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Research Article

Effect of Esketamine Combined with Sufentanil-Based Patient-Controlled Intravenous Analgesia on Postoperative Pain in Elderly Total Hip Arthroplasty Patients: A Three-Arm Randomized Trial

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Abstract

Background: Total hip arthroplasty (THA) is a common procedure for end-stage hip disorders, yet postoperative pain management remains challenging due to opioid-related complications, particularly in elderly patients vulnerable to respiratory depression and delirium. Multimodal analgesia strategies are increasingly prioritized to mitigate these risks. Esketamine, an NMDA receptor antagonist with opioid-sparing and anti-neuroinflammatory properties, shows promise in enhancing analgesia while reducing adverse effects. Preliminary studies suggest its efficacy in lowering postoperative pain and delirium risk, though optimal dosing in elderly THA populations remains unclear. This study aimed to evaluate the analgesic efficacy and safety of different dosages of esketamine combined with sufen-tanil for patient-controlled intravenous analgesia (PCIA) in elderly patients undergoing total hip arthroplasty. Methods: In this randomized, prospective, double-blind trial, 120 elderly patients were randomly divided into three groups: the control group (Group S, n = 40) received sufentanil 2 μg/kg; the experimental group SE1 (n = 40) received sufentanil 1.5 μg/kg combined with esketamine 1 mg/kg; and the experimental group SE2 (n = 40) received sufentanil 1 μg/kg combined with esketamine 2 mg/kg. Primary outcomes included resting and movement-associated Visual Analogue Scale (VAS) scores at 4, 8, 12, 24, and 48 h postoperatively. Secondary outcomes encompassed Ramsay Sedation Scale (RSS) scores, Quality of Recovery-15 (QoR-15) scores at 48 h, time to first walk, the number of patients requiring remedial analgesia, and adverse events (nausea/vomiting, hallucinations, pruritus, delirium, dizziness).

Results: The SE1 and SE2 groups demonstrated significantly superior analgesic efficacy compared to the S group across all outcomes. Resting and movement-associated VAS scores were significantly lower in both esketamine-combined groups at all postoperative time points (4, 8, 12, 24, and 48 h; $P < 0.05$). Sedation levels (Ramsay scores) were dose-dependently enhanced with esketamine. Group SE2 exhibited higher sedation scores than Group S at 24 h ($P < 0.01$) and 48 h ($P < 0.05$). The QoR-15 scores at 48 h were significantly higher in Groups SE1 and SE2 compared to Group S ($P < 0.001$). Time to first walk was shorter in Groups SE1 and SE2 than in Group S ($P < 0.001$). No significant differences were observed in the requirement for rescue analgesia between groups. Adverse events showed a significant reduction in postoperative delirium (POD) incidence ($P < 0.01$) and nausea/vomiting ($P < 0.05$) in Groups SE1 and SE2 compared to Group S, with no significant differences in dizziness, hallucinations, or pruritus. Conclusion: This randomized controlled trial demonstrated that esketamine combined with reduced-dose sufentanil significantly improved postoperative analgesia and recovery outcomes in elderly patients undergoing THA.

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Keywords

Esketamine, Sufentanil, Total Hip Arthroplasty, Patient-Controlled Intravenous Analgesia, Postoperative Pain

