, Group I had a significant reduction in serum TNF-α levels on the first postoperative day and before anesthesia (*P*=0.005), while Group E showed no significant change in TNF-α levels (*P*>0.05) (**Table 3**).

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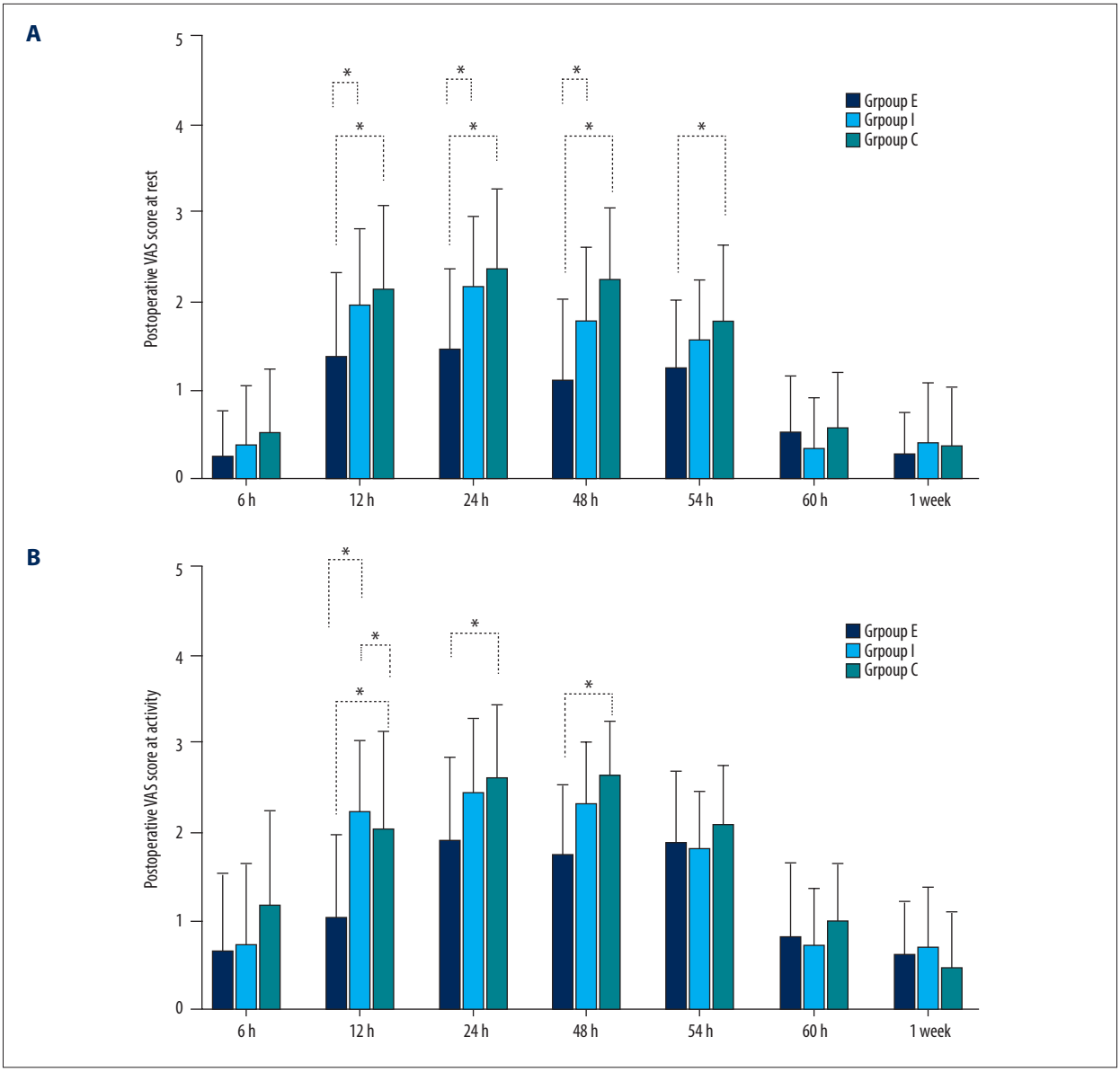

Figure 4. (**A**) Postoperative VAS pain scores at rest in the 3 groups. (**B**) Postoperative VAS pain scores at activity in the 3 groups. Utilizing one-way analysis of variance (ANOVA), followed by the Bonferroni correction for multiple tests. * Significant differences in comparison between groups, *P*<0.05. VAS – Visual Analog Scale; h – hours. 1 week represents 1 week after discharge from hospital. Group E, perineural DEX adjuvant+IPACK+ACB. Group I, intravenous DEX+IPACK+ACB. Group C, (IPACK+ACB) control group.

