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Ultrasound-guided dexmedetomidine combination with modified high fascia iliaca compartment block for arthroscopic knee surgery: what is the optimal dose of dexmedetomidine?

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Abstract

Background Total knee arthroplasty (TKA) is a common orthopedic procedure for end-stage knee osteoarthritis. Although effective in relieving pain and improving function, postoperative pain is still a common and distressing problem for many patients. This study aims to investigate efficacy of combined administration of dexmedetomidine and modified high fascia iliaca compartment block (H-FICB) in managing acute and chronic pain after TKA, as well as to identify the optimal dosage of dexmedetomidine.

Methods A double-blind, randomized controlled trial was conducted to evaluate the effects of dexmedetomidine in patients undergoing TKA. A total of 96 patients undergoing TKA were randomly assigned to one of three groups, were treated with different doses of dexmedetomidine All groups received H-FIB. Pain scores, opioid consumption, side effects, and quality of life were recorded 48 h postoperatively.

Results The intraoperative consumption of remifentanil and propofol in Group D_b was significantly reduced compared with that in Group D_0 and D_a ($P<0.05$). Compared with D_0 and D_a group, D_b group had the lowest number of rescue analgesia, analgesia time and morphine accumulative dosage 48 h after operation ($P<0.05$). The D_b group had the lowest scores on the numerical rating scale at rest ($P<0.05$) and during movement ($P<0.01$), followed by the D_a group and then the D_0 group. Additionally, the incidence of nausea and vomiting was significantly reduced in the D_b group ($P<0.05$). Furthermore, the D_b group had the lowest incidence of chronic pain ($P<0.05$).

Discussion In comparison to the other two groups, the administration of combined dexmedetomidine and H-FIB resulted in a significant reduction in pain scores, opioid consumption, and side effects. The optimal dosage of dexmedetomidine was determined to be 1 μg/kg, which provided the most favorable pain relief with minimal adverse effects.

Keywords Modified high fascia iliaca compartment block, Total knee arthroplasty, Postoperative chronic pain

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Introduction

Total knee arthroplasty (TKA) is a widely performed orthopedic surgical procedure used to address various knee joint pathologies [1]. With the increase in the number of TKA surgeries, Anesthesiologists are increasingly focusing on patient satisfaction and comfort after surgery [2]. However, most patients experience varying degrees of pain after surgery, postoperative pain relief had a significant impact on early ambulation, initiation of physical therapy, and improvement in healing [3]. In addition, effective pain management can reduce the risk of hospitalization and thrombosis and improve patient satisfaction. Numerous analgesic techniques, including patient-controlled analgesia (PCA), epidural analgesia, and peripheral nerve blocks, have been demonstrated to be effective in reducing postoperative pain following TKA [4]. Headache and urinary retention are common in patients receiving epidural analgesia [5]. Multimodal analgesia with peripheral nerve blocks has been recommended and considered the best approach for pain management in total knee arthroplasty [6]. However, recent studies have indicated that the fascia iliaca compartment block (FIB) technique might offer superior postoperative pain control following TKA compared to other nerve block techniques such as femoral nerve block (FNB) or adductor canal block (ACB) [7]. Now, the analgesic effects of modified high fascia iliaca compartment block were more significant and had fewer side effects than traditional iliac fascia nerve block [8]. In addition, the use of adjunctive medications such as dexmedetomidine and dexamethasone has been found to enhance the analgesic effect of peripheral nerve blocks and reduce opioid consumption [9–11]. Among these adjunctive medications, the use of intravenous [12] or local infiltration of the α_2-adrenergic agonist [13], dexmedetomidine has gained increasing attention due to its potential to enhance the quality and duration of analgesia [12, 14]. However, the optimal dose of dexmedetomidine for use in combination with the modified high fascia iliaca compartment block (H-FICB) for postoperative pain management after TKA remains unclear.