1. Introduction

THA is a cornerstone surgical procedure for end-stage hip disorders. In the United States alone, nearly 600,000 operations are projected to be performed annually by 2030 [1]. Despite advancements in surgical techniques, postoperative pain management following THA remains a significant clinical challenge [2]. Conventional analgesia protocols exhibit excessive reliance on opioid administration, which may precipitate clinically significant adverse effects, including postoperative nausea and vomiting (PONV), respiratory depression, and malignant hypotension [3]. These challenges are particularly pronounced in elderly patients, who demonstrate heightened vulnerability to opioid-related complications such as respiratory depression, gastrointestinal dysfunction, and POD due to age-related pharmacokinetic and pharmacodynamic changes [4]. These limitations have spurred interest in multimodal analgesia strategies to reduce opioid-related side effects while maintaining therapeutic efficacy. Ketamine has emerged as a promising adjunct due to its dual mechanisms as an *N*-methyl-D-aspartate (NMDA) receptor antagonist and a modulator of descending monoaminergic pain pathways [5, 6]. As the S(+)-enantiomer of ketamine, esketamine exhibits superior binding affinity to NMDA and μ-opioid receptors compared to racemic ketamine, enabling dose reduction while maintaining equipotent anesthetic and analgesic efficacy with an improved safety profile [7-10]. Esketamine not only demonstrates synergistic interactions with opioid analgesics but also attenuates central sensitization and neuroinflammatory responses, concurrently reducing the incidence of postoperative neurocognitive disorders (POND) and accelerating rehabilitation outcomes [11]. For instance, Liu et al. demonstrated that esketamine combined with low-dose sufentanil significantly reduced postoperative pain and serum interleukin-6 (IL-6) levels in elderly gastrointestinal surgery patients, correlating with a lower incidence of POD [12]. Similarly, Wu et al. reported that esketamine-based patient-controlled intravenous analgesia (PCIA) provided superior pain relief compared to sufentanil alone in THA patients, alongside improved satisfaction and reduced nausea/vomiting rates [13]. While low-dose esketamine (0.5–1 mg/kg) demonstrates favorable safety profiles, higher doses (e.g., 2 mg/kg) may offer enhanced analgesia without compromising tolerability—a hypothesis requiring rigorous validation in elderly cohorts. This three-arm randomized controlled trial aimed to evaluate the analgesic efficacy and safety of two esketamine-sufentanil combinations compared to conventional opioid-based PCIA in elderly THA patients. We hypothesized that esketamine would dose-dependently improve pain control, enhance recovery quality, and reduce opioid-related complications.

2. Materials and Methods

2.1. Study Participants

Between February 2022 and January 2023, 120 patients undergoing total hip arthroplasty (THA) were enrolled at Deyang People's Hospital. Inclusion criteria comprised: 1. scheduled for elective unilateral THA; 2. age 60–90 years; 3. American Society of Anesthesiologists (ASA) physical status I–III; 4. requirement for postoperative patient-controlled intravenous analgesia (PCIA); and 5. capacity to comprehend the study protocol and voluntarily provide written informed consent. Exclusion criteria included: 1. significant comorbidities (e.g., poorly controlled hypertension [blood pressure > 160/100 mmHg], severe ischemic heart disease [NYHA class III/IV], congestive heart failure [LVEF < 40%], or hepatic/renal dysfunction [Child-Pugh B/C or eGFR < 30 mL/min/1.73 m^2]); 2. hypersensitivity to esketamine or its excipients; 3. high-risk conditions for elevated intracranial or intraocular pressure (e.g., glaucoma or intracranial mass lesions); 4. active psychiatric disorders (e.g., schizophrenia or major depressive disorder); 5. untreated or refractory hyperthyroidism; 6. history of substance abuse or dependence within the past 6 months.

A computer-generated randomization sequence (block size = 6) was created by an independent statistician using SPSS software (version 26.0; IBM Corp., Armonk, NY, USA). Patients were allocated to Group S, SE1, or SE2 in a 1:1:1 ratio. Concealed allocation was implemented using sequentially numbered, opaque, sealed envelopes. Envelopes were opened by a research nurse after patient enrollment and immediately prior to anesthesia induction. Patients, anesthesiologists, surgeons, and outcome assessors remained blinded to group assignments. Patient-controlled intravenous analgesia (PCIA) solutions were prepared by an independent pharmacist using identical infusion pumps. No preoperative sedatives or analgesics were administered.

