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Effects of adding dexmedetomidine versus fentanyl to intrathecal bupivacaine on inflammatory markers, and postoperative outcomes after total knee arthroplasty; a randomized clinical trial

Mahdi Nazari[1], **Vahid Fattahi**[2], **Aliakbar Zia-Azar**[1], **Abbasali Dorosti**[1*]

[1]Department of Anesthesiology, School of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran
[2]Department of Anesthesiology, Faculty of Medicine, Tabriz Medical Sciences, Islamic Azad University, Tabriz, Iran

***Correspondence to**
Abbasali Dorosti, Email: Dorostia@tbzmed.ac.ir

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Abstract

Introduction: Systemic inflammation plays a pivotal role in postoperative pain and complications after total knee arthroplasty (TKA). Intrathecal adjuvants may modulate this response by influencing inflammatory markers such as C reactive protein (CRP) and systemic immune inflammation index (SII) to test analgesic efficacy and overall postoperative outcomes.

Objectives: This study aimed to compare the effects of adding intrathecal dexmedetomidine versus fentanyl to bupivacaine on postoperative inflammatory markers, perioperative and clinical outcomes in patients undergoing .

Patients and Methods: This randomized single blind clinical trial enrolled patients undergoing elective who received intrathecal bupivacaine (12.5 mg, 0.5% hyperbaric) supplemented with either dexmedetomidine (25 µg) or fentanyl (25 µg). Postoperative complications were recorded. Venous blood samples were collected preoperatively, 24 and 48 hours postoperatively to measure serum CRP and the SII.

Results: Postoperative inflammatory markers showed a significantly attenuated response in the dexmedetomidine group, with lower CRP levels and SII values at 24 and 48 hours compared with fentanyl ($P < 0.001$). Clinically, dexmedetomidine was associated with a lower incidence of postoperative nausea and vomiting ($P=0.036$), fewer episodes of intraoperative hypoxia ($P=0.009$), reduced postoperative pain scores ($P=0.039$) and a longer time to first opioid request ($P=0.017$), despite a modest prolongation of anesthesia duration ($P=0.035$).

Conclusion: Dexmedetomidine as an intrathecal adjuvant to bupivacaine in was associated with lower postoperative CRP and SII levels, reduced pain intensity, and fewer postoperative complications compared with fentanyl, indicating superior attenuation of the systemic inflammatory response, despite fentanyl demonstrating relatively greater perioperative blood pressure stability.

Trial Registration: The trial protocol was approved in the Iranian registry of clinical trial (identifier: IRCT20190325043107N58; https://irct.behdasht.gov.ir/trial/84871, Ethical code; IR.TBZMED.REC.1402.390).

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Introduction

Total knee arthroplasty (TKA) is a common orthopedic procedure performed to alleviate pain and restore function in patients with advanced knee osteoarthritis (1). Despite advancements in surgical techniques and perioperative care, the management of postoperative pain remains a significant challenge (2). Central neuraxial anesthesia, particularly spinal anesthesia with intrathecal bupivacaine, has gained widespread acceptance as an effective method for perioperative pain control in TKA due to its favorable analgesic profile and reduced systemic opioid requirements (3).

In recent years, the addition of adjuvants such as dexmedetomidine and fentanyl to intrathecal bupivacaine has garnered attention as a means to enhance the quality and duration of spinal anesthesia for TKA (4,5). Dexmedetomidine, a highly selective α2-adrenergic agonist, and fentanyl, a potent opioid analgesic, have both been shown to prolong the duration of sensory and motor block, reduce intraoperative and postoperative analgesic requirements, and improve overall patient satisfaction in various surgical settings (6). However, limited evidence exists regarding the comparative effects of dexmedetomidine versus fentanyl when added to intrathecal bupivacaine specifically in the context of TKA (7,8).

The hemodynamic stability and occurrence of postoperative complications, including bradycardia, hypotension, vomiting and nausea, shivering, and headache, are important

Key point

Intrathecal dexmedetomidine, compared with fentanyl, significantly attenuated the postoperative systemic inflammatory response after total knee arthroplasty, as evidenced by lower C-reactive protein (CRP) and systemic immune inflammation index (SII) levels. This anti inflammatory effect was accompanied by reduced pain intensity, delayed opioid requirement, and fewer postoperative complications, indicating a more favorable inflammatory and clinical profile.

considerations in the selection of adjuvants for intrathecal anesthesia in TKA (9,10). Dexmedetomidine and fentanyl may exert differential effects on hemodynamic parameters and the incidence of common postoperative complications, potentially influencing perioperative management and patient outcomes (11,12).