Chronic postoperative pain (CPSP) was defined as pain that occurred after surgery and persisted for at least 2 months. In the context of TKA, chronic pain refers to persistent pain that lasts for more than three months after the surgical procedure and proves challenging to alleviate [15]. Research has found that approximately 10–34% of patients experience long-term unpleasant pain after TKA [16], including hyperalgesia, burning, and tingling sensations [17]. These symptoms may be caused by surgical trauma, postoperative inflammatory reactions, nerve compression, or other factors [18].

Therefore, the purpose of this study is to investigate the optimal dose of dexmedetomidine when combined with H-FICB for postoperative pain management after TKA. Specifically, we aim to compare the efficacy and safety of different doses of dexmedetomidine (e.g., 0.25 μg/kg, 0.5 μg/kg, and 1 μg/kg) when used in combination with H-FICB for postoperative pain management after TKA. This study has the potential to provide valuable insights into the optimal use of dexmedetomidine as an adjunct to H-FICB for postoperative pain management after TKA.

Methods

Patients

This prospective study included a total of 120 patients who were scheduled for elective TKA and were enrolled at the Affiliated Hospital of Nantong University from October 2022 to December 2022. Study approval was obtained from the Institutional Review Board of Ethics Committee of Affiliated Hospital of Nantong University (number: 2022-K023) and the PODCAST trial is registered with clinicaltrials.gov, number NCT05533970 on 09/09/2022. Patients and their family members were informed about the treatment and signed a consent form. The trial was conducted in accordance with the Declaration of Helsinki.

The inclusion criteria for participants in this study were as follows: patients aged between 18 and 65 years, patients with an American Society of Anesthesiology (ASA) score of I, II, or III, and a body mass index (BMI) ranging from 18 to 38 kg/m2. The primary exclusion criteria included the presence of cerebrovascular diseases, coagulopathy, complications related to mental illness, hepatic, renal, or cardiorespiratory failure, allergy to local anesthetics, and pregnancy.

Randomization and blinding

Randomization tables generated by computers randomly assigned patients to three groups (n=32) to receive 30 mL of plain ropivacaine 0.375% plus 0.25 μg/kg dexmedetomidine (D_0 group), 30 mL of plain ropivacaine 0.375% plus 0.5 μg/kg dexmedetomidine (D_a group), or 30 mL of plain ropivacaine 0.375% plus 1 μg/kg dexmedetomidine (D_b group). The investigator who creates the random sequence is the investigator who logs in and assigns study patients to study groups according to the random list.

Group work was hidden in sealed, numbered, opaque envelopes until the day of surgery. The anesthesiologist's assistant opened each bag and prepared appropriate study medication. This anesthesiologist is no longer involved in research or patient care. Anesthetists who performed postoperative patient assessments, surgeons, physical therapists, acute pain nurses, and researchers were blinded to treatment group assignment.

Anesthesia

All patients were intubated through the peripheral vein of the arm in the anesthesia preparation room, and blood oxygen saturation (SpO_2), heart rate (HR), end-tidal carbon dioxide ($EtCO_2$), invasive blood pressure (IBP) and electrocardiogram (ECG) were routinely monitored. The modified high fascia iliaca compartment block was administered 30 minutes prior to surgery. The patient was positioned supine, and the anterior superior iliac spine was identified as a reference point, 5 cm below which the iliac crest was determined. Using ultrasound guidance, the 'bow-tie sign' was identified, and the puncture site was disinfected with a skin disinfectant. Various drug concentrations were utilized based on the assigned groups. After entering the operating room, anesthesia was induced with midazolam 0.15 mg/kg, propofol 4 mg/kg, sufentanil 0.25 μg/kg, cisatracurium 0.2 mg/kg Intubation. While propofol and remifentanil were used for the maintenance of anesthesia. Intraoperatively, Lactated Ringer's solution was administered at a rate of 6 to 8 ml/kg per hour. The consumption of remifentanil and propofol during operation was recorded.

