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The effects of intrathecal fentanyl on postoperative opioid utilization rates in elderly patients undergoing lower extremity orthopedic surgery: a randomized controlled trial

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Abstract

Background Various types of lower extremity orthopedic surgeries can cause severe postoperative pain in elderly patients. Achieving adequate pain control while minimizing the use of opioids is advantageous, as it helps reduce postoperative complications and facilitates recovery. In this randomized trial, we compared the opioid utilization rates of elderly patients who received or not receive intrathecal fentanyl as an anesthesia adjuvant.

Methods A total of 180 elderly patients were enrolled in the study. They were randomly assigned to the BF1 group (bupivacaine plus 25 μg of fentanyl), the BF2 group (bupivacaine plus 50 μg of fentanyl), or the B group (bupivacaine), achieving a final between-group ratio of 2:2:1. Our primary outcome was the rate of opioid use, while secondary outcomes included the NRS score and the utilization rate of analgesic drugs on PODS1–3.

Results The usage rate of opioid analgesics within the POD3 was higher in B group compared to BF1 and BF2 groups (100% vs. 79.2% and 80.3%, respectively; $P < 0.05$). However, there was no significant difference in the usage rate of opioid analgesics among the groups within the PODS1–2 ($P > 0.05$). The incidence of patients with NRS scores ≥ 4 was significantly lower in BF1 and BF2 groups compared to B group on PODS2–3 (POD2, 62.2% and 68.9% vs. 93.8%, respectively; $P < 0.05$; POD3, 16.2% and 17.6% vs. 40.6%, respectively; $P < 0.05$). Additionally, BF1 group had a lower incidence of NRS scores ≥ 4 compared to B group on POD1 ($P < 0.05$). The rate of analgesic drug use was similar among the three groups on POD1–3 ($P > 0.05$).

Conclusion In elderly patients undergoing lower extremity surgery, intrathecal fentanyl as an anesthetic adjuvant may correlate with reduced pain scores on PODS1–3 and decreased opioid requirements on POD3.High-dose fentanyl does not provide significant therapeutic advantages.

Trial registration The study registered on the Chinese Clinical Trial Registry (www.chictr.org.cn), Clinical Trials identifier ChiCTR2200058362 (2022/04/07).

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Keywords Intrathecal, Fentanyl, Elderly patients, Abreviations, APostoperative days, PRDPreoperative day, PCIAPatient controlled intravenous analgesia, PCAPatient controlled analgesia, NRSNumeric Rating Scale, NSAIDsNon-steroidal anti-inflammatory drugs

Background

Due to the increasing prevalence of an aging population, there is a greater number of elderly patients undergoing orthopedic surgery on their lower limbs, which often leads to severe postoperative pain. Alongside patient controlled analgesia (PCA), opioids are frequently utilized as the main rescue analgesic approach for managing acute pain in elderly patients after lower limb orthopedic surgery (Griffioen and O'Brien 2018). However, the administration of postoperative opioids may potentially increase the risk of chronic opioid use (Baboli et al. 2020; Lim and Lee 2020). Furthermore, physical frailty, complex comorbidities, and cognitive impairment often complicate the assessment and treatment of pain in this specific population following orthopedic surgery (Lim and Lee 2020). Therefore, achieving appropriate pain control while minimizing postoperative opioid consumption is crucial to prevent adverse reactions associated with opioids and maximize the analgesic benefits derived from lower limb orthopedic surgery in elderly patients. However, it poses significant challenges for physicians.

Intrathecal local anesthesia drugs and adjuvants are widely used in clinical anesthesia to improve the quality of analgesia. Among them, opioids are frequently used as adjuvants for intrathecal injections (Grape et al. 2023). Recent studies have demonstrated the benefits of intrathecal morphine for pain relief and reduction of opioid consumption after surgery for gynecological malignant tumors (Bang et al. 2023). Although fentanyl is commonly used as a fat-soluble opioid in intrathecal injections, few studies have investigated the analgesic effects with 50 ug fentanyl on elderly patients undergoing lower limb orthopedic surgery or its potential to reduce opioid consumption.

In this prospective, randomized controlled study, we hypothesize that the use of intrathecal fentanyl as an anesthesia adjuvant can reduce postoperative opioid requirements in elderly patients undergoing lower limb orthopedic surgery. Furthermore, we aim to investigate the differences in opioid savings associated with varying doses of fentanyl. Additionally, we will compare secondary outcomes such as Numeric Rating Scale (NRS) scores and the rate of analgesic drug usage among the different groups.

Methods

Ethical approval

This prospective randomized controlled trial was approved by the hospital Ethics Committee (2022-LL-080, registration date: 2022/3/30). All subjects participating in the experiment had signed informed consent. The trial was registered in the Chinese Clinical Trials Registry before the patients were enrolled (ChiCTR2200058362, registration date: 2022/04/07). This article adhered to the applicable Consolidated Standards of Reporting Trials (CONSORT) guidelines and was conducted at a university affiliated hospital from July 2023 to January 2024.

