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CLINICAL TRIAL REPORT

Effect of Opioid-Free Anesthesia on the Quality of Early Recovery After Total Hip Arthroplasty in Elderly Patients (Aged 65-80 Years) as Assessed by the QoR-15 Score: A Randomized Controlled Trial

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Purpose: Opioid administration in elderly surgical patients is link to multiple adverse effects that may impede postoperative recovery. We aimed to compare the impact of opioid-free anesthesia (OFA) versus conventional opioid-based anesthesia on postoperative recovery quality in elderly patients undergoing total hip arthroplasty (THA).

Methods: We randomized 68 elderly patients undergoing primary total hip arthroplasty under general anesthesia into either an opioid-free anesthesia group (Group OFA) or conventional opioid-based group (Group C). The primary outcome was quality of recovery assessed by the Quality of Recovery-15 (QoR-15) scores at 24h postoperatively. Secondary outcomes included: QoR-15 scores at 72h postoperatively, perioperative hemodynamic parameters, extubation time and PACU duration, NRS pain scores, postoperative sufentanil consumption and adverse event incidence.

Results: The QoR-15 scores statistically significant differed between the two groups at 24h postoperatively (112.2±5.0 vs 102.6±4.7, mean difference = 9.6,95% CI: 7.3–12.0, *P*<0.001) and 72h postoperatively (123.5±3.9 vs 120.4±3.9, mean difference = 3.1,95% CI: 1.2–5.0, *P*= 0.02). However, by 72h, the observed difference did not reach minimum clinical important difference (MCID). Group OFA exhibited shorter extubation times and a reduced duration of stay in the PACU. Mean arterial pressure (MAP) showed statistically significant differences at T1, T2, and T4, as did the heart rates (HR) at T1–T4. NRS scores differed both at rest and during passive hip flexion in the PACU, and at 6 and 24 hours postoperatively. Additionally, Group OFA demonstrated reduced sufentanil consumption within the first 24 and 48 hours after surgery and a lower incidence of nausea and vomiting.

Conclusion: We concluded that OFA provided superior early recovery outcomes compared to conventional opioid-based anesthesia in elderly total hip arthroplasty patients, with improvements in pain, emotional state, and physical comfort domains.

Keywords: opioid-free anesthesia, total hip arthroplasty, elderly, postoperative recovery quality

Introduction

Globally, the elderly population is growing, and total hip arthroplasty (THA) has become a widely adopted surgical intervention for elderly patients, offering substantial improvements in quality of life. However, THA is highly invasive, and the associated intraoperative stress response is pronounced.

Intraoperative analgesia, a cornerstone of general anesthesia, relies heavily on opioids to mitigate the intraoperative stress response and maintain hemodynamic stability within traditional general anesthetic protocols. Nevertheless, opioid use carries significant risks of multiple complications including nausea, vomiting, respiratory depression, drowsiness, urinary retention, and postoperative cognitive dysfunction, as well as the potential for tolerance development and induced nociceptive hypersensitivity,[1,2] all of which can impede postoperative recovery. In elderly patients, age-related

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physiological changes heighten sensitivity to opioids and markedly increase the incidence of adverse drug reactions,[3] impairing early postoperative recovery. Minimizing perioperative opioid use aligns with the principles of Enhanced Recovery After Surgery (ERAS) protocols.[4]

Opioid-Free Anesthesia (OFA) employs multimodal analgesia, blocking pain signaling through multiple pathways by combining non-opioid medications (NMDA receptor antagonists, sodium channel blockers, α2 agonists) with regional techniques (nerve blocks, epidural analgesia) to eliminate intraoperative opioid use.[5–7] Studies demonstrate that OFA enhances postoperative recovery quality[8] and has proven effective across various surgical procedures.[5,9–11] Existing studies also indicate that opioid-free anesthesia may be associated with certain potential risks, such as hypotension and bradycardia induced by dexmedetomidine.[12] Particular attention should be paid to these concerns in elderly patients. The current evidence base lacks robust randomized controlled trials examining opioid-free anesthesia in elderly patients undergoing THA.

This study employed the 15-item Quality of Recovery scale (QoR-15) to evaluate the impact of the anesthetic protocol on postoperative recovery quality. As a validated instrument with demonstrated sensitivity and responsiveness, it reliably discriminates clinically meaningful differences in recovery outcomes across multiple dimensions.[13]

Materials and Methods

Study Design and Ethics

This prospective, randomized, controlled trial utilized a study protocol designed by the investigators. The study complied with the Declaration of Helsinki and received approval from the Ethics Committee of the Second Affiliated Hospital of Xuzhou Medical University (Approval No. [2024] 051602). Participants meeting the inclusion criteria submitted signed informed consent forms prior to study participation. This trial was registered on China Clinical Trial Registry (Registration No. ChiCTR2400093360) prior to patient enrollment.