The choice between dexmedetomidine and fentanyl as adjuvants to intrathecal bupivacaine in TKA requires careful consideration of their pharmacological properties, potential side effects, and impact on perioperative outcomes (13). Dexmedetomidine, through its central sympatholytic and analgesic effects, has been associated with a reduction in sympathetic tone, leading to bradycardia and hypotension, albeit to a lesser extent compared to other α2-adrenergic agonists (14). Additionally, dexmedetomidine has antiemetic properties and may attenuate the incidence of postoperative nausea and vomiting and shivering. However, concerns have been raised regarding the potential for delayed recovery and sedation with dexmedetomidine, which could prolong time to ambulation and discharge following TKA (15,16).

In contrast, fentanyl, a μ-opioid receptor agonist, primarily exerts its analgesic effects through supraspinal mechanisms, with minimal impact on sympathetic tone (17). While fentanyl is not associated with significant hemodynamic alterations at analgesic doses, its use may increase the risk of respiratory depression, particularly in the postoperative period (18). Additionally, fentanyl has been implicated in the development of postoperative nausea and vomiting and pruritus, albeit at lower incidences compared to other opioids (19).

Moreover, both fentanyl and dexmedetomidine have been widely conducted as effective intrathecal adjuvants, growing evidence suggests that these agents differ substantially in their hemodynamic effects and side-effect profiles (11). Findings reported by Gupta et al, highlight that the distinct pharmacodynamic properties of dexmedetomidine and fentanyl may lead to different patterns of hemodynamic responses and postoperative adverse events (20).

In recent years, increasing emphasis has been placed on the role of the postoperative systemic inflammatory response as a major determinant of acute pain intensity and recovery following major orthopedic procedures such as TKA (21). Inflammatory biomarkers, including C-reactive protein (CRP) and the systemic immune-inflammation index (SII), reflect activation of cytokine-mediated pathways triggered by surgical trauma (22). Elevations in these indices have been associated with enhanced peripheral and central sensitization, leading to greater acute postoperative pain, delayed functional recovery, and a higher risk of postoperative complications (23). Consequently, attenuation of the inflammatory response has emerged as an important target in perioperative anesthetic and analgesic strategies (24).

The choice of intrathecal adjuvants may substantially influence postoperative inflammatory profiles (25). Dexmedetomidine, through selective α2-adrenergic receptor activation, exerts anti-inflammatory effects by suppressing cytokine release and modulating sympathetic activity, which may result in lower CRP and SII levels and improved control of acute postoperative pain (26). In contrast, fentanyl provides effective analgesia, its impact on systemic inflammatory pathways appears limited, potentially allowing a more pronounced postoperative inflammatory response (27). Comparative evaluation of these agents based on inflammatory biomarkers may therefore provide valuable insights into optimizing pain management and inflammatory modulation after TKA (28).

Total knee arthroplasty induces substantial surgical trauma that triggers a systemic inflammatory response, which plays a critical role in the development of acute postoperative pain, delayed recovery, and perioperative complications. Inflammatory markers such as CRP and the SII provide reliable and accessible measures of inflammatory burden and its clinical relevance. Despite the widespread administration of dexmedetomidine and fentanyl as intrathecal adjuvants to bupivacaine, comparative evidence regarding their effects on inflammatory markers, and postoperative outcomes remains limited.

Objectives

This randomized clinical trial was designed to compare the effects of adding dexmedetomidine versus fentanyl to intrathecal bupivacaine on inflammatory markers, and postoperative outcomes in patients undergoing TKA.

Patients and Methods

Study design and participants

This study was a randomized single-blind clinical trial designed to compare the effects of dexmedetomidine and fentanyl as adjuvants to bupivacaine in intrathecal injections during knee joint replacement surgery on postoperative complications. In our study, a total of 80 patients were enrolled in the study and were randomly assigned into two equal groups; the dexmedetomidine group (n=40) and the fentanyl group (n=40). The study was conducted from the beginning of 2025 to the end of 2025 at Shohada hospital, Tabriz University of Medical Sciences, Tabriz, Iran.