Enrollment

Patients aged ≥ 60 and < 90, with an ASA physical status of I–III, who were undergoing surgery for lower extremity orthopedic surgery including hip joint, knee joint arthroplasty, and fracture surgery under intrathecal anesthesia, were eligible for enrollment. Exclusion criteria included intrathecal anesthesia contraindications (blood coagulation dysfunction, schizophrenia, history of spinal trauma, lumbar disease not easy to perform intraspinal anesthesia, puncture site infection); previous bed rest, epilepsy, Parkinson's disease or myasthenia gravis; severe renal impairment (needing renal replacement therapy); severe liver impairment (Child–Pugh grade C); severe cardiac insufficiency (NYHA $\geq$ III); and refusal to participate in this study.

Randomization and blinding

Patients were recruited based on the inclusion and exclusion criteria and fully informed of the study risks. Upon obtaining their consent to participate, the patients were randomized into 3 groups in a 2:2:1 ratio. Adopting a randomized, single-blind, controlled clinical study, the random numbers generated by the table of random digit are placed in sequentially encoded, sealed, opaque envelopes and assigned to different groups according to a predetermined random scheme. In a single-blind study, participants have the right to be informed of any serious security incidents or termination events through the provided grouping information. This study was designed as a parallel-controlled randomized trial. A study coordinator was assigned to maintain and distribute the random numbers and coordinate information among the researchers. Additionally, one or more attending physicians were responsible for administering anesthesia, while the assistant recorded intraoperative information. Follow-up personnel did not participate in the administration of clinical anesthesia or postoperative

management and were unaware of the records kept by the other researchers.

Anesthesia procedures

A 25G needle was used at the L3–L4 lumbar interspace for a single lumbar puncture. B group received an injection of 15 mg bupivacaine (5 ml: 37.5 mg, Shanghai Chaohui Pharmaceutical Co., Ltd., China.) + 1 ml cerebrospinal fluid, while BF1 group received 15 mg bupivacaine + 25 μg fentanyl (2 ml: 0.1 mg, Yichang Humanwell Pharmaceutical Co., Ltd., China) + 0.5 ml cerebrospinal fluid. Lastly, BF2 group received an injection of 15 mg bupivacaine + 50 μg fentanyl. After the injection was completed, an assessment of sensory block in the lower extremities was conducted using a needle prick test, starting from the T12 dermatome level. Additionally, the degree of motor block in the lower extremities was evaluated according to the modified Bromage scale (Grade 0: no motor block; Grade 1: inability to raise the extended leg; Grade 2: inability to flex the knee; Grade 3: complete motor block with inability to flex the ankle).

Intraoperative management

Patients who had changed the anesthesia method to general anesthesia or experienced significant blood loss (≥ 24 ml/kg) would be excluded from the study. The following anesthetic effects should be recorded: The highest sensory block plane assessed using a needle prick test (defined as the plane measured every 2 min after injection, with the highest sensory block plane being recorded when the same result is obtained three consecutive times). The same method was used for the duration of sensory block (defined as the time from the administration of intrathecal anesthesia to the restoration of pain sensation at the surgical site). The onset time of lower extremity motor block assessed using the modified Bromage scale (defined as Bromage grade 1). The duration of lower limb motor block (defined as the time from the onset of motor block (Bromage grade 1) to the recovery of motor function in the lower extremities (Bromage grade 0)). The following adverse reactions should also be recorded: hypotension (systolic blood pressure < 90 mmHg or more than 30% lower than baseline), hypertension (systolic blood pressure > 180 mmHg or more than 30% higher than baseline), bradycardia (HR < 50 bpm or more than 30% lower than baseline), tachycardia (HR > 120 bpm or more than 30% higher than baseline), respiratory depression (respiratory rate < 10 beats per minute), and hypoxemia (SpO2 < 90% without oxygen inhalation).

Postoperative analgesia

All patients received the same formula for patient-controlled intravenous analgesia (PCIA), which consisted of sufentanil 1.5–2 μg/kg mixed in 100 ml of solution infused at a rate of 2 ml/h. The PCA bolus dose was 1 μg, with a lockout time of 10 min. No analgesic adjuvants were included in the PCIA formula.