Assessment of outcomes

Degree of pain was evaluated by the numerical rating scale at rest (NRS.R) and during movement (NRS.M) at the same time points. The patients were provided with patient-controlled intravenous anesthesia (PCIA) devices contained 100-mg morphine (1 mg/ml) without continuous infusion and set with a lock-out time of 15 min. Patients were instructed to use the device by pushing the button when needed. The devices were set to a maximum dose of 20 mg morphine per day. The post-operative button-push count for PCIA demand and PCIA usage dosage were calculated and recorded at the first 48 h postoperative.

We systematically assess and record the occurrence of adverse events every 8 h was conducted to determine the incidence of adverse events following surgery, including nausea, vomiting, hypotension, bradycardia, arrhythmia, respiratory depression, mechanical ventilation, pruritus, and sedation. Using the three-point scale (1=mild, 2=moderate, 3=severe) above, postoperative nausea, vomiting, and pruritus were assessed.

Six-month follow-up assessment

During the patients' visits to the pain clinic in the third and sixth months after surgery, an untrained physician unknowingly assessed them. The assessment included evaluating pain intensity, nature, duration, aggravating and mitigating factors, and analgesic medication. The Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) Pain Scale was used as the assessment tool to evaluate chronic neuropathic pain in this study [19].

Sample size calculation

Our primary outcome parameter was the difference in NRS scores at movement during the first 48 h postoperatively. According to the preliminary experiment, expected post-treatment the NRS scores at movement during the first 48 h postoperatively was 3.9±1.2 in group D_0, 3.5±0.9 in group D_a and 2.9±0.5 in group D_b. We use PASS 15 software to estimate the sample size required for this study, multiple independent samples one-way ANOVA was used. Power analysis indicated that a minimum sample size of 29 patients in each group was needed, with a significance level of 0.05 and a power of 0.8. To account for patient dropout and protocol violations, the final is derived as at least 32 cases per group, we recruited a total of 96 patients.

Data analysis

The distribution of baseline variables was assessed using the Shapiro-Wilk test. Continuous variables were reported as mean (±SD) and analyzed using one-way ANOVA with post-hoc multiple comparisons. Categorical data were reported as numbers and percentages and analyzed using the chi-squared test or Fisher's exact test with the Bonferroni correction to calculate adjusted *P*-values. Nonparametric data were analyzed using the Mann-Whitney U test. Statistical significance was defined as a *p*-value less than 0.05. All statistical analyses were performed using IBM SPSS Statistics version 26.

Result

A total of 120 patients were included in the study and each group received the study treatment after randomization. Twenty-four patients were withdrawn from the study due to loss to follow-up, declining to participate, or not receiving the allocated intervention (Fig. 1).

There were no statistically significant differences in age, sex, side of operation, body mass index (BMI), operative time, or between the three groups (Table 1). Compared withD_0, D_a Group, the intraoperative consumption of remifentanil and propofol in Group D_b was significantly decreased ($P<0.05$) (Table 1).

Usage condition of PCIA in the first 48 h postoperative

In the D_b group, fourteen patients (43.8%) required rescue analgesics within the first 48 h after surgery. In the D_0 group, twenty-five patients (78.1%) required postoperative rescue analgesia, and in the D_a group, twenty patients (62.5%) required it ($P<0.001$). The cumulative analgesia time and morphine consumption were measured as 8.03±3.66 h and 10.24±4.34 h and 13.12±2.51 mg and 8.60±2.85 mg in the D_0 and D_a groups, respectively, compared to 19.95±2.78 h and 4.14±1.01 mg in the D_b group ($P<0.001$) (Table 2).