Sampling

Based on the results of a similar study (29), the sample size was calculated based on the assumption of a 25% difference in the primary pain intensity outcome between the two groups. Using a two-sided significance level of 0.05 and a statistical power of 80%, the following formula for comparison of two proportions was applied:

$$n = \frac{2\left(Z1 - \frac{\alpha}{2} + Z1 - \beta\right)2.p(1-p)}{(\Delta)2}$$

Where p is the mean proportion of the outcome in both groups, and Δ represents the expected difference (0.25). Based on these assumptions, the estimated sample size was approximately 36 participants per group. To account for potential dropouts and missing data, we included 40 patients in each group.

Eligibility criteria

Eligible participants were adult patients (≥ 18 years) who provided written informed consent and were classified as American Society of Anesthesiologists (ASA) physical status I or II, with a confirmed diagnosis of knee osteoarthritis and scheduled to undergo TKA under spinal anesthesia. Participants were excluded from the study and final analysis if they voluntarily withdrew their consent at any stage, required a conversion from spinal to general anesthesia due to intraoperative complications, or failed to adhere to the postoperative assessment and follow-up protocol.

Blinding

In the present single-blind trial study, participants were blinded to the group allocation and the type of intrathecal adjuvant administered. Patients were not informed whether dexmedetomidine or fentanyl had been added to intrathecal bupivacaine.

Randomization

Randomization was performed using a computer-generated simple randomization sequence created with Random Allocation Software (version 2.0). Allocation concealment was ensured by placing group assignments in sealed, opaque, sequentially numbered envelopes, which were opened only at the time of patient enrollment. Therefore, both participants and investigators remained unaware of group allocation until assignment occurred.

Procedure

All patients adhered to a fasting period of at least eight hours before surgery and underwent a preoperative anesthesia evaluation on the evening preceding the procedure. Upon arrival in the operating room, standard monitoring, including heart rate, non-invasive blood pressure, and arterial oxygen saturation was continuously applied. Patients then received 500 mL of intravenous normal saline. Following fluid administration, spinal anesthesia was performed by the same anesthesiologist for all patients in the sitting position using a 25-gauge spinal needle at the L4-L5 interspace. A solution of bupivacaine (20 mg) was administered intrathecally, supplemented with either dexmedetomidine or fentanyl. Participants were allocated into two groups; group A received intrathecal bupivacaine combined with dexmedetomidine (25 µg), whereas group B received intrathecal bupivacaine combined with fentanyl. Group B; patients receive intrathecal bupivacaine with the addition of fentanyl (25 µg) (30). Anesthesia administered by experienced anesthesiologists according to the assigned group.

Intraoperative sedation was administered according to a standardized and uniform protocol for all patients. When clinically indicated, intravenous midazolam at controlled doses was conducted to achieve mild-to-moderate sedation and no propofol or opioid agents were administered during surgery.

A standardized data collection form was developed for each participant to systematically record relevant demographic and perioperative variables. Collected data included age, sex and body mass index (BMI), ASA physical status, and duration of surgery. Thereafter, these variables were recorded at five-minute intervals until the end of surgery.

Intraoperative and postoperative adverse events, including bradycardia, hypotension, nausea and vomiting, headache, and hypoxia requiring supplemental oxygen, were prospectively documented. Postoperative shivering, pain intensity assessed using the Visual Analog Scale (VAS) (31), cumulative doses of atropine, ondansetron, and ephedrine, and the total duration of anesthesia were also recorded. Postoperative assessments were conducted hourly during the first six hours following surgery. Pain intensity was assessed over a 24-hour postoperative period at six-hour intervals. The mean pain score for each group was subsequently calculated, and a single representative value was reported for statistical analysis.

In this study, bradycardia was defined as a heart rate of less than 55 beats per minute (32). Hypotension was defined as a decrease in systolic blood pressure of more than 30% from baseline values. Hypoxia was defined as a reduction in arterial oxygen saturation (SpO_2) below the clinically acceptable threshold (SpO_2 < 95%)(33). Shivering was defined as the presence of observable involuntary muscular tremors during or after surgery (34). Nausea was defined as the subjective sensation of the urge to vomit reported by the patient, whereas vomiting was defined as the expulsion of gastric contents through the mouth (35). All adverse events were monitored and recorded uniformly throughout the study according to predefined clinical criteria.