Patients

Eligible participants were aged 65–80 years, ASA physical status I–III, with BMI 20–30 kg/m², scheduled for primary total hip arthroplasty under general anesthesia. Exclusion criteria comprised: 1) known hypersensitivity to study medications; 2) opioid dependence or substance use disorder; 3) severe cardiac conduction abnormalities (heart rate <50 bpm or second/third-degree AV block); 4) esketamine contraindications; 5) neuromuscular diseases; 6) severe hepatic (Child-Pugh B/C) or renal (eGFR <30 mL/min/1.73m²) impairment; 7) history of psychiatric disorders; 8) preoperative cognitive dysfunction; 9) contraindications to regional anesthesia; 10) impaired communication capacity;11) patients who discontinued study participation prior to completion.

Randomization and Blinding Patients

Following informed consent, a research assistant blinded to study objectives randomly allocated participants to either the OFA group (Group OFA) or conventional opioid-based group (Group C) in a 1:1 ratio using a computer-generated randomization sequence created in SPSS Statistics (Version 27.0, IBM Corp). Allocation was concealed using sequentially numbered, opaque, sealed envelopes. The attending anesthesiologist opened the envelope preoperatively to implement the assigned protocol, while patients, surgical teams, and outcome assessors remained blinded throughout the study.

Anesthesia Method

Following entering operating rooms, all patients received supplemental oxygen via face mask and peripheral IV access. Continuous multimodal monitoring was implemented for all study participants throughout the procedure.

In Group OFA, patients received dexmedetomidine (0.6 μg/kg) over 10 minutes, followed by induction with propofol (1.5–2.0 mg/kg), esketamine (0.1 mg/kg), and rocuronium bromide (0.6 mg/kg). Laryngeal mask airway placement was performed 3 minutes after induction. Immediately post-induction, ultrasound-guided suprainguinal fascia iliaca block (SFIB) with pericapsular nerve group (PENG) block was performed. SFIB was performed according to the technique described by Bullock et al.[14] Following confirmation of negative aspiration for blood, 20 mL of 0.375% ropivacaine was administered. Proper needle positioning was verified by observing cephalad displacement of the deep circumflex iliac artery while maintaining compression of the iliopsoas muscle against its deep surface. The pericapsular nerve group (PENG) block was performed by administering 20 mL of 0.375% ropivacaine according to the technique described by Girón-Arango et al.[15] Intraoperative analgesia was maintained with supplemental esketamine boluses (0.1 mg/kg), administered according to hemodynamic parameters at the anesthesiologist's discretion.

Group C received standard induction with propofol (1.5–2.0 mg/kg), sufentanil (0.3 μg/kg), and rocuronium bromide (0.6 mg/kg), followed by laryngeal mask airway placement after 3 minutes. No regional blocks were performed. Intraoperative analgesia was maintained with incremental sufentanil boluses (0.1 μg/kg) based on clinical requirements.

General anesthesia was maintained with sevoflurane in both groups using volume-controlled ventilation (tidal volume 6–8 mL/kg ideal body weight, respiratory rate 12–16 breaths/min) to target $EtCO_2$ 35–45 mmHg. Anesthesia depth was titrated to maintain BIS 40–60. Vasoactive agents were administered as needed to keep hemodynamics within ±20% of baseline.

All surgical procedures were performed by the same experienced medical team to minimize variability in technique. As part of multimodal analgesia, flurbiprofen axetil (50 mg IV) was administered 20 minutes before the end of surgery, while palonosetron (0.25 mg IV) was given at wound closure for prophylaxis against postoperative nausea and vomiting. Upon completion of surgery, sevoflurane was discontinued, and neuromuscular blockade was reversed with sugammadex, dosed according to train-of-four monitoring. The laryngeal mask was removed once extubation criteria were met. Patients were transferred to PACU and discharged upon achieving an Aldrete score ≥9.

Postoperative Analgesia

Postoperative pain was assessed in PACU using an 11-point NRS (0=no pain, 10=worst pain). Patients with NRS ≥4 received rescue sufentanil 5 μg IV. All patients were provided with standardized sufentanil PCIA (0.5 μg/mL; 2 μg bolus, 10-minute lockout) after preoperative training, supplemented by scheduled flurbiprofen axetil 50 mg IV q12h postoperatively.