Secondary Outcomes

Postoperative Analgesic Remedy Times and Consumption

The number of analgesic interventions administered on the first postoperative day (PD1) did not show statistically significant differences among the 3 groups (*P*>0.05). However, a significant difference emerged in the number of analgesic interventions required on the second postoperative day (PD2), with Group E and Group I requiring fewer interventions compared to Group C (*P*<0.001). Among the cases, the distribution across groups was as follows: 2 (5.9%) in group E, 7 (21.2%) in group I, and 18 (52.6%) in group C. Regarding analgesic consumption 1 week after hospital discharge, no significant differences were noted among the groups (*P*>0.05) (**Table 4**).

Maximum Postoperative Walking Distance

Compared to Group C, Group E had significantly greater maximum walking distances at 24 h (*P*<0.001, mean difference

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Table 2. Comparison of Postoperative VAS scores between Groups E and C.

	Standard error	Mean difference (95% CI)	*P* value
Resting state			
12 h	0.22	-0.77 (-1.30 to -0.23)	0.002
24 h	0.21	-0.91 (-1.42 to -0.41)	<0.001
48 h	0.20	-1.15 (-1.65 to -0.65)	<0.001
54 h	0.18	-0.53 (-0.98 to -0.08)	0.015
Active state			
12 h	0.20	-1.82 (-2.30 to -1.35)	<0.001
24 h	0.21	-0.71 (-1.22 to -0.20)	0.003
48 h	0.17	-0.91 (-1.32 to -0.50)	<0.001

Utilizing one-way analysis of variance (ANOVA), followed by the Bonferroni correction for multiple tests. VAS – Visual Analog Scale; h – hours. Group E, DEX local anesthetic adjuvant. Group C, blank control. Group E, perineural DEX adjuvant+IPACK+ACB. Group I, intravenous DEX+IPACK+ACB. Group C, (IPACK+ACB) control group.

Table 3. The difference value of inflammatory factors between the first day after surgery and before surgery in the 3 groups (mean±SD).

Project	Group E (n=34)	Group I (n=33)	Group C (n=34)	H	*P* value
(&) IL-1β	0.07±0.83*	-0.69±1.36#	1.54±3.86	19.06	<0.001
(&) IL-6	4.21±6.34	1.03±13.51	8.31±20.91	1.17	0.558
(&) TNF-α	0.29±3.12	-2.18±8.84#	2.01±5.61	9.99	0.007

We used the independent-samples Kruskal-Wallis test to check for differences between groups. # Indicates comparison with Group C, *P*<0.05. * Comparison with Group I, *P*<0.05. It was statistically significant. (&) indicates difference value of inflammatory factors between the first day after surgery and before surgery. H stands for statistic. Group E, perineural DEX adjuvant+IPACK+ACB. Group I, intravenous DEX+IPACK+ACB. Group C, (IPACK+ACB) control group.

Table 4. Frequency of postoperative rescue analgesia and the dose oral analgesics administered at 1-week after discharge in the 3 groups [(%), (mean±SD)].

Project	Group E (n=34)	Group I (n=33)	Group C (n=34)	F/χ^2	*P* value
[b]PD1	2 (5.9)	6 (18.2)	8 (23.5)	2.111	0.127
[b]PD2	2 (5.9)	7 (21.2)	18 (52.9)	12.087	<0.001
[a]1-week discharge analgesics (capsules)	2.32±1.77	2.64±1.71	2.59±2.05	0.280	0.757

[a] Single-factor ANOVA; [b] χ^2 tests. PD1, Number of rescues and analgesia on the first day after surgery. PD2, Number of rescues and analgesia on the second day after surgery. The *P* value is the comparison between groups. Group E, perineural DEX adjuvant+IPACK+ACB. Group I, intravenous DEX+IPACK+ACB. Group C, (IPACK+ACB) control group.

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Table 5. Maximum postoperative distance in the 3 groups (mean±SD).