For pain assessment, we utilized the NRS pain scores, which consists of a total of 11 points ranging from 0 to 10. These points are categorized into four grades: absence of pain (0), mild pain (1–3), moderate pain (4–6), and severe pain (7–10). Follow-up personnel evaluate the patient's NRS scores every 4 h during rest on the preoperative day 1 (PRD1) and postoperative days (PODS) 1–3 (POD1 means end of surgery) in the ward. The median NRS score for each day is taken as the representative value. When the postoperative NRS score was 3, non-steroidal anti-inflammatory drugs (NSAIDs) such as celecoxib (0.2 g bid po) or diclofenac sodium (75 mg qd po) were administered. When the NRS score was between 4 and 9 rescue analgesics such as dezocine (5 mg im), parecoxib (40 mg im), or lofentanil and codeine (12.5 mg bid po) were administered by a surgeon. When the NRS score was 10, the patients were administered hydromorphone (5 mg IV). Among the medications used, dezocine, lofentanil and codeine, and hydromorphone are the opioids. We strictly adhered to the selection criteria for postoperative analgesia methods outlined in this study.

Sample size

The PASS software (version 2021) was used to calculate the sample size. The sample size was based on previous preliminary experiments in which the rates of postoperative opioid use were 69% and 75% with 25 and 50 μg fentanyl, respectively, and 95% without fentanyl for POD1. It was calculated that 166 patients were needed, with a power of 90% and an alpha error of 0.05. We chose to include 191 patients considering the potential for 15% of missing data.

Statistical analysis

SPSS software (version 25.0) and GraphPad Prism (version 9.4.1) were used for statistical analysis. The missing value processing involves replacing numeric null values with the average value of all other data in the item, while non-numeric null values are filled using the mode. The data were presented as the mean ± standard deviation ($\overline{x} \pm s$) and subjected to analysis of variance (ANOVA) if the distributions exhibited normality across the three groups. Tukey's test was used for post hoc tests. The Kruskal–Wallis (K-W) test was employed to analyze the

data that deviated from normal distribution, and data were presented as median values with interquartile range (IQR). Percentages or constituent data were compared using the chi-square or Fisher's exact test and expressed as percentages (*n* %). All tests were conducted as two-tailed tests, and a *P*-value of less than 0.05 was considered statistically significant.

Results

A total of 208 patients were recruited, due to changes in the anesthesia method or experiencing significant blood loss, ultimately, there were 74 patients in BF1 and BF2 group respectively, and 32 patients in B group (Fig. 1). Patients' characteristics were shown in Table 1. Preoperative variables were comparable among the groups ($P > 0.05$).

Primary outcomes

The use of opioid analgesics was higher in B group than in BF1 and BF2 groups on POD3 (100% vs 79.2% and 80.3%, $P < 0.05$), while there was no difference among groups on PODS1–2 ($P > 0.05$, Table 4).

Secondary outcomes

The distribution of patients with varying pain levels across the three groups, based on the NRS pain score on PODS1–3, was depicted in Fig. 2. For POD1, the BF1 and BF2 groups had the proportion of patients with a pain score ranging from 7 to 9 was 36.5% respectively, while B group was 50%. For POD2, all three groups showed varying proportions: BF1 group had 51.4% of patients scoring between 4 and 6; BF2 group had a slightly higher percentage at 54.1%; and B group exhibited significantly more patients (84.4%) within this range (Table 2). For POD3, there was a shift towards lower pain scores across all groups: both BF1 and BF2 groups were recorded an equal highest proportion (82.4%) of patients scoring between 1 and 3, whereas B group saw a slightly lower percentage at 59.4%. Patients in BF1 and BF2 groups had significantly lower NRS scores ≥ 4 at POD2–3 than those in B group (POD2, 62.2% and 68.9% vs 93.8%; $P < 0.05$; POD 3, 16.2% and 17.6% vs 40.6%, $P < 0.05$, Table 3). BF1 group had a lower NRS score ≥ 4 than B group on POD1 ($P < 0.05$, Table 3). The rate of analgesic drug use was the same