Outcome Messures

The primary outcome was the 15-item Quality of Recovery (QoR-15) score at 24h postoperatively. This validated instrument measures recovery status across five dimensions: (1) pain, (2) physical comfort, (3) physical independence, (4) psychological support, and (5) emotional state. Each item is scored 0–10, yielding a global score range of 0–150 points, with higher scores indicating better recovery quality.[16]

Secondary outcomes included: the Qor-15 score at 72h postoperatively; mean arterial pressure (MAP) and heart rate (HR) at baseline upon admission (T0), immediately following induction (T1), during skin incision (T2), at femoral neck osteotomy (T3), and upon procedure completion (T4); time to extubation; PACU length of stay; the NRS scale scores at the PACU, at 6,24,48, and 72 hours postoperatively at rest and during passive hip flexion; and postoperative 0–24, 0–48 hours postoperative sufentanil consumption; incidence of postoperative adverse events, including nausea/vomiting, drowsiness, respiratory depression (SpO_2 <90% for >1 minute), hemodynamic instability (MAP <65 mmHg or HR <50 bpm for >1 minute).

Statistical Analysis

Sample size calculation: the sample size was calculated using PASS 2021 software, (NCSS, LLC) based on preliminary data showing mean ± SD QoR-15 scores of 113.0 ± 9.1 (Group OFA) versus 104.7 ± 10.3 (Group C) at 24 hours postoperatively. To detect this difference with a two-tailed α of 0.05, 90% power (β = 0.10), and an anticipated 10% attrition rate, a minimum of 34 patients per group (total N= 68) was required.

Analyses were conducted in SPSS Statistics 27.0 (IBM Corporation). The normality of data distributions was evaluated using Shapiro–Wilk tests. Continuous variables following normal distributions were expressed as mean ± standard deviation (mean ± SD), while non-normally distributed variables were reported as median with interquartile range (IQR). Categorical variables were presented as frequency counts and percentages. For between-group comparisons, independent samples *t*-tests were used for normally distributed continuous data, and Mann–Whitney *U*-tests were applied for non-normally distributed continuous variables. Categorical variables were analyzed using χ^2-tests or Fisher's exact tests when appropriate. Repeated measures analysis of variance (ANOVA) were employed to compare longitudinal changes between the two treatment groups across multiple assessment time points. Post hoc analyses were performed with Bonferroni correction to control Type I error. All statistical tests were two-tailed, with a significance level set at α = 0.05.

Results

From 76 screened patients, 68 were randomized (34 per group) after excluding 5 ineligible and 3 who declined participation (Figure 1). All completed the study, maintaining equal group allocation for final analysis.

Recovery quality, assessed by QoR-15 scores, revealed no preoperative differences (Table 1) but significantly better outcomes in the OFA group at 24h postoperatively (112.5±5.0 vs 102.6±4.7, mean difference = 9.6,95% CI: 7.3–12.0, P<0.001), particularly in pain (15.0±1.5 vs 12.5±1.3, mean difference = 2.6,95% CI: 1.9–3.2, P<0.001), emotional state (32.3±2.3 vs 31.1±2.3, mean difference = 1.2,95% CI: 0.1–1.0, P = 0.04), and physical comfort (36.1±3.6 vs 33.3±2.7, mean difference = 2.8,95% CI: 0.4–1.4, P < 0.001) domains (Figure 2). By 72h postoperatively, only total scores (123.5 ±3.9 vs 120.4±3.9, mean difference = 3.1,95% CI: 0.3–1.3, P = 0.002) and physical comfort scores (41.5±2.2 vs 40.1 ±2.2, mean difference = 1.5,95% CI: 0.2–1.2, P = 0.008) remained improved, with other domains showing comparable results between groups (Figure 3).

Patients receiving opioid-free anesthesia (OFA) exhibited significantly faster extubation times (15.3±2.9 vs 17.6±2.9, P = 0.002) and shorter PACU length of stay (34.9±3.5 vs 37.4±4.3, P = 0.009) compared to opioid-based anesthesia (Table 2).