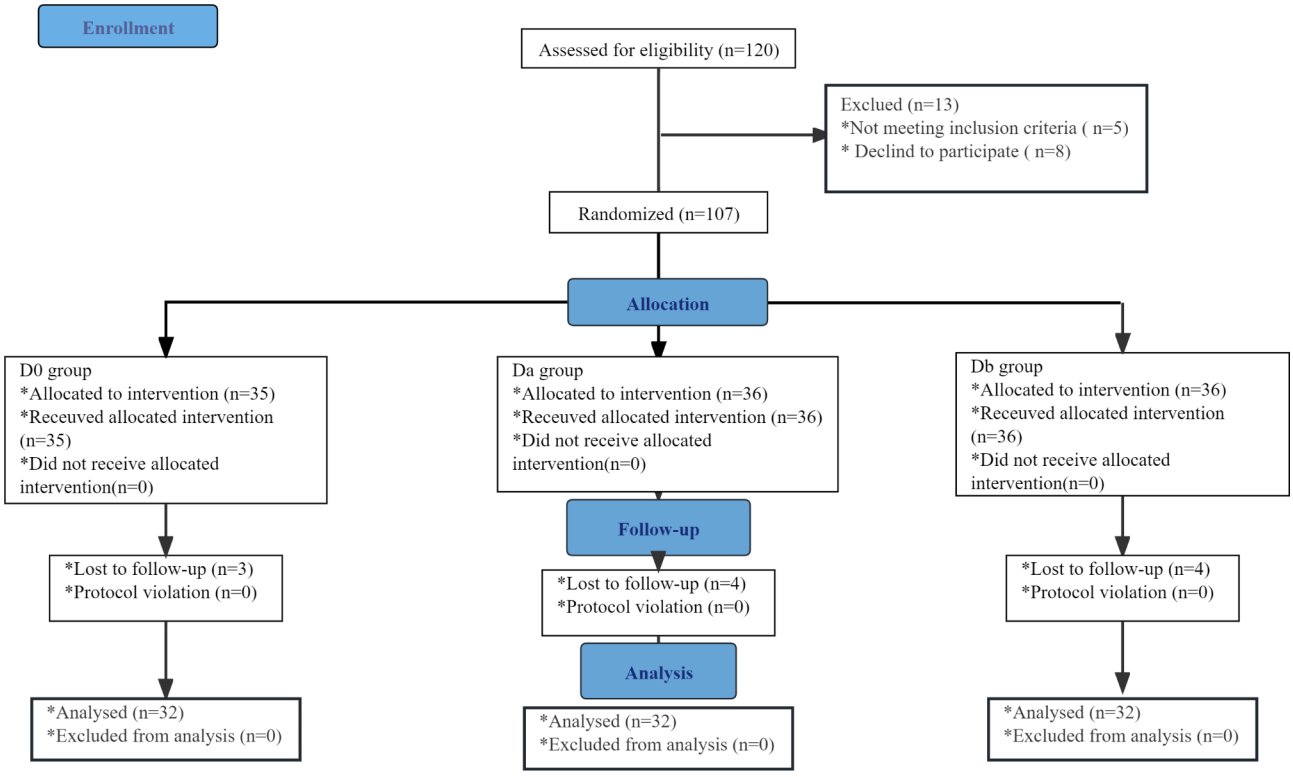

Fig. 1 A flow diagram of inclusion and exclusion criteria according to the CONSORT (Consolidated Standards of Reporting Trials) statement

Table 1 Patients' Demographic and Clinical Data

Item	D_0 Group (n = 32)	D_a Group (n = 32)	D_b Group (n = 32)	*P*
Age, y	69.03 ± 6.87	69.60 ± 5.37	67.25 ± 5.83	*P* = 0.242
Sex, no. male/no. female	17/15	16/16	15/17	*P* = 0.623
BMI, kg/m^2	22.81 ± 1.62	22.94 ± 1.50	22.44 ± 1.74	*P* = 0.357
ASA I/II/III	1/26/5	0/26/6	1/28/3	*P* = 0.525
Side of operation (right/left)	14/18	16/16	15/17	*P* = 0.591
Duration of surgery, min	91.44 ± 8.29	87.66 ± 9.68	84.81 ± 7.80	*P* = 0.121
Total remifentanil(mg)	1.18 ± 0.10	1.15 ± 0.05	1.13 ± 0.06	*P* = 0.013
Total propofol (mg)	210.59 ± 15.18	196.66 ± 13.84	187.50 ± 8.37	*P* = 0.001*