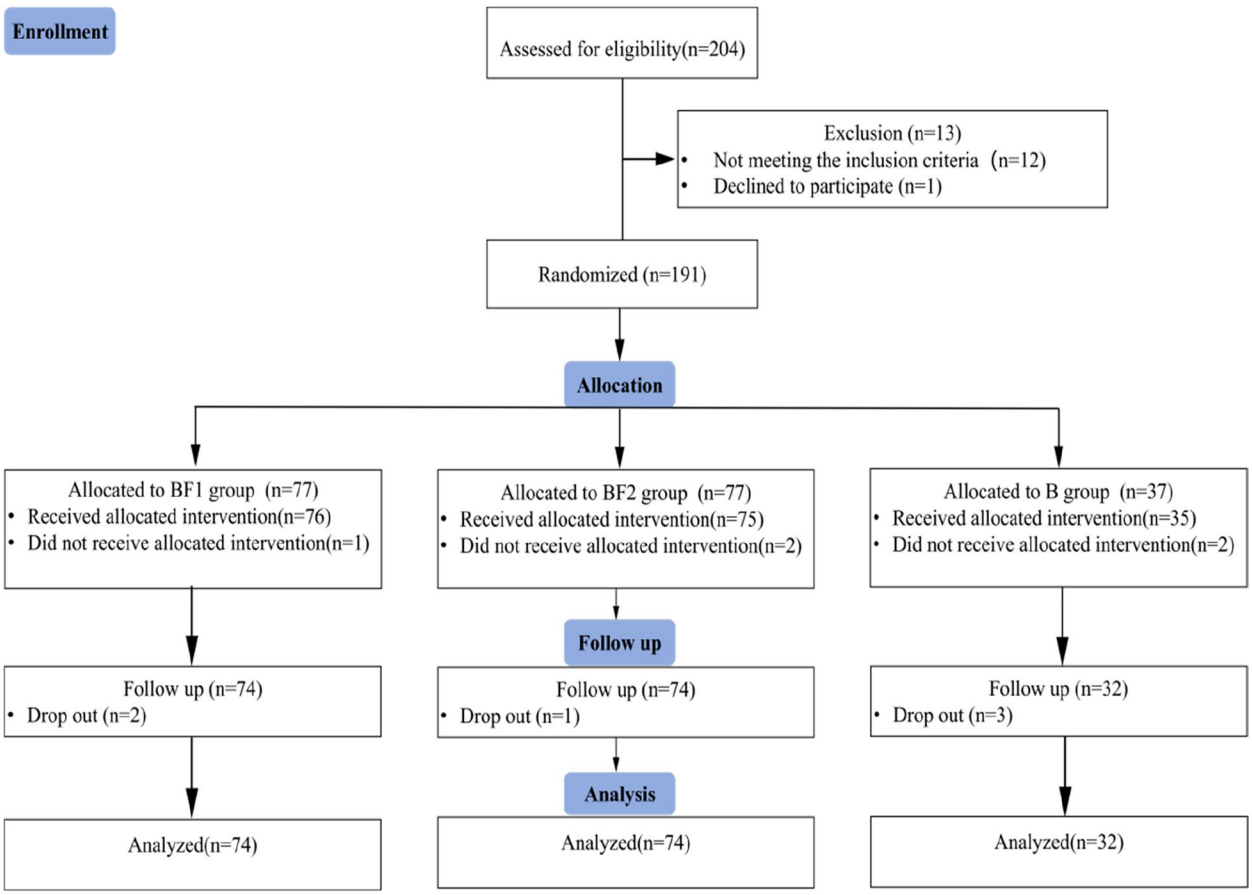

Fig. 1 CONSORT flow diagram. CONSORT indicates Consolidated Standards of Reporting Trial, B group, bupivacaine. BF1 group, bupivacaine + 25 μg fentanyl. BF2 group, bupivacaine + 50 μg fentanyl

Table 1 Patient baseline characteristics

	BF1 group	BF2 group	B group	*P* value
Sex, female, *n* (%)	48 (64.9)	49 (66.2)	27 (84.4)	0.112
Age, y, mean (SD)	69.24 (5.3)	69.18 (5.9)	69.52 (4.9)	0.958
Weight, kg, mean (SD)	64.49 (10.4)	67.89 (9.4)	65.44 (8.0)	0.094
Body mass index, kg m^{-2}, mean (SD)	24.54 (3.5)	25.62 (3.1)	25.70 (2.2)	0.068
ASA physical status, *n* (%)				0.923
I	0 (0.0)	0 (0.0)	0 (0.0)	
II	53 (71.6)	51 (68.9)	23 (71.9)	
III	21 (28.4)	23 (31.1)	9 (28.1)	
Comorbidities, *n* (%)				
Hypertension	33 (44.6)	41 (55.4)	20 (62.5)	0.184
Diabetes	13 (17.6)	11 (14.9)	8 (25.0)	0.455
Coronary heart disease	9 (12.2)	9 (12.2)	6 (18.8)	0.610
Cerebrovascular disease	2 (2.7)	6 (8.1)	0 (0.0)	0.185
Others	15 (20.3)	14 (18.9)	6 (18.8)	0.973
History of operation, *n* (%)	44 (59.5)	47 (63.5)	23 (71.9)	0.476
History of anesthesia, *n* (%)	43 (58.1)	47 (63.5)	23 (71.9)	0.398
Preoperative complications, *n* (%)				
Pruritus, *n* (%)	3 (4.1)	4 (5.4)	2 (6.3)	0.905
Nausea, *n* (%)	2 (2.7)	1 (1.4)	0 (0.0)	> 0.999
Vomiting, *n* (%)	1 (1.4)	1 (1.4)	0 (0.0)	> 0.999
Headache, *n* (%)	1 (1.4)	1 (1.4)	0 (0.0)	> 0.999
Low back pain, *n* (%)	8 (10.8)	9 (12.2)	2 (6.3)	0.659

Values are the mean ± SD, median (IQR), or number (%)