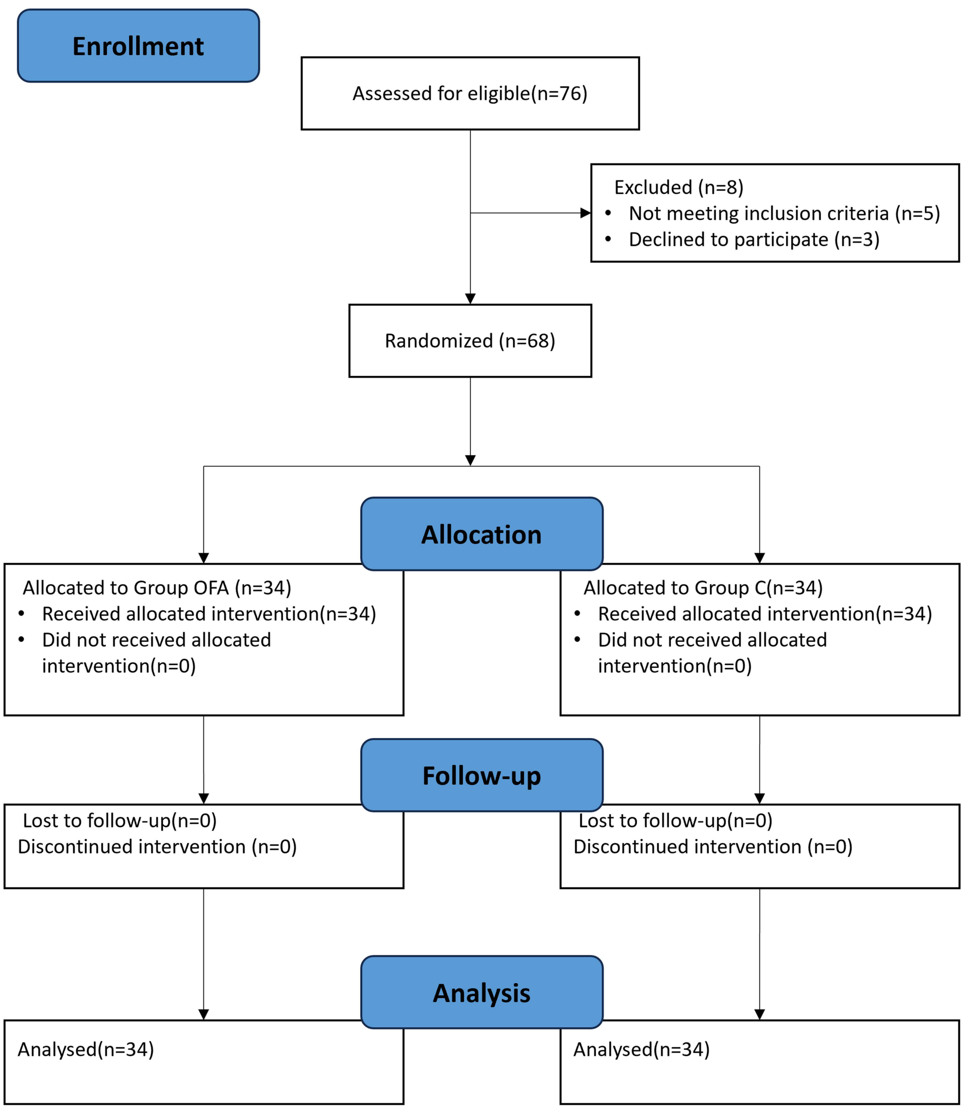

Figure 1 Flow diagram of the study.

Table 1 Clinical Characteristics for All Patients

	Group OFA(n=34)	Group C(n=34)	P
Age (years)	71.9±5.9	71.3±4.2	0.619
BMI (kg/m^{2})	23.9±2.6	24.2±2.2	0.589
Gender, n (%)			0.625
Male	16 (47.1)	14 (41.2)	
Female	18 (52.9)	20 (58.8)	
Type of surgery, n (%)			0.625
Femoral head necrosis	16 (47.1)	14 (41.2)	
Hip fracture	18 (52.9)	20 (58.8)	
ASA, n (%)			0.401
II	10 (29.4)	7 (20.6)	
III	24 (70.6)	27 (79.4)	
Surgical side, n (%)			0.804
Left	13 (38.2)	14 (41.2)	
Right	21 (61.8)	20 (58.8)	
Preoperative QoR-15	122.6±4.8	123.6±4.1	0.387
Preoperative blood glucose (mmol/L)	5.3 (4.9,6.1)	5.4 (5.2,6.0)	0.667

Notes: Data were presented as mean ± standard deviation, median (IQR) or number (percentage). No statistically significant difference between groups were noted.
Abbreviations: BMI, Body Mass Index; ASA, American society of Anesthesiologists; OFA, Opioid-free anesthesia.