Note: The data are expressed as the mean ± SD. *P < 0.05 versus D_0 group

Abbreviations: BMI, body mass index; ASA, American Society of Anesthesiologists

Table 2 Consumption of Rescue Analgesic Medications in the First 48 h Postoperative

Item	D_0 Group (n = 32)	D_a Group (n = 32)	D_b Group (n = 32)	*P*
Analgesia time, h	8.03 ± 3.66(n = 25)	10.24 ± 4.34(n = 20)	19.95 ± 2.78(n = 14)	P_a=0.057
The postoperative button-push count for PCIA times				P_b<0.001* P_c<0.001*
No request	7(21.9%)	12(37.5%)	18(56.2%)	
1–5	0(0%)	3(9.4%)	12(37.5%)	
6–10	5(15.6%)	11(34.4%)	2(6.3%)	P_a<0.001*
> 10	20(62.5%)	6(18.8%)	0(0%)	P_b<0.001*
Cumulative morphine consumption in 1st 48 h postoperative, mg	13.12 ± 2.51	8.60 ± 2.85	4.14 ± 1.01	P_c<0.001*

NOTE: Data are express as mean ± SD and number. *P < 0.001; P_a, significance between D_0 and D_a groups; P_b, significance between D_0 and D_b groups; Pc, significance between D_a and D_b groups

There were no significant differences observed between the groups in terms of the mean NRS.R scores at recovery ($P=0.494$) and the postoperative 4th hour ($P=0.819$). However, starting from the 6th hour postoperatively and continuing until the 48th hour, the D_b group consistently demonstrated the lowest NRS.R scores, followed by the D_a group, and finally the D_0 group ($P<0.05$). Similarly, during the same time period (6th to 48th hour), the D_b group exhibited the lowest mean NRS.M scores, followed by the D_a group, and then the D_0 group ($P<0.01$) (Fig. 2, A and B).

Compared to the other two groups, D_b group, the number of cases of nausea and vomiting after surgery was significantly reduced ($P<0.05$), and there were no symptoms of delay in awakening, or respiratory depression. (Table 3) No instances of severe vomiting, nausea, or pruritus were reported in any of the study groups.

Chronic pain assessments

The mean LANSS score was found to be the lowest in the D_b group during the third postoperative month (5.44±2.03 vs. 7.72±3.41 and 9.72±2.96, $P<0.05$), as well as the sixth postoperative month (5.09±2.41 vs. 7.53±3.08 and 9.66±3.16, $P<0.05$). In comparison to the D_0 and D_a groups, the D_b group demonstrated a significant reduction in the occurrence of neuropathic pain