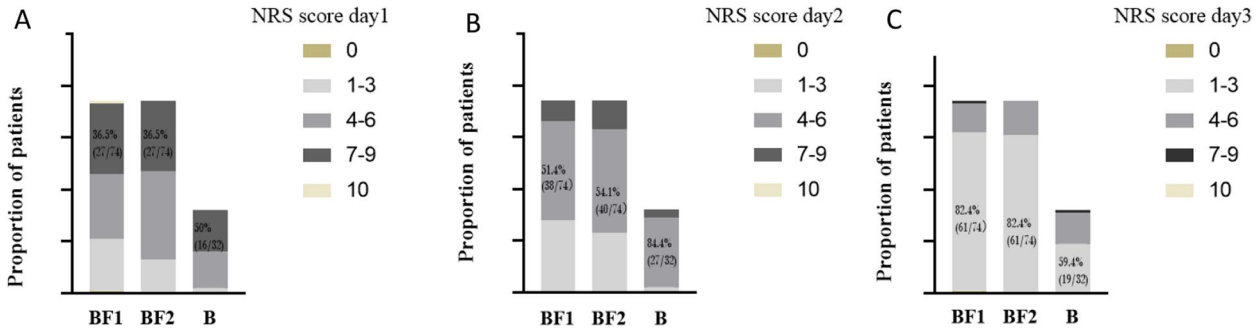

Fig. 2 The accumulation chart illustrates the proportion of individuals with varying NRS ratings

among the three groups on PODS1–3 (BF1 group vs BF2 group vs B group, 77.0% vs 78.4% vs 84.4%, $P = 0.689$ for POD1; 74.3% vs 85.1% vs 93.8%, $P = 0.039$ for POD2; 71.6% vs 61% vs 81.3%, $P = 0.250$ for POD3) (Table 4).

Others

There was no difference in the highest sensory blocking plane ($P > 0.05$, Table 5). And there was no significant difference in the median onset time (IQR) of lower limb motor block among BF1 group (2 min [2–3.25]), BF2 group (3 min (Baboli et al. 2020; Lim and Lee 2020; Grape et al. 2023)), and B group (2 min (Baboli et al. 2020; Lim and Lee 2020)) ($P = 0.046$, Table 5). The sensory block time of B group was 348 min, when BF1 group (461 min) and BF2 group (467) was longer, but the differences among the three groups were not statistically significant ($P > 0.05$, Table 5). There was also no difference in motor block time among the three groups: 316 min for BF1 group, 306 min for BF2 group, and 264 min for B group ($P > 0.05$, Table 5). The incidence of intraoperative hypotension in BF2 group was lower than that in B group and BF1 group (4.1% vs 18.8% vs 16.2%, $P < 0.05$), but the

Table 2 Surgery and anesthesia characteristics

	BF1 group ($n=74$)	BF2 group ($n=74$)	B group ($n=32$)	*P* value
Type of surgery, *n* (%)				0.316
Femoral head arthroplasty	3 (4.1)	5 (6.8)	2 (6.3)	
Hip joint arthroplasty	10 (13.5)	4 (5.4)	0 (0.0)	
Knee joint arthroplasty	53 (71.6)	57 (77.0)	26 (81.3)	
Open reduction of fracture or removal of internal fixation for fracture	8 (10.8)	8 (10.8)	4 (13.5)	
Surgery time, min, mean, (SD)	87.7 (29.0)	96.4 (38.7)	101.6 (27.8)	0.096
Volume expansion, mL, *n* (%)				0.949
≤ 500	1 (1.4)	0 (0.0)	0 (0.0)	
500–1000	14 (18.9)	14 (18.9)	7 (21.9)	
> 1000	59 (79.7)	60 (81.1)	25 (78.1)	
Time to complete injection, s, median (IQR)	20(16–28)	22.5 (16.8–30)	21 (16.3–23.8)	0.244

Values are the mean ± SD, median (IQR), or number (%)

Table 3 NRS pain scores within PRD1 and PODS1–3

Parameter	BF1 group ($n=74$)	BF2 group ($n=74$)	B group ($n=32$)	*P* value
Pain score within PRD1 (NRS, 0–10), median (IQR)	2 (0–4)	2 (1–3)	2 (0–2)	0.356
Pain score within POD1 (NRS, 0–10), median (IQR)	6 (3–8)	6 (4–7)	7 (6–8)	0.740
≥ 4, *n* (%)	53 (71.6)[a]	61 (82.4)	30 (93.8)	0.026
Pain score within POD2 (NRS, 0–10), median (IQR)	4 (3–6)	4.5 (3–6)	5 (4–6)	0.157
≥ 4, *n* (%)	46 (62.2)[a]	51 (68.9)[a]	30 (93.8)	0.004
Pain score within POD3 (NRS, 0–10), median (IQR)	2 (2–3)	3 (2–3)	3 (2–3)	0.465
≥ 4, *n* (%)	12 (16.2)[a]	13 (17.6)[a]	13 (40.6)	0.011