A statistically significant difference was observed in both MAP and HR between the two patient groups during the intraoperative period (all *P*< 0.001). Group OFA demonstrated significantly higher mean arterial pressure (MAP) at key intraoperative time points, including immediately after induction (T1) (*P* < 0.001), skin incision (T2) (*P* = 0.002), and procedure completion (T4) (*P* = 0.004), compared to the Group C and exhibited elevated heart rates at all measured intraoperative time points: immediately after induction (T1) (*P* =0.005), skin incision (T2) (*P* < 0.001), femoral neck osteotomy (T3) (*P* < 0.001), and procedure completion (T4) (*P* = 0.008) (Figure 4).

The sufentanil consumption differed significantly between the two groups at 24 and 48 hours postoperatively (27.7 ±7.0 vs 34.4±6.5, *P* < 0.001; 43.6±9.9 vs 52.4±9.3 *P* < 0.001) (Table 2). The Numeric Rating Scale (NRS) scores were lower in the OFA group at rest and during passive hip flexion PACU (rest:2(1,2) vs 2(2,3), *P* < 0.001; motion:4(4,5) vs 5 (5,6), *P* = 0.02),6 hours (rest:3(2,3) vs 3(3,4), *P* = 0.02; motion:5(4,5) vs 5(4.75,6), *P* = 0.024) and 24 hours post-operatively (rest:1(1,2) vs 2(1,2), *P* < 0.001; motion:3(2,3) vs 4(3,4), *P* < 0.001). However, no statistically differences were observed in NRS scores between the groups at 48 and 72 hours postoperatively (Figure 5).

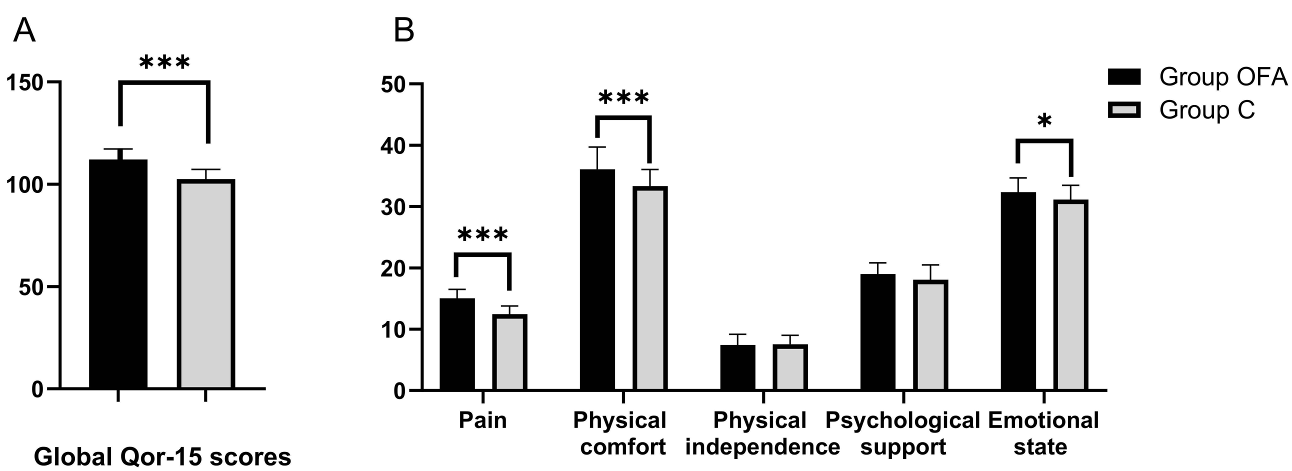

Figure 2 Quality of Recovery-15 global scores (**A**) and sub-dimensions scores (**B**) at 24h postoperatively (n=34 per group). *P<0.05, ***P<0.001.