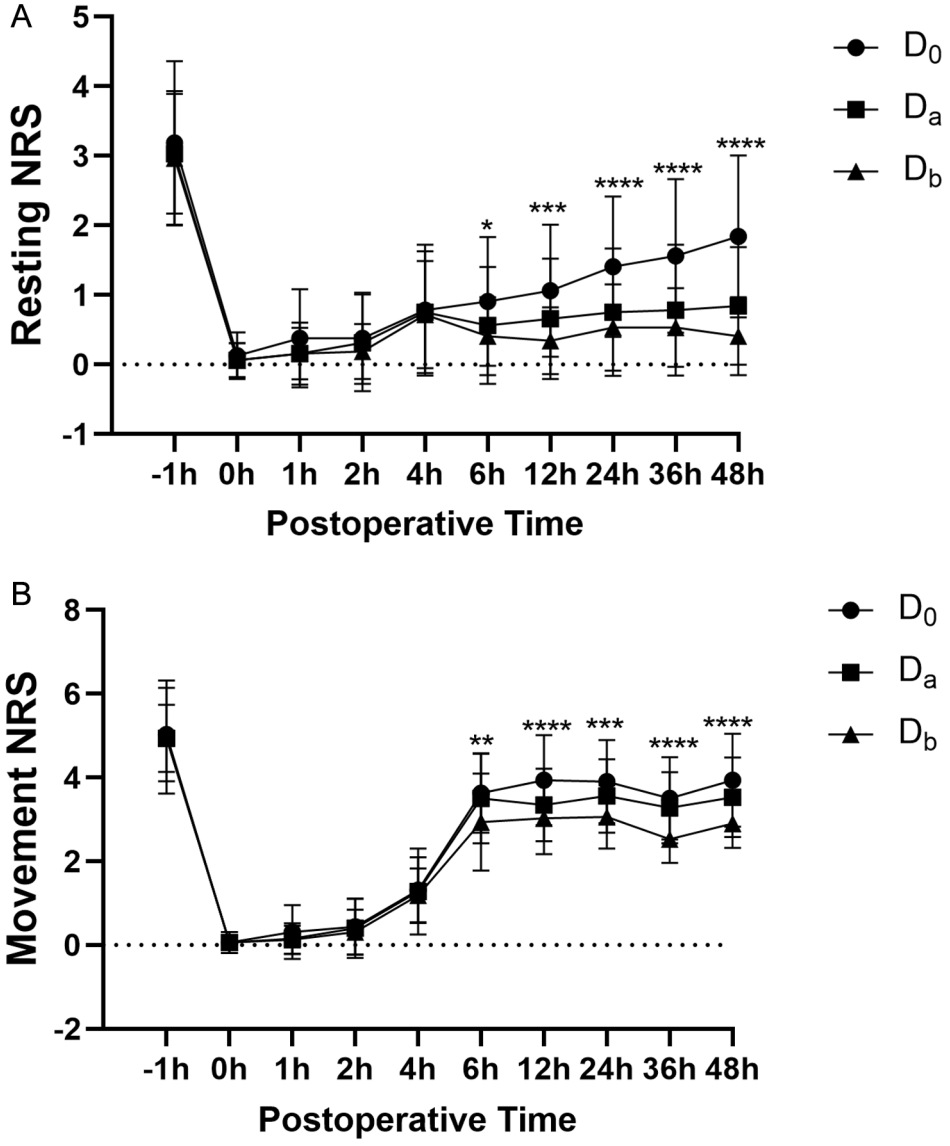

Fig. 2 (**A**) NRS.R scores in the three groups at different postoperative periods. A line graph represents the results. $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$, $^{****}P<0.0001$ compared with Group D_0. (**B**) NRS.M scores in the three groups at different postoperative periods. A line graph represents the results. $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$, $^{****}P<0.0001$ compared with Group D_0

Abbreviation: NRS.R, Numeric Rating Scale of Rest; NRS, Numeric Rating Scale of Movement

Table 3 Adverse events in patients

Item	D_0 Group (n = 32)	D_a Group (n = 32)	D_b Group (n = 32)	*P*
Nausea	11(34.4%)	5(15.6%)	1(3.1%)	*P* = 0.001*
Vomiting	8(25%)	4(12.5%)	2(6.1%)	*P* = 0.003*
Pruritus	6(18.8%)	4 (12.5%)	1(3.1%)	*P* = 0.006*
Delay in awakening	0(0%)	0(0%)	0(0%)	*P* = NA
Respiratory depression	0(0%)	0(0%)	0(0%)	*P* = NA