Values are the mean ± SD, median (IQR), or number (%). Pain was assessed using a NRS, ranging from 0 to 10

[a] Compared with B group, the difference is statistically significant

Table 4 Utilization rate of opioids and analgesic drugs within POD1–3

Parameter	BF1 group ($n=74$)	BF2 group ($n=74$)	B group ($n=32$)	*P* value
Analgesic use on POD1, *n* (%)				
YES	57 (77.0)	58 (78.4)	27 (84.4)	0.689
NO	17	16	5	
Opioids	41 (71.9)	50 (86.2)	25 (92.6)	0.048
Analgesic use on POD2, *n* (%)				
YES	55 (74.3)	63 (85.1)	30 (93.8)	0.039
NO	19	11	2	
Opioids	42 (76.4)	49 (77.8)	28 (93.3)	0.133
Analgesic use on POD3, *n* (%)				
YES	53 (71.6)	61 (82.4)	26 (81.3)	0.250
NO	21	13	6	
Opioids	42 (79.2)[a]	49 (80.3)[a]	26 (100.0)	0.022

Values are the mean ± SD, median (IQR), or number (%). "YES" indicates that postoperative analgesics were used, while "NO" indicates that no postoperative analgesics were administered

[a] Compared with B group, the difference is statistically significant

Table 5 Anesthetic effect, and intraoperative and postoperative adverse reactions

	BF1 group ($n=74$)	BF2 group ($n=74$)	B group ($n=32$)	*P* value
Highest sensory block plane, *n* (%)				0.391
≤ T4	6 (8.1)	2 (2.7)	2 (6.3)	
> T4	68 (91.9)	72 (97.3)	30 (93.8)	
Time to onset of lower extremity motor block, min, median, IQR	2 (2–3.25)	3 (2–4)	2 (2–3)	0.046
Duration of sensory block, min, mean (SD)	461 (309)	467 (336)	348 (121)	0.138
Duration of lower limb motor block, min, mean (SD)	316 (183)	306 (167)	264 (94)	0.316
Intraoperative adverse event, *n* (%)				
Low body temperature	0 (0.0)	0 (0.0)	0 (0.0)	> 0.999
Hypotension	12 (16.2)	3 (4.1)[a,b]	6 (18.8)	0.027
Hypertension	4 (5.4)	4 (5.4)	2 (6.3)	0.982
Bradycardia	15 (20.3)	10 (13.5)	6 (18.8)	0.536
Tachycardia	0 (0.0)	0 (0.0)	0 (0.0)	> 0.999
Depression of respiration	0 (0.0)	0 (0.0)	0 (0.0)	> 0.999
Hypoxemia	4 (5.4)	4 (5.4)	0 (0.0)	0.455
Shiver	0 (0.0)	0 (0.0)	0 (0.0)	> 0.999
Vomiting	0 (0.0)	6 (8.1)[a]	0 (0.0)	0.014
Nausea	8 (10.8)	14 (18.9)[b]	0 (0.0)	0.015
Pruritus	1 (1.4)	3 (4.1)	0 (0.0)	0.525
Adverse event on POD1, *n* (%)				
Depression of respiration	0 (0.0)	0 (0.0)	0 (0.0)	> 0.999
Hypoxemia	5 (6.8)	4 (5.4)	0 (0.0)	0.446
Shiver	0 (0.0)	0 (0.0)	0 (0.0)	> 0.999
Vomiting	3 (4.1)	9 (12.2)	1 (3.1)	0.100
Nausea	9 (12.2)	22 (29.7)[a]	3 (9.4)	0.008
Pruritus	0 (0.0)	0 (0.0)	0 (0.0)	> 0.999
Headache	0 (0.0)	1 (1.4)	0 (0.0)	> 0.999
Low back pain	11 (14.9)	10 (13.5)	6 (18.8)	0.786
No urinary catheterization	65 (87.8)	67 (90.5)	32 (100.0)	0.202
Adverse event on POD3, *n* (%)				
Depression of respiration	0 (0.0)	0 (0.0)	0 (0.0)	> 0.999
Hypoxemia	2 (2.7)	1 (1.4)	0 (0.0)	> 0.999
Shiver	0 (0.0)	0 (0.0)	0 (0.0)	> 0.999
Vomiting	0 (0.0)	0 (0.0)	0 (0.0)	> 0.999
Nausea	0 (0.0)	0 (0.0)	0 (0.0)	> 0.999
Pruritus	0 (0.0)	0 (0.0)	0 (0.0)	> 0.999
Headache	0 (0.0)	0 (0.0)	0 (0.0)	> 0.999
Low back pain	8 (10.8)	5 (6.8)	3 (9.4)	0.683