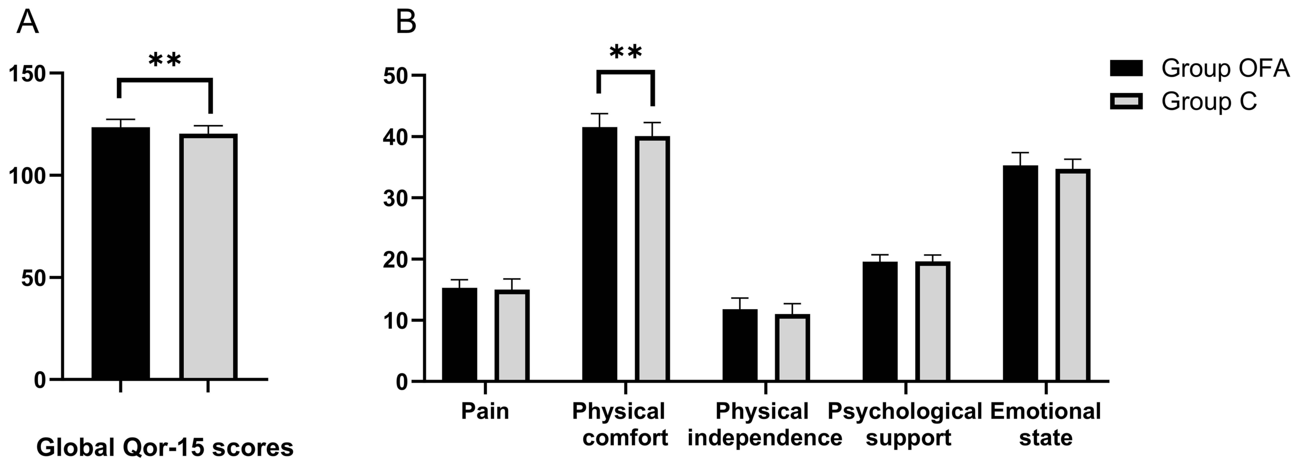

Figure 3 Quality of Recovery-15 global scores (**A**) and sub-dimensions scores (**B**) at 72h postoperatively (n=34 per group). ***P*<0.01.

Additionally, the incidence of postoperative nausea and vomiting (PONV) was lower in the OFA group than in the control group (5.8% vs 28.5%, *P* = 0.04), while other adverse reactions were similarly between two groups (Table 2).

Discussions

Our study found that opioid-free general anesthesia protocol, combining nerve blocks with non-opioid analgesics, enhanced early recovery quality for elderly patients undergoing total hip arthroplasty. This strategy yielded significant improvements across multiple recovery domains, including pain, emotion state, and physical comfort.

This trail implemented an opioid-free anesthesia (OFA) protocol combining dexmedetomidine, esketamine, and regional nerve blocks. To mitigate the hemodynamic risks associated with dexmedetomidine infusion in elderly patients,[12,17] we employed a single loading dose strategy (0.6 μg/kg), which when combined with nerve blocks demonstrated synergistic analgesic effects.[18] Esketamine provided analgesia via NMDA receptor antagonism, preventing nociceptive sensitization and lowering perioperative opioid demand.[19] Preoperative administration of esketamine at a subanesthetic dose (0.15 mg/kg) reduces postoperative cognitive dysfunction (POCD) risk in elderly patients, potentially mediated through its anti-neuroinflammatory and neuroprotective properties.[20] As a critical element of OFA strategies, peripheral nerve blockade played a critical role in our study protocol. The regional anesthesia component

Table 2 Intraoperative and Postoperative Outcomes

	Group OFA(n=34)	Group C(n=34)	*P*
Extubation time(min)	15.3±2.9	17.6±2.9	0.002**
PACU length of stay(min)	34.9±3.5	37.4±4.3	0.009**
Postoperative blood glucose (mmol/L)	7.5 (6.3,8.1)	7.0 (6.0,7.9)	0.523
Sufentanil consumption (μg)			
0–24h	27.7±7.0	34.4±6.5	<0.001***
0–48h	43.6±9.9	52.4±9.3	<0.001***
Adverse events, n (%)			
Nausea/Vomiting	2 (5.8)	8 (23.5)	0.040*
Drowsiness	2 (5.8)	4 (11.5)	0.393
Respiratory depression	1 (2.9)	3 (8.8)	0.210
Hemodynamic instability	3 (8.8)	4 (11.5)	0.520

Notes: Data were presented as mean ± standard deviation, median(IQR) or number(percentage). **P*<0.05, ***P*<0.01, ****P*<0.001.
Abbreviations: PACU, Post-anesthesia care unit; OFA, Opioid-free anesthesia.