NOTE: $^{*}P < 0.05$ versus D_0 group

Table 4 LANSS Score in the Third and Sixth Months Postoperatively

	D_0 Group (n = 32)	D_a Group (n = 32)	D_b Group (n = 32)	
LANSS (3)				P_a=0.004
Total score (mean ± SD)	9.72 ± 2.96	7.72 ± 3.41	5.44 ± 2.03	P_b<0.001
<12	23	28	31	P_c=0.006
≥ 12	9	4	1	
LANSS (6)				
Total score (mean ± SD)	9.66 ± 3.16	7.53 ± 3.08	5.09 ± 2.41	P_a=0.004
<12	23	28	31	P_b<0.001
≥12	9	4	1	P_c=0.001

NOTE: Data are express as mean ± SD and number. LANSS (3), LANSS score in the third month postoperative; LANSS (6), LANSS score in the sixth month postoperative; P_a, significance between D_0 and D_a groups; P_b, significance between D_0 and D_b groups; P_c, significance between D_a and D_b groups

(LANSS score ≥ 12) during the third and sixth postoperative months. Only one patient in the D_b group reported neuropathic pain, while nine and four patients in the D_0 and Da groups, respectively, reported such pain. No significant differences were observed between the D_0 and D_a groups (Table 4).

Discussion

The objective of this study was to assess the impact of three different doses of topical dexmedetomidine (0.25 μg/kg, 0.5 μg/kg, and 1 μg/kg) in conjunction with H-FICB on acute pain management and the incidence of chronic pain in patients undergoing total knee arthroplasty. The study findings indicated that all three treatment groups demonstrated efficacy and tolerability, with few systemic serious adverse effects. Notably, patients administered with a dosage of 1 μg/kg dexmedetomidine displayed the lowest average postoperative NRS scores and the lowest average LANSS scores throughout the first to sixth postoperative months.

Our results showed that this combination technique provided effective postoperative pain control, with lower pain scores and reduced postoperative opioid consumption compared to the control group receiving local anesthetic alone [20]. Moreover, we identified a dose-response relationship between dexmedetomidine and its analgesic effect, with the optimal dose of 1 μg/kg resulting in the greatest pain relief and fewest adverse effects. However, most of the adverse reactions in group D_0 may be caused by various reasons. The dosage of opioid administration can influence the incidence of post-operative nausea and vomiting (PONV). Due to the early occurrence of post-operative pain in group D_0, more opioids are used. High doses of opioids, especially when administered intravenously, are associated with a greater risk of PONV. Further studies of larger sample size are needed to confirm the dose-dependent effect of opioid on the incidence of PONV.

Dexmedetomidine is a highly selective α_2-adrenergic receptor agonist [21] that produces potent sedative [10], anxiolytic, and analgesic effects [22]. Its analgesic mechanisms involve decreasing the release of norepinephrine and substance P in the spinal cord [13], inhibiting pain signaling pathways [23], and modulating descending inhibitory pathways. Dexmedetomidine also has anti-inflammatory properties and can attenuate the neuroinflammatory response to surgery [24], which may contribute to its analgesic efficacy in the postoperative period.

Chronic pain after total knee arthroplasty (TKA) refers to persistent pain lasting more than three months post-surgery that poses a challenge for management and relief [15]. The strength of early postoperative pain memory has been proven to be the most important factor in the development of chronic pain [18]. Neural influence may play a significant role in the development of chronic pain following TKA [18], while another study has demonstrated the effectiveness of neural modulators in reducing such pain. These neural modulators include antidepressants [25], antiepileptic drugs [26], and anticonvulsants [27], can alter the transmission of nerve impulses by affecting neurotransmitters, relieving pain, and ameliorating symptoms of neural dysfunction. Rekatsina et al. have demonstrated that perioperative iv infusion of dexmedetomidine had a beneficial effect on the prevention of chronic postoperative pain at 3 months, the exact mechanism of action is still unclear [28]. We think chronic pain conditions are often associated with sympathetic hyperactivity, dexmedetomidine can inhibits the release of norepinephrine, resulting in a reduction of sympathetic nervous system activity [29], also by binding to α-2 receptors in the spinal cord, it reduces the release of excitatory neurotransmitters, such as glutamate, and enhances the activity of inhibitory neurotransmitters, likeγ-aminobutyric acid (GABA) [30]. Chronic pain conditions often involve neuroinflammatory processes, and highest dose of dexmedetomidine's ability to more suppress pro-inflammatory cytokine release and reduce glial cell activation more help