All patients underwent unilateral TKA using a standard cemented prosthesis under a uniform surgical protocol. All procedures were performed by experienced orthopedic surgeons employing the same operative technique. In all

cases, a pneumatic tourniquet was applied prior to skin incision and remained inflated throughout the main stages of the operation. Patient positioning, surgical approach, and intraoperative management were standardized across both groups to minimize the influence of surgical factors on operative duration, blood loss and fluid requirements.

Primary outcomes included the incidence of intraoperative and postoperative complications related to intrathecal anesthesia, including bradycardia, hypotension, hypoxia, nausea and vomiting, shivering, and headache (36). Additional secondary endpoints consisted of postoperative pain intensity assessed using the VAS, time to first postoperative opioid requirement, total anesthesia duration, and the need for rescue medications (37).

Serum levels of CRP and the SII were measured in all patients at three predefined time points (38). Baseline measurements were obtained prior to transfer to the operating room, followed by repeat assessments at 24 and 48 hours postoperatively. Blood samples were collected by a trained nurse and promptly transferred to the central laboratory of the same institution. All analyses were performed using a single standardized analyzer under the supervision of an experienced pathologist to ensure consistency and reliability of the measurements.

Data analysis

Statistical analysis was conducted using SPSS software (version 25, IBM Corp., Armonk, NY, USA). Descriptive statistics were provided as means ± standard deviations for continuous variables and as frequencies (%) for categorical variables. The normality of the data was verified using the Kolmogorov-Smirnov test, confirming a normal distribution. To compare variables between groups, independent samples T-tests, repeated measures tests, and chi-square statistical tests were utilized. We also employed Fisher's exact test and Mann–Whitney U test. Meanwhile, a P value of less than 0.05 was considered statistically significant in all analyses.

Results

During the specified period, a total of 80 patients were enrolled in the study, randomly assigned to one of the two study groups, and received the allocated intervention. Statistical analysis was carried out for all participants, and the study was completed without any losses to follow-up or exclusions (Figure 1).

Comparisons of demographic variables between the dexmedetomidine and fentanyl groups are presented in Table 1. No statistically significant differences were observed between the two groups for age, gender, body mass index and ASA classification, or duration of surgery.

During the intraoperative period, the occurrence of bradycardia was comparable between the dexmedetomidine and fentanyl groups. However, postoperative bradycardia was more frequent among patients who received dexmedetomidine. Intraoperative hypotension was observed less often with fentanyl, whereas postoperative hypotension was more common in this group (Table 2). No cases of headache were reported in either group, and no patient experienced intraoperative shivering. Postoperative shivering occurred less frequently in the dexmedetomidine group. The incidence of intraoperative nausea and vomiting was similar between groups, while postoperative nausea and vomiting were notably less frequent after dexmedetomidine administration (Table 2).

During surgery, hypoxia requiring supplemental oxygen was observed more often with fentanyl than with dexmedetomidine, although no postoperative hypoxic events occurred in either group (Table 2). Postoperative pain intensity was lower among patients receiving dexmedetomidine, and the time to first opioid requirement was longer in this group. The frequency of