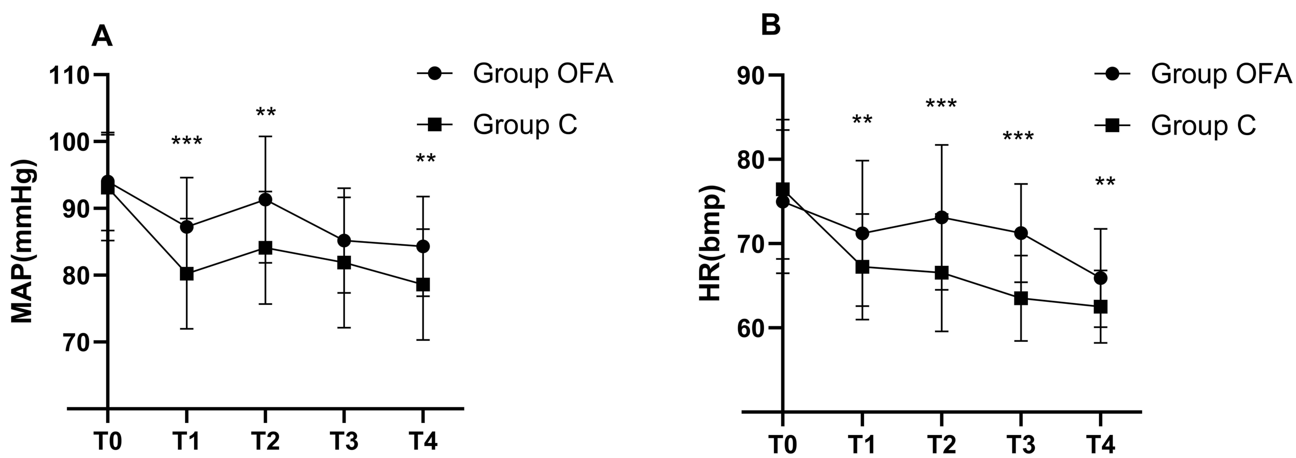

Figure 4 Hemodynamic parameters including mean arterial pressure (MAP) and heart rates (HR) at specified perioperative time (n=34 per group); (**A**)MAP, (**B**)HR. $^{**}P<0.01$, $^{***}P<0.001$.

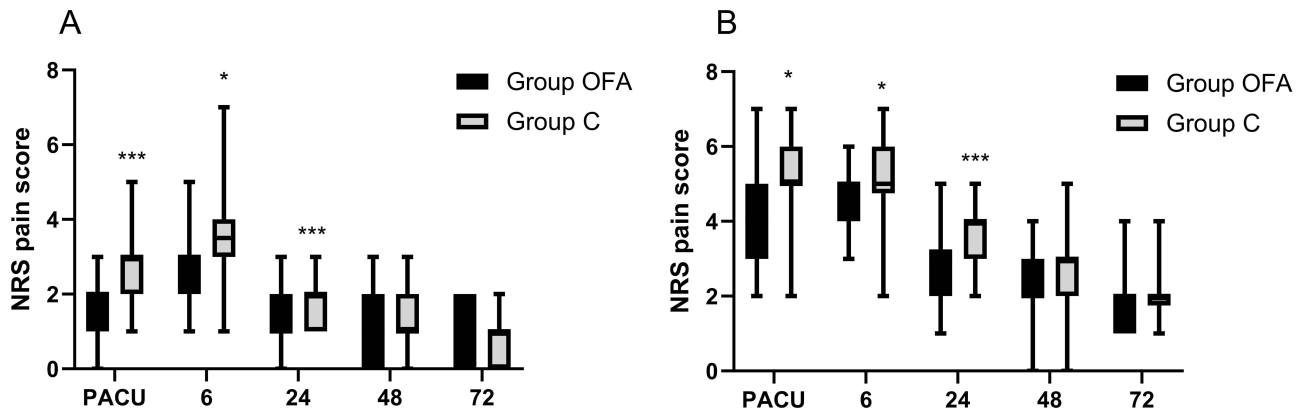

Figure 5 Numerical Rating Scale (NRS) pain scores during rest (**A**) and motion (**B**) at various postoperative time points (n=34 per group). $^{*}P<0.05$, $^{***}P<0.001$.

utilized ultrasound-guided suprainguinal fascia iliaca block (SFIB) with pericapsular nerve group (PENG) block. This dual approach provides comprehensive sensory blockade of the obturator, femoral, accessory obturator, and lateral femoral cutaneous nerves,[15,21] offering relatively complete analgesia for THA while significantly reducing opioid consumption and minimizing systemic side effects.