Values are the mean ± SD, median (IQR), or number (%)

[a] Compared with BF1, the difference is statistically significant

[b] Compared with B, the difference is statistically significant

incidence of intraoperative nausea (18.9%) and vomiting (8.1%) was higher in BF2 group ($P< 0.05$, Table 5). Similarly, the nausea incidence of BF2 (29.7%) was still higher than that of BF1 (12.2%) and B (9.4%) on POD1 ($P< 0.001$, Table 5). There was no difference in pruritus rate among the three groups in intraoperation and postoperation: 1.4% for BF1 group, 4.1% for BF2 group, 0% for B group in intraoperation. Other variables, including respiratory depression, shivering, and headache, were similar among groups in intraoperation and postoperation (Table 5). The median injection time did not differ significantly among the three groups: BF1 group had a median injection time of 20 s (16–28), BF2 group was 22.5 s (16.8–30), and B group was 21 s (16.3–23.8) ($P=0.244$, Table 5). The distribution of surgical types was balanced across the three groups (Table 2). Likewise,

there were no significant differences in surgical duration among the three groups (87.7 min in BF1 group, 96.4 min in BF2 group, 101.6 min in B group, $P = 0.096$). Similarly, no significant variations were observed in the other variables (Table 2).

Discussion

Preliminary observations from this study suggest that intrathecal anesthesia with bupivacaine combined with fentanyl in patients aged over 60 undergoing lower limb surgery may be associated with reduced pain scores on PODS 1–3. A trend toward decreased opioid use was also observed by POD3. Notably, the adverse reactions observed in this study were mild in nature and demonstrated manageable characteristics within the current sample size.

Although numerous studies have confirmed the dose-dependent nature of fentanyl's sensory block duration (Rajbhandari et al. 2020a; Sabertanha et al. 2023). Limited research has been conducted to investigate whether increasing the intraoperative intrathecal fentanyl dosage can reduce postoperative pain intensity. The findings of this study indicate that intrathecal administration of fentanyl significantly alleviated postoperative pain in elderly patients; however, increasing the fentanyl dose to 50 μg did not demonstrate significant therapeutic advantages and instead increased the incidence of nausea. It is important to note that the type of surgery also plays a crucial role in determining the degree of pain experienced (Greenstein and Gorczyca 2019). The severity of postoperative pain for hip joint arthroplasty is greater compared to that other lower limb surgeries. In this study, the percentage of various types of surgeries was balanced among the three groups, and the postoperative pain levels among them were found to be comparable. Previous studies have reported that intrathecal morphine can reduce opioid dosage in patients with gynecological malignant tumors postoperatively (Bang et al. 2023). Interestingly, our results also showed that intrathecal administration of fentanyl (25 μg or 50 μg) in addition to bupivacaine can reduce the opioid consumption on POD3, which is consistent with the aforementioned study. Another prospective, randomized study demonstrated that a combination of 25 μg fentanyl and bupivacaine significantly reduced the need for supplementary analgesics at 2, 6, and 24 h postoperatively (intramuscular diclofenac sodium was administered when the VAS score exceeded 3) (Kılıçkaya et al. 2016). This finding is consistent with our results, as it confirms that adjunctive intrathecal fentanyl effectively decreases the requirement for postoperative opioid analgesics. However, while that literature focused on opioid conservation within 24 h postoperatively, our study emphasized opioid conservation at 72 h postoperatively. This difference in the timing of opioid conservation may be attributed to the fact that the previous study did not mention the utilization of PCA in postoperative patients. A recent retrospective study has demonstrated that intrathecal opioids effectively decreased pain scores on POD1 and reduced opioid requirements on both POD1 and POD2 in patients undergoing transforaminal lumbar fusion, without increasing the risk of any opioid-related side effects (Villavicencio et al. 2022). However, the addition of fentanyl did not enhance immediate postoperative pain control. This study compared the combination of intrathecal fentanyl with morphine to intrathecal morphine alone. It is well-known that morphine has superior analgesic intensity and duration compared to fentanyl. Therefore, the study results can only suggest that, when morphine is used as the basic analgesic drug, the addition of fentanyl did not significantly reduce postoperative opioid usage. However, it is noteworthy that both our research and theirs have indicated that intrathecal fentanyl, used as an adjuvant anesthetic, can effectively decrease the NRS pain score on POD1.