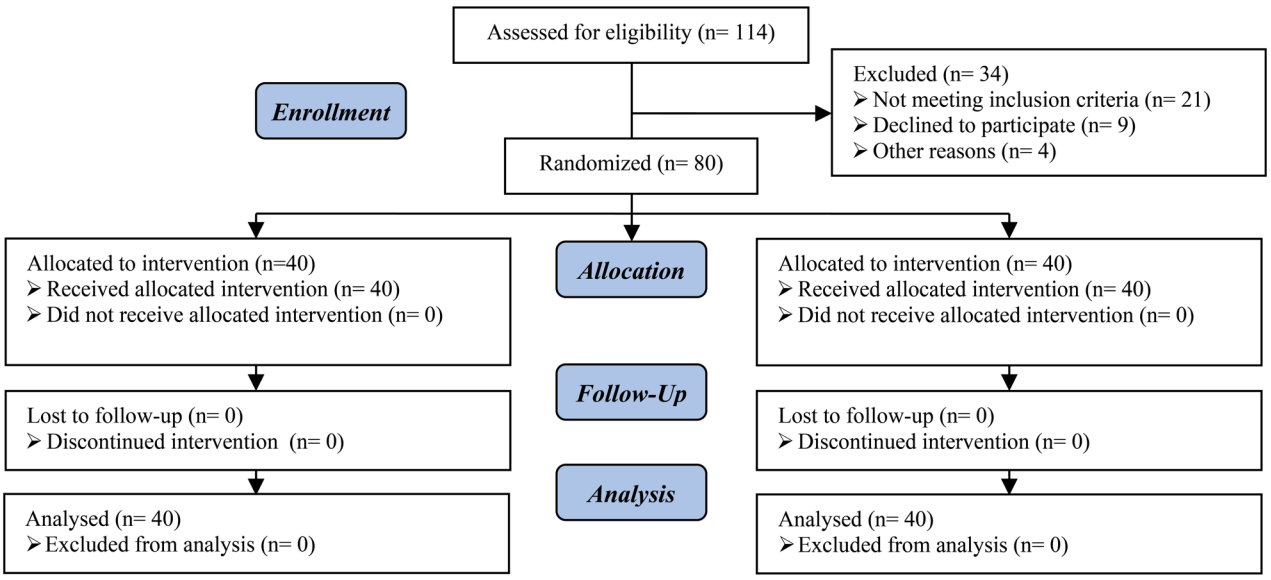

Figure 1. Patient enrollment and follow-up process based on the CONSORT flowchart.

Table 1. Demographic variables between two study groups

Variable	Study groups (N = 80)		*P* value
	Dexmedetomidine group (n = 40)	Fentanyl group (n = 40)	
Age (years)	54.3 ± 8.9	55.1 ± 9.5	0.532*
Gender (female, %)	22(55 %)	20 (50 %)	0.634**
BMI (kg/m²)	27.8 ± 3.6	28.2 ± 3.9	0.421*
ASA classification			
I (%)	24(60 %)	22(55 %)	0.387**
II (%)	16(40 %)	18(45 %)	
Duration of surgery (min)	102.5 ± 15.2	104.3 ± 16.5	0.486*

BMI, body mass index; ASA, American Society of Anesthesiologists.
* Independent samples T test; ** Chi-square test. *P* value < 0.05 was statistically significant.

Table 2. Comparison of complications intra and post-operative between the two study groups

Variable	Time	Dexmedetomidine group (n=40)	Fentanyl group (n=40)	Absolute risk difference % (95% CI)	RR (95% CI)	*P* value
Bradycardia	Intraoperative	5 (12.5%)	3 (7.5%)	5.0% (–7.2%, 17.2%)	1.67 (0.43–6.40)	0.712**
Bradycardia	Postoperative	8 (20.0%)	2 (5.0%)	15.0% (2.2%, 27.8%)	4.00 (0.90–17.79)	0.087**
Hypotension	Intraoperative	4 (10.0%)	6 (15.0%)	–5.0% (–17.0%, 7.0%)	0.67 (0.19–2.34)	0.737*
Hypotension	Postoperative	5 (12.5%)	11 (27.5%)	–15.0% (–30.7%, 0.7%)	0.45 (0.16–1.31)	0.161*
Headache	Intraoperative	0 (0.0%)	0 (0.0%)	—	—	1.000
Headache	Postoperative	0 (0.0%)	0 (0.0%)	—	—	1.000
Shivering	Intraoperative	0 (0.0%)	0 (0.0%)	—	—	1.000
Shivering	Postoperative	5 (12.5%)	7 (17.5%)	–5.0% (–19.1%, 9.1%)	0.71 (0.23–2.22)	0.755*
Nausea and vomiting	Intraoperative	3 (7.5%)	4 (10.0%)	–2.5% (–13.0%, 8.0%)	0.75 (0.17–3.28)	1.000**
Nausea and vomiting	Postoperative	4 (10.0%)	8 (20.0%)	–10.0% (–23.0%, 3.0%)	0.50 (0.15–1.65)	0.348*
Hypoxia	Intraoperative	1 (2.5%)	6 (15.0%)	–12.5% (–23.1%, –1.9%)	0.17 (0.02–1.26)	0.108**
Hypoxia	Postoperative	0 (0.0%)	0 (0.0%)	—	—	1.000
Atropine injection	—	5 (12.5%)	4 (10.0%)	2.5% (–9.3%, 14.3%)	1.25 (0.35–4.46)	1.000*
Ephedrine injection	—	3 (7.5%)	4 (10.0%)	–2.5% (–13.0%, 8.0%)	0.75 (0.17–3.28)	1.000**
Ondansetron injection	—	3 (7.5%)	8 (20.0%)	–12.5% (–25.6%, 0.6%)	0.37 (0.10–1.33)	0.193*
Pain intensity (VAS)	—	3.2 ± 1.3	5.1 ± 1.9	MD: –1.9 (–2.6, –1.2)	—	0.039***
First opioid time (hr)	—	4.5 ± 1.2	1.6 ± 0.8	MD: 2.9 (2.4, 3.4)	—	0.017***
Anesthesia duration (hr)	—	5.8 ± 1.4	3.7 ± 1.1	MD: 2.1 (1.6, 2.6)	—	0.035***