The improvements are consistent with prior evidence. Qingfen Zhang et al[22] reported that thoracic paravertebral block (TPVB) combined with lidocaine and dexmedetomidine enhances early recovery quality at 24 hours postoperatively in patients undergoing breast cancer surgery. At 24h and 72h postoperatively, the Group OFA showed superior physical comfort scores compared to Group C, likely due to reduced postoperative nausea and vomiting, and then improved sleep and dietary intake. A recent meta-analysis confirmed that opioid-free anesthesia (OFA) significantly reduces postoperative nausea and vomiting (PONV) incidence,[8] which aligns with our finding. The observed differences in postoperative emotional state likely resulted from esketamine's antidepressant and and dexmedetomidine's anxiolytic properties.[23,24] Multimodal analgesic strategies implemented during OFA maintained postoperative analgesia. While NRS scores at 24 hours showed statistical significance, the difference lacked clinical meaning, potentially due to sufentanil PCA minimizing intergroup pain variation. Similarly, while QoR-15 scores at 72h postoperatively were statistically significant, they did not meet the minimal clinically important difference threshold.[16] These findings are consistent with a recent randomized controlled trial by Léger et al,[25] which demonstrated that while opioid-free anesthesia (OFA) produced statistically significant improvements in postoperative recovery quality following major surgery at 48 and 72 hours, these differences did not reach clinical significance. This observation may be attributed to drug metabolism. Over time,

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as the agents were metabolized, the clinical differences between the two groups diminished, which is consistent with pharmacokinetic principles. Future studies remain necessary to explore strategies for extending its clinical benefits.

Whereas opioids and propofol may cause circulatory instability in elderly patients through sympathetic inhibition and peripheral vasodilation,[26] esketamine's sympathetic activation appears to counteract these effects. In THA procedures, where surgical stimulation primarily occurs during skin incision and femoral neck osteotomy, high iliac fascial block combined with pericapsular nerve block provides partial analgesia. However, due to the complex innervation of the hip joint capsule, supplemental non-opioid analgesics (dexmedetomidine, esketamine) were required to maintain adequate pain control while preventing hemodynamic fluctuations. Our results showed that the OFA group maintained a higher mean arterial pressure and heart rate intraoperatively. While this may indicate a more stable hemodynamic profile against anesthesia-induced hypotension, it also raises important safety considerations for elderly patients, who often have a high prevalence of cardiovascular comorbidities such as coronary artery disease, hypertension, and heart failure. In our study, no severe adverse cardiac events were observed. Nonetheless, OFA strategies are not without risk. They must be cautiously titrated and accompanied by intensive hemodynamic monitoring, particularly in patients with known cardiac disease. No significant intergroup differences in preoperative or postoperative blood glucose levels suggested comparable intraoperative stress responses. Elderly patients exhibit enhanced opioid receptor affinity and diminished drug clearance - factors that may promote drug accumulation and consequently prolong extubation times.[3] This contrasts markedly with esketamine's rapid metabolic clearance, which facilitates earlier extubation.[27,28] Contrary to our findings, Feng et al[5] reported prolonged extubation times with OFA, possibly due to excessive dexmedetomidine sedation. In our protocol, using only a single pre-induction loading dose minimized this effect.

This study has several limitations. First, this is a single-center trial with a limited sample size. And the sample size in this study was calculated from a preliminary QoR-15 effect size and did not adjust for geriatric-specific variables (such as comorbid disease and consistency of surgical operations). The results may lack generalizability to broader populations or different clinical settings. A future large-scale, multi-center trial is warranted to confirm our results and explore the benefits of OFA in broader patient populations. Second, owing to the differences in anesthetic protocols, blinding of the attending anesthesiologists was not feasible, introducing a potential source of performance bias. Third, the clinical benefits may vary with different drug combinations and dosages, necessitating further research to optimize OFA regimens. Forth, this study did not assess postoperative cognitive function, which is a limitation considering the elevated risk of postoperative cognitive dysfunction in elderly patients. Further exploration in this area remains necessary. Finally, the constrained duration of follow-up in this study prevents definitive conclusions regarding the sustained benefits of OFA on recovery and its potential to mitigate chronic pain development. Further studies with prolonged assessment timelines are essential to comprehensively evaluate the long-term efficacy and safety profile of this anesthetic technique in elderly patients.

Conclusion

In conclusion, opioid-free anesthesia (OFA) combining nerve blocks and non-opioid analgesics improves the quality of early recovery after hip arthroplasty in elderly patients, improving postoperative pain, emotional state, and physical comfort. Future studies should involve larger sample sizes and extended follow-up periods to evaluate its long-term clinical benefits.

Data Sharing Statement

Research data supporting this study's conclusions can be obtained through a reasonable data-sharing agreement with the institutional review body at the Second Affiliated Hospital of Xuzhou Medical University. Further inquiries about the datasets can be directed to the corresponding author on reasonable request.

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Disclosure

The authors report no conflicts of interest in this work.

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