Approximately 30–60% of patients undergoing orthopedic surgery experience pruritus following intrathecal administration of opioids (Gonvers et al. 2021). Therefore, intrathecal fentanyl used in any surgical procedure should be monitored for the occurrence of pruritus (Grape et al. 2023), as pruritus may be dose-dependent. The threshold dose of intrathecal fentanyl that triggers pruritus remains unknown (Grape et al. 2023). Additionally, our study observed a very low incidence of pruritus caused by intrathecal administration of 25 μg of fentanyl, which occurred only intraoperatively and did not necessitate specific treatment. The incidence of pruritus did not exhibit a dose-dependent pattern, potentially due to the limited sample size in our study. However, our study found that 50 μg of fentanyl caused increased nausea, which persisted until 48 h postoperatively, although it was mild and did not require intervention. The result is consistent with previous studies on the impact of intrathecal fentanyl on nausea and vomiting in lower limb orthopedic surgery, which indicated that intrathecal fentanyl increases the incidence of nausea and vomiting (Lee et al. 2011). However, a meta-analysis has reported that intrathecal fentanyl can effectively reduce the incidence of nausea or vomiting (Uppal et al. 2020). There are many factors that can cause nausea and vomiting, such as abdominal surgeries like cesarean section, which may also lead to intestinal adverse effects. This analysis may have a publication bias towards certain types of surgery. Nevertheless, it should be noted that the incidence of hypotension with 50 μg fentanyl is lower compared to both 25 μg fentanyl and bupivacaine alone, which consistent with the study by Hassani V et al. (Hassani et al. 2014). It may be justifiable to overlook nausea

as an adverse reaction for elderly patients who cannot tolerate fluctuations in blood pressure (Wong 2020). The occurrence of fentanyl's respiratory inhibitory effect is uncommon, (Grape et al. 2023) a phenomenon that can be attributed to its high lipid solubility. Furthermore, research has confirmed the restricted diffusion of lipid-soluble fentanyl towards the brain (Stanley 2014). It is also plausible that our sample size was too small to adequately assess the impact of fentanyl on respiratory depression (Stanley 2014; Uppal et al. 2020). In our investigation, although there was no statistical significance, we observed a prolongation of sensory block duration with increasing doses of fentanyl. This is consistent with the conclusion reported by Rajbhandari D et al. in patients undergoing emergency appendectomy (Rajbhandari et al. 2020b). However, it is worth noting that our study demonstrated a longer sensory block time compared to an earlier publication from our research group (Wang et al. 2021). This difference can be attributed to the different types of surgery. Specifically, we defined the duration of sensory block as the period from intrathecal anesthesia until the patient perceives pain at the surgical site. In previous studies on cesarean section surgeries, the surgical site was higher than that of lower limb orthopedic surgery, resulting in naturally shorter sensory block time. Consistent with previous research, fentanyl did not affect the duration of motor block and there was no significant difference in the proportion of patients achieving sensory block up to T4 level. However, two patients in the bupivacaine group experienced a T2 block, which was promptly resolved with treatment. The treatment involved positioning the patients in a head-up, feet-down position, providing oxygen via a face mask, performing volume expansion, and administering an intravenous injection of 5–10 mg of ephedrine.

The primary advantage of our study was the collection of pain scores on POD1–3. Baseline characteristics, including previous medication and surgery histories, as well as preoperative pain intensity, were investigated to account for known factors influencing postoperative pain. However, no significant differences were observed among the three groups in these baseline characteristics. Secondly, considering variations in pain severity across different surgical types, we evaluated the types of surgeries within the three groups and found no statistically significant differences among them. Thirdly, in terms of assessing adverse reactions related to intrathecal fentanyl administration, complications such as pruritus and nausea were evaluated preoperatively in all three groups, with no discernible variations observed. This enhanced the comparability of the results.

However, the present study does have certain limitations. Firstly, our evaluation of pain using NRS focused solely on postoperative time points excluding pain assessment during postoperative activity. Secondly, this study has a modest sample size. Future research will involve expanding the sample size or conducting multicenter clinical studies to further evaluate the effects of fentanyl as an intrathecal adjuvant anesthetic agent on opioid consumption in the postoperative period.

In conclusion, the current findings suggest that intrathecal fentanyl as an adjunct to bupivacaine may represent a relatively safe and effective option for postoperative pain management in elderly patients undergoing lower extremity orthopedic surgery. Compared with bupivacaine alone, the combined regimen appears associated with reduced postoperative pain intensity during the initial 3 days and demonstrates a trend toward lower opioid consumption on POD3. Importantly, current evidence suggests that higher fentanyl doses do not confer additional clinical benefits.

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Authors' contributions
GYH and LY wrote the main manuscript text, and LWX prepared figures. LXprepared tables. YQS review and proofread the article.All authors reviewed the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This prospective randomized controlled trial was approved by the hospital Ethics Committee (2022-LL-080, registration date: 2022/3/30). All subjects participating in the experiment had signed informed consent. The trial was registered in the Chinese Clinical Trials Registry before the patients were enrolled (ChiCTR2200058362, registration date: 2022/04/07). Written informed consent was obtained all participants.

Consent for publication
No personal data or images were used in this study. Therefore, consent for publication is not applicable.

Competing interests
The authors declare no competing interests.

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