Project	Group E (n=34)	Group I (n=33)	Group C (n=34)	F	*P* value
[a]Postoperative 24 h (m)	30.38±6.75#,*	23.70±8.58	19.22±8.52	16.821	<0.001
[a]Postoperative 48 h (m)	79.06±20.72#,*	62.67±26.40#	48.53±18.29	16.370	<0.001

Use the Single-factor ANOVA. # Indicates comparison with Group C, *P* <0.05; * indicates *P*<0.05 for comparison with Group I, it was statistically significant. The *P* value is the comparison between groups. Group E, perineural DEX adjuvant+IPACK+ACB. Group I, intravenous DEX+IPACK+ACB. Group C, (IPACK+ACB) control group.

Table 6. Maximum postoperative walking distance.

	Standard error	Mean difference (95% CI)	*P* value
24 hours after surgery			
Group E vs C	1.93	11.16 (6.44 to 15.88)	<0.001
Group I vs C	1.95	4.48 (-0.28 to 9.22)	=0.072
48 hours after surgery			
Group E vs C	5.34	30.53 (17.52 to 43.54)	<0.001
Group I vs C	5.38	14.14 (1.03 to 27.24)	=0.03

Use the single-factor ANOVA followed by Bonferroni correction for multiple tests. 95% CI, 95% confidence interval. The *P* value is the comparison between groups. Group E vs C, Group E was compared with Group C. Group I vs C, Group I was compared with Group C. Group E, perineural DEX adjuvant+IPACK+ACB. Group I, intravenous DEX+IPACK+ACB. Group C, (IPACK+ACB) control group.

Table 7. The incidence of postoperative complications in 3 groups (%).

Project	Group E (n=34)	Group I (n=33)	Group C (n=34)	χ^2	*P* value
Nausea	1 (2.9)	5 (15.2)	6 (17.6)	4.012	0.135
Vomiting	1 (2.9)	2 (6.0)	5 (15.2)	3.459	0.177
Retention of urine	0 (0.0)	1 (0.0)	1 (2.9)	1.036	0.596
Nerve damage	0 (0.0)	0 (0.0)	0 (0.0)	–	–
Foot drop	1 (2.9)	0 (0.0)	0 (0.0)	1.990	0.370
Hypertension	0 (0.0)	3 (9.1)	1 (2.9)	3.779	0.151
Sinus bradycardia	0 (0.0)	6 (18.2)	2 (5.6)	7.882	0.019

Use the χ^2 tests. The *P* value is the comparison between groups. Group E, DEX local anesthetic adjuvant+IPACK+ACB. Group I, intravenous DEX+IPACK+ACB. Group C, (IPACK+ACB) control group.

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11.16; 95% CI, 6.44 to 15.88) and 48 h (P<0.001, mean difference 30.53; 95% CI, 17.52 to 43.54) after surgery, Group I had significantly greater maximum walking distances at 24 h (P=0.072, mean difference 4.48; 95% CI, -0.28 to 9.22) and 48 h (P=0.03, Mean difference,14.14; 95% CI, 1.03 to 27.24) after surgery. Additionally, Group I exhibited a significant increase in walking distance at 48 h postoperatively (P<0.05). Compared with Group I, Group E showed a statistically significant improvement in maximum walking distance at both 24 h (P=0.003, mean difference 6.69; 95% CI, 1.93 to 11.44) and 48 h (P=0.009, mean difference 16.39; 95% CI, 3.29 to 29.50) (**Tables 5, 6**).

Incidence of Adverse Reactions

Regarding postoperative complications, there were significant differences in the incidence of sinus bradycardia among the 3 groups (P=0.019). The incidence was zero in Group E, 6 (18.2%) cases in Group I, and 2 (5.6%) cases in Group C. However, there were no significant differences in other complications between the 3 groups, including nausea, vomiting, urinary retention, nerve damage, foot drop, or hypertension (P>0.05). The incidence of nausea and vomiting in group E was the lowest (2.9%), but the incidence of postoperative nausea in group I and Group C was 15.2% and 17.6%, respectively, and the incidence of postoperative vomiting in group C was 15.2% (**Table 7**).