CI: Confidence interval; OR: Odds ratio; VAS: Visual analog scale; SD: Standard deviation; MD: Mean difference.
* Pearson›s chi-squared test; ** Fisher's exact test; *** Independent samples T-test

atropine and ephedrine use was comparable between groups. Conversely, the need for ondansetron was lower in patients receiving dexmedetomidine, and the total duration of anesthesia was longer in this group compared with fentanyl (Table 2).

We also found no statistically significant difference of serum CRP between dexmedetomidine and fentanyl groups at the baseline of the study prior to surgery, indicating comparable preoperative inflammatory status between the two groups. However, at 24 hours following TKA, mean serum CRP levels were significantly lower in the dexmedetomidine group compared with the fentanyl group, reflecting a reduced postoperative inflammatory response in patients receiving dexmedetomidine. This statistically significant difference persisted at 48 hours postoperatively, with serum CRP concentrations remaining significantly lower in the dexmedetomidine group than in the fentanyl group (Figure 2, Table 3).

The SII did not differ significantly between the two groups at baseline, with a comparable distribution of values. At 24 hours postoperatively, SII increased markedly in both groups; however, levels were significantly higher in the fentanyl group compared with the dexmedetomidine group, indicating a more pronounced systemic inflammatory response. Although SII values declined in both groups at 48 hours after surgery, they remained significantly elevated in the fentanyl group relative to the dexmedetomidine group (Figure 3, Table 4).

Discussion

The comparison between adding dexmedetomidine and fentanyl to intrathecal bupivacaine during TKA yielded valuable insights into their effects on postoperative complications. Our study aimed to elucidate the

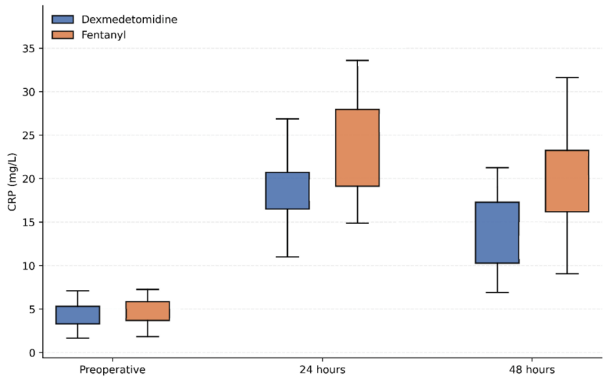

Figure 2. Comparison of serum CRP levels between study groups

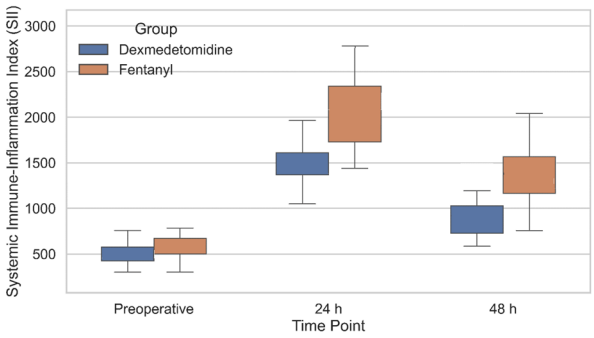

Figure 3. Comparison of SII between study groups.

Table 3. Comparison of serum CRP levels study groups at different time points

Time point	Dexmedetomidine (Median [IQR])	Fentanyl (Median [IQR])	*P* value
Preoperative	4.5 [3.5–6.0]	5.0 [4.0–6.5]	0.622
24 hours	18.5 [16.0–21.0]	24.0 [19.0–28.0]	< 0.001
48 hours	14.0 [10.0–17.0]	20.0 [16.0–23.0]	< 0.001

Data are presented as median (interquartile range) due to non-normal distribution of CRP values. Between-group comparisons were performed using the Mann–Whitney U test.