alleviate the chronic inflammatory component of pain [31]. Dexmedetomidine also can produce neuroprotective effects through various mechanisms, such as antioxidation and anti-infection activities, the inhibition of apoptosis, the promotion of neurogenesis, and the influence of cell signaling pathways [32]. Highest dose of dexmedetomidine's ability to reduce chronic pain is rooted in its multifaceted pharmacological actions. Therefore, further studies of the specific mechanism of action by which the highest doses of dexmedetomidine relieve chronic pain require.

Based on our research, it appears that the H-FICB technique offers a more comprehensive and effective approach to regional anesthesia for knee joint procedures when compared to other methods like femoral nerve block or adductor canal block [3, 20, 33]. This is due in part to its ability to provide a wider range of sensory and motor blockade throughout the surrounding tissues [34]. Furthermore, we have found that by incorporating dexmedetomidine into the local anesthetic mixture used during this procedure, patients can experience even greater pain relief and improved overall outcomes. This combination has been shown to enhance the analgesic effect of the treatment, providing patients with a more comfortable and safe recovery period. Overall, our study suggests that utilizing the H-FICB technique along with dexmedetomidine can offer significant benefits for those undergoing TKA. By providing superior pain management and broader coverage of affected areas, this approach become an important link forward in regional anesthesia techniques for these types of surgeries. In short, the combination of dexmedetomidine and H-FICB has the potential to reduce opioid analgesic requirements, thereby minimizing associated risks such as respiratory depression, sedation, and nausea. Furthermore, this combination may improve postoperative recovery by enhancing patient mobility and reducing the incidence of chronic pain.

Limitations

Our study has several limitations that should be acknowledged. Firstly, the sample size was relatively small, which may limit the generalizability of our findings. Additionally, the absence of a placebo control group restricts our ability to establish a direct comparison between the intervention and a non-treatment condition. Future investigations incorporating larger sample sizes and including a placebo control group are warranted to validate our results and provide further insights into the long-term effects of this combination therapy. Furthermore, longer follow-up periods and studies exploring the optimal duration and frequency of dexmedetomidine administration would be beneficial in enhancing our understanding of its therapeutic potential. Finally, additional research is warranted to investigate the safety and potential adverse effects of dexmedetomidine, particularly in vulnerable populations such as elderly patients and those with comorbidities.

Conclusion

In comparison to the other two groups, the administration of combined dexmedetomidine and H-FIB resulted in a significant reduction in pain scores, opioid consumption, and side effects, while also improving patient comfort and enhancing postoperative recovery. The optimal dosage of dexmedetomidine was determined to be 1 μg/kg, which provided the most favorable pain relief with minimal adverse effects. These findings suggest that the combination of dexmedetomidine and H-FICB is a safe and effective approach for pain management following TKA, and a dosage of 1 μg/kg is recommended for optimal analgesic effects.

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Author contribution
XGX conceptualized and designed the study, and AC, WQD, RJLH, and CW contributed to the acquisition of data. AC, and WQD contributed to the analysis and interpretation of data, and RJLH, CW contributed to the analysis of data and determination of postoperative pain. XGX drafted the initial work, and all authors substantively revised it. All authors read and approved the final manuscript.

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Data Availability
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Study approval was obtained from the Institutional Review Board of Ethics Committee of Affiliated Hospital of Nantong University (registration number 2022-K023) on 20/04/2022 and the PODCAST trial is registered with clinicaltrials.gov, number NCT05533970 on 09/09/2022. Patients and their family members informed the treatment and signed a consent form. The trial was conducted in accordance with the Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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