Discussion

This study aimed to assess the efficacy of 1 μg/kg DEX, administered as either a perineural adjuvant or by intravenous injection, in managing postoperative pain and facilitating rehabilitation following AKS. The selection of 1 μg/kg DEX was based on its well-established safety and efficacy profile. DEX, when used as a perineural adjuvant, has been shown to prolong the duration of postoperative analgesia in tibial and femoral nerve blocks [21,22]. Although IPACK and ACB are peripheral nerve blocks in the fascial space, given that the IPACK and ACB blocks involve innervation from the tibial and femoral nerves [23,24], we think that the design of local anesthetic adjuvant is reasonable. The use of 1 μg/kg DEX appeared appropriate for this study, and previous studies have validated the use of 20 ml of 0.25% ropivacaine for ACB and IPACK blocks as a reliable protocol [4,5].

In this study, VAS scores for the perineural adjuvant group (Group E) were significantly lower than those of the control group (Group C), both at rest (52 h after surgery) and during activity (48 h after surgery). This indicates a substantially better analgesic effect in Group E. In contrast, the intravenous DEX group (Group I) showed a significant reduction in VAS scores compared to the control group only during activity at 12 h after surgery. No significant differences were observed between Group I and the control group at other time points. Previous research has shown that the combination of IPACK and ACB blocks significantly reduces VAS scores at 24 h postoperatively in AKS patients [5]. Compared to these earlier findings, the current study suggests that using perineural DEX can extend the duration of analgesia to 48 h postoperatively. Additionally, VAS scores in Group E were significantly lower than those in Group I during rest at multiple time points within 48 h after surgery and during activity within the first 24 h. These results suggest that perineural DEX provides more effective postoperative analgesia than intravenous DEX alone. These findings are consistent with those of Rodrigues et al, who found that intravenous DEX did not significantly extend the duration of nerve block [25,26].

Mou's study emphasized that combining ACB with IPACK blocks could reduce early postoperative pain following total knee arthroplasty (TKA), and highlighted the need for further research into extending the duration of these blocks [4]. Our findings demonstrate that perineural DEX can prolong the analgesic effects of ACB and IPACK. A study comparing DEX combined with dexamethasone to DEX alone as an adjuvant for ropivacaine suggested that the combination prolonged the duration of peripheral nerve blocks with minimal adverse effects [27]. Future research could build on these insights, exploring the potential benefits of combining DEX with other agents to further enhance analgesic efficacy while minimizing complications.

Research has demonstrated that intravenous administration of DEX can lower serum levels of IL-1β, IL-6, and TNF-α during the perioperative period in thoracoscopic lung cancer surgery [28]. The decrease of serum IL-1β value in perineural adjuvant DEX on the first day after surgery was better than that in intravenous group, and DEX in intravenous group was better than that in the control group. This finding aligns with previous research and is consistent with the reduction in IL-1β observed following DEX application perineural adjuvant in animal models [8,10].

However, no significant differences in serum IL-6 (the difference value between the first postoperative day and before anesthesia) were noted among the 3 groups, which contrasts with the findings of Li et al [22]. The lack of significant IL-6 changes in this study may be attributed to the routine postoperative administration of 1 mg/kg flurbiprofen axetil, a non-steroidal anti-inflammatory drug (NSAID) known to significantly reduce postoperative IL-6 levels [29,30]. This suggests that NSAIDs may play a beneficial role in multimodal analgesia following AKS, and this conclusion can help guide the selection of postoperative intravenous analgesics in AKS patients.

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Regarding serum TNF-α (the difference value between the first postoperative day and before anesthesia), the intravenous DEX group showed a significant reduction compared to the control group, whereas no significant difference was observed between the perineural adjuvant group and the control group. This indicates that intravenous DEX has a more pronounced effect in reducing serum TNF-α levels, consistent with findings that intravenous DEX significantly reduces TNF-α [11,28]. Nevertheless, in this study, we found that the incidence of sinus bradycardia was 18.2% in the intravenous DEX group, which also raises concern about the cardiovascular systemic risk of intravenous DEX use [21,31]. While combining perineural and intravenous routes could theoretically maximize anti-inflammatory/analgesic synergy, our data caution against this approach without rigorous hemodynamic monitoring. Future studies should explore lower DEX doses (eg, 0.5 μg/kg) or alternative adjuvants (eg, dexamethasone) to balance efficacy and safety [27].