Table 4. Comparison of SII between dexmedetomidine and fentanyl groups at different time points

Time point	Dexmedetomidine (Median [IQR], mg/L)	Fentanyl (Median [IQR], mg/L)	*P* value
Preoperative	500 [420–600]	600 [500–700]	0.414
24 hours	1500 [1400–1650]	2100 [1750–2350]	< 0.001
48 hours	900 [700–1050]	1400 [1200–1600]	< 0.001

Data are presented as median (interquartile range) due to non-normal distribution of SII values. Between-group comparisons were performed using the Mann–Whitney U test.

mechanisms underlying these observations and their implications for perioperative care.

The findings of the present study demonstrated that serum CRP value and the SII remained significantly lower in patients receiving dexmedetomidine compared with those in the fentanyl group at 24 and 48 hours after surgery. This pattern suggests a more effective attenuation of the systemic inflammatory response by dexmedetomidine (25). The anti-inflammatory properties of dexmedetomidine are likely mediated through activation of α2-adrenergic receptors, suppression of sympathetic nervous system activity, reduction in the release of pro-inflammatory cytokines, and modulation of the hypothalamic–pituitary–adrenal axis (28). In contrast, fentanyl provides potent analgesia, it appears to exert limited influence on the inflammatory cascade triggered by surgical trauma and stress (24). The more pronounced elevation of SII observed in the fentanyl group reflects greater activation of innate immune components, particularly neutrophils and platelets, along with a relative suppression of lymphocyte-mediated responses, culminating in a heightened systemic inflammatory state (21).

From a clinical perspective, amplification of the systemic inflammatory response plays a critical role in the development and persistence of acute postoperative pain (21). Elevated serum CRP and SII levels are associated with increased release of inflammatory mediators and both peripheral and central sensitization of nociceptive pathways, leading to a reduced pain threshold and increased postoperative analgesic requirements (23). The significantly lower levels of these inflammatory markers in the dexmedetomidine group may therefore contribute to attenuation of inflammation-driven pain mechanisms, reduced hyperalgesia, and improved postoperative pain control (25). Accordingly, these findings suggest that dexmedetomidine may alleviate acute postoperative pain not only through its central analgesic and sedative effects, but also by diminishing the systemic inflammatory burden, thereby improving overall postoperative outcomes (26).

The differential effects observed between dexmedetomidine and fentanyl can be attributed to their distinct pharmacological mechanisms of action. Dexmedetomidine acts as a selective α2-adrenergic agonist, primarily targeting presynaptic α2 receptors in the locus coeruleus, resulting in sympatholysis and sedation without significant respiratory depression. In contrast, fentanyl is a potent opioid analgesic that primarily acts on μ-opioid receptors in the central nervous system, leading to analgesia, sedation, and respiratory depression. These mechanisms underline the differences in hemodynamic stability and oxygenation observed between the two groups (39,40).

The findings of our study have significant clinical implications for the management of patients undergoing TKA. Dexmedetomidine may offer advantages over fentanyl in terms of heart rate control, blood pressure stability, and oxygen saturation maintenance during surgery. These benefits may lead to improved perioperative outcomes, reduced postoperative complications, and

enhanced patient safety. Further research is warranted to validate these findings and optimize the dosing and administration of dexmedetomidine as an adjuvant in intrathecal anesthesia (41,42).

During surgery, no statistically significant difference in bradycardia incidence was noted between the two groups, suggesting that both dexmedetomidine and fentanyl had comparable effects on heart rate regulation. We found, post-surgery, patients receiving dexmedetomidine exhibited a significantly higher incidence of bradycardia compared to those receiving fentanyl. This difference could be attributed to dexmedetomidine's potent α2-adrenergic agonist activity, which results in sympatholysis and bradycardia. Conversely, hypotension during surgery was non-significantly lower in the fentanyl group, likely due to its less pronounced effects on sympathetic tone compared to dexmedetomidine. Accordingly, post-surgery hypotension was significantly higher in the fentanyl group, possibly due to rebound vasodilation following the cessation of fentanyl's analgesic effects (43,44).

Headache was not reported in either group, indicating that both dexmedetomidine and fentanyl were well-tolerated in terms of central nervous system effects. Shivering during surgery was infrequent and similar between the groups, suggesting that both adjuvants had minimal impact on thermoregulation. Nevertheless, the incidence of postoperative shivering tended to be lower in dexmedetomidine recipients, emphasizing its potential to mitigate thermoregulatory disturbances. Nausea and vomiting during surgery did not significantly differ between the groups, but post-surgery, dexmedetomidine recipients experienced significantly fewer instances, likely due to its antiemetic properties mediated through central α2-adrenergic receptor activation (45,46).

Hypoxia during surgery was more common in the fentanyl group, reflecting its propensity for respiratory depression. Dexmedetomidine, with its minimal respiratory depressant effects, resulted in a lower incidence of hypoxia. This difference underscores the importance of selecting adjuvants that minimize respiratory compromise, particularly in patients susceptible to respiratory complications. Moreover, dexmedetomidine recipients reported significantly lower postoperative pain intensity and delayed requirement for opioid medication compared to fentanyl recipients, indicating its efficacy in providing analgesia and reducing opioid consumption (47,48).

There were no significant differences in the administration of atropine or ephedrine, suggesting comparable management of intraoperative complications between the groups. Notably, the reduced need for ondansetron in the dexmedetomidine group shows the capability of dexmedetomidine to mitigate postoperative nausea and vomiting. Additionally, the longer duration of anesthesia in the dexmedetomidine group may be attributed to its pharmacokinetic properties, including prolonged duration of action and slower clearance compared to fentanyl (49,50).

Conclusion

Overall, this study demonstrated that dexmedetomidine and fentanyl, when administered as intrathecal adjuvants to bupivacaine in patients undergoing TKA are associated with distinct perioperative clinical and inflammatory profiles. In addition to a lower incidence of reduced postoperative pain intensity, dexmedetomidine was associated with significantly lower serum levels of CRP and the SII at 24 and 48 hours after surgery. These findings indicate a more effective attenuation of the postoperative systemic inflammatory response and a reduced inflammatory burden with dexmedetomidine compared with fentanyl. Although fentanyl provided relatively greater perioperative blood pressure stability, the greater elevation of inflammatory markers observed in this group suggests a stronger inflammatory response than dexmedetomidine group.

Limitations of the study

Several limitations should be acknowledged when interpreting the results of this study. i) The relatively modest sample size and single-center design may have reduced statistical power and limited the generalizability of the findings. ii) Although surgical techniques were standardized, intraoperative anesthetic management and postoperative care variables can be as residual confounders. iii) The absence of long-term follow-up restricted outcome assessment to the perioperative period, precluding conclusions regarding longer-term analgesic efficacy, functional recovery or late adverse events. Accordingly, future multicenter investigations with larger patient populations, rigorous perioperative standardization and extended follow-up periods are required to validate and expand upon these findings.

Authors' contribution

Conceptualization: Vahid Fattahi.
Data curation: Vahid Fattahi, Aliakbar Zia-Azar.
Formal analysis: Aliakbar Zia-Azar, Mahdi Nazari.
Funding acquisition: Aliakbar Zia-Azar.
Investigation: Mahdi Nazari.
Methodology: Mahdi Nazari, Abbasali Dorosti.
Project administration: Vahid Fattahi.
Resources: Mahdi Nazari, Abbasali Dorosti.
Software: Mahdi Nazari.
Supervision: Mahdi Nazari.
Validation: Mahdi Nazari, Abbasali Dorosti.
Visualization: Abbasali Dorosti.
Writing–original draft: Abbasali Dorosti.
Writing–review & editing: Abbasali Dorosti, Mahdi Nazari.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

The research was conducted in accordance with the principles outlined in the Declaration of Helsinki. The Ethics Committee of

Tabriz University of Medical Sciences approved this study. The institutional ethical committee at Tabriz University of Medical Sciences accepted all study protocols (Ethical code #IR.TBZMED.REC.1402.390). Accordingly, written informed consent was taken from all participants before any intervention. This study was part of "Comparison of the effect of adding dexmedetomidine, fentanyl and magnesium sulfate to bupivacaine in the management of acute pain after knee replacement surgery" thesis in the department of anesthesiology at this university (Thesis #71729). The trial protocol was approved by the Iranian Registry of Clinical Trials (identifier: IRCT20190325043107N58; https://irct.behdasht.gov.ir/trial/84871).

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors utilized ChatGPT to refine grammar points and language style in writing. Subsequently, the authors thoroughly reviewed and edited the content as necessary, assuming full responsibility for the publication's content.

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