Considering the literature, the hypothesis that DEX, when used perineural adjuvant, provides a more substantial prolongation of nerve block duration in peripheral nerves compared to intravenous administration can be explained by several mechanisms. First, direct injection of DEX into peripheral nerves activates α2-adrenergic receptors (α2-AR) in the surrounding vasculature, leading to localized vasoconstriction. This vasoconstriction delays absorption of the anesthetic, thereby extending the duration of the nerve block [32]. Second, DEX's peripheral administration inhibits the hyperpolarization-activated current (commonly known as the pacemaker current) in nerve cells, maintaining cell depolarization by blocking potassium channels, amplifying sodium channel inhibition, and thus enhancing the local anesthetic's efficacy [33]. Third, while intravenous DEX is known for its systemic anti-inflammatory effects, our data suggest that peripheral nerve injection of DEX also significantly reduces the release of serum IL-1β. This reduction in postoperative IL-1β levels may contribute to extending the duration of the IPACK and ACB blocks. Notably, while intravenous DEX reduced TNF-α (Group I vs C: P=0.005), its failure to prolong analgesia beyond 12 h suggests inflammatory modulation alone is insufficient for sustained pain relief. This dichotomy suggests that route-specific mechanisms, not global anti-inflammatory effects, primarily govern IPACK-ACB duration.

Several studies have demonstrated that the combined use of IPACK and ACB for postoperative knee analgesia can reduce analgesic requirements on the first postoperative day [5,34,35]. In this study, all participants across the 3 groups received IPACK and ACB blocks. The quantity of analgesics administered on PD1 did not significantly differ among the groups, consistent with previous findings. However, a marked difference was observed in analgesic consumption on PD2, with the local anesthetic adjuvant group requiring significantly fewer analgesics than the other 2 groups, and the intravenous DEX group required fewer than the control group.

In the group where DEX was used as a perineural adjuvant, a significantly longer maximum walking distance was observed at 24 and 48 hours after surgery compared to the intravenous DEX group and the control group, and the incidence of postoperative nausea and vomiting was significantly lower. This underscores the effectiveness of IPACK and ACB blocks in knee surgeries, confirming that these blocks do not hinder patient mobility [35]. In addition, the use of DEX on peripheral nerves reduced the incidence of postoperative nausea and vomiting in patients, so the postoperative comfort of patients was improved to a certain extent. The administration of perineural DEX extends the duration of analgesia provided by IPACK and ACB, thereby improving postoperative ambulation. Additionally, patients in the intravenous DEX group also had a significantly longer walking distance at 48 hours after surgery compared to the control group. Our results demonstrate the clinical relevance of sustained analgesia, aligning with enhanced recovery protocols.

Strengths and Limitations

The study has 2 advantages:

1) Research on the use of perineural DEX for IPACK and ACB analgesia in AKS remains limited. This study compared the effects of perineural DEX and intravenous injection on postoperative analgesia and rehabilitation of AKS patients, and provided safe and reliable analgesia strategies for AKS patients after surgery.
2) By analyzing fluctuations in inflammatory markers before and after surgery, this study explored the underlying mechanisms through which perineural DEX prolongs the blockade of IPACK and ACB from a microscopic perspective. This contributes to a deeper understanding of how DEX extends nerve block duration.

However, the study has certain limitations. It was a single-center study with a relatively small sample size, which limits the generalizability of the findings. Future research involving larger sample sizes is necessary to corroborate these results. Additionally, single postoperative IL-1β/TNF-α measurements limit insight into longitudinal inflammatory trajectories. This should be addressed in future studies and further research is needed to explore the changes in serum inflammatory factors, which can eventually guide clinical diagnosis and treatment. In addition, the dose of DEX used in this study was 1 ug/kg. Although this dose was commonly used in previous studies, the dosage of perineural adjuvant DEX or intravenous injection could not guarantee that the dose of DEX was equivalent.

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Conclusions

Perineural dexmedetomidine at 1 μg/kg optimally extends IPACK-ACB analgesia to 48 hours, facilitating earlier ambulation without motor compromise. While intravenous dexmedetomidine demonstrates anti-inflammatory advantages, its transient analgesic effects and bradycardia risk limit its utility as a standalone adjunct. These findings suggest the need for integration of route-specific dexmedetomidine within ERAS protocols for arthroscopic knee surgery.

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Declaration of Figures' Authenticity

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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