2.2. Study Protocol

All patients underwent 8-hour preoperative fasting and

received standardized general anesthesia via laryngeal mask airway (LMA). Invasive arterial access was established upon operating room entry for continuous monitoring of electrocardiography (ECG), pulse oximetry (SpO_2), invasive arterial blood pressure (IBP), and bispectral index (BIS). After 3-minute preoxygenation with 100% oxygen, intravenous premedication (tropisetron 5 mg, atropine 0.2 mg) was administered. Anesthesia induction comprised midazolam (0.02 mg/kg), sufentanil (0.05 μg/kg), cisatracurium (0.2 mg/kg), and etomidate (0.3 mg/kg), followed by LMA placement. Anesthesia maintenance was achieved with propofol (0.5–1 mg/kg/h) and sevoflurane (1–3%), titrated to maintain BIS values at 40–60. All surgeries were performed by a single surgical team using identical protocols.

Patient-controlled intravenous analgesia (PCIA) was initiated 30 minutes before surgical closure with three regimens: Group S: Sufentanil 2 μg/kg + tropisetron 10 mg in 100 mL saline; Group SE1: Sufentanil 1.5 μg/kg + esketamine 1 mg/kg + tropisetron 10 mg; Group SE2: Sufentanil 1 μg/kg + esketamine 2 mg/kg + tropisetron 10 mg. All groups used identical parameters: 2 mL loading dose, 2 mL/h background infusion, 2 mL bolus on demand with 15-minute lockout (maximum 6 mL/h). Patients were discharged from the post-anesthesia care unit (PACU) after achieving Aldrete score ≥9. Rescue analgesia (intravenous tramadol 100 mg) was administered if resting visual analog scale (VAS) scores remained ≥4 after two consecutive PCIA boluses within 30 minutes.

2.3. Outcome Measures

Demographic characteristics and surgical parameters were systematically recorded across all three groups. The primary outcome assessed postoperative pain intensity at rest and during movement (passive leg elevation to 30°) using the visual analog scale (VAS; 0 = "no pain," 10 = "worst imaginable pain") at 4, 8, 12, 24, and 48 hours [14]. Secondary outcomes included sedation depth evaluated by the Ramsay Sedation Scale (RSS; scores 1–3: awake, 4–6: asleep) at identical time points [15], recovery quality measured with the validated Chinese version of the Quality of Recovery-15 (QoR-15) questionnaire (score range: 0–150) at 48 hours [16], the number of patients requiring rescue analgesia, time to first ambulation, and the incidence of adverse events (nausea/vomiting, pruritus, hallucinations, delirium, dizziness) within 48 hours. All assessments adhered to standardized protocols to ensure measurement consistency.

2.4. Statistical Analysis

All statistical analyses were performed using SPSS software (version 26.0; SPSS Inc., Chicago, IL, USA). Normality of data distribution was assessed via Shapiro-Wilk tests. Normally distributed continuous variables were expressed as mean ± standard deviation (SD) and analyzed by one-way analysis of variance (ANOVA), with post hoc Tukey's test for intergroup comparisons. Non-normally distributed data were reported as median (interquartile range, IQR) and analyzed using the Kruskal-Wallis test. Categorical variables were compared via chi-square test and summarized as frequencies (percentages). A two-tailed significance threshold of $P < 0.05$ was applied.

3. Results

A total of 133 patients were initially assessed for eligibility, with 13 excluded due to failure to meet inclusion criteria or refusal to participate. The remaining 120 patients were randomly allocated to three groups (Group S, SE1, SE2; n = 40 per group), all of whom completed the study protocol (Figure 1). Baseline demographic and clinical characteristics were comparable among groups (P > 0.05 for all variables; Table 1).

The multimodal analgesia regimens incorporating esketamine demonstrated significant dose-dependent pain control advantages over sufentanil monotherapy. High-dose esketamine (Group SE2) consistently achieved the lowest pain scores across all postoperative intervals, with statistically and clinically meaningful reductions in both resting and movement-evoked pain compared to the sufentanil-only group (Group S) (all P_{SE2 vs S} < 0.05; Cohen's d = 0.55–0.78). Low-dose esketamine (Group SE1) exhibited intermediate efficacy, showing significant late-phase improvements at 48 h (resting: $P = 0.039$, $d = 0.46$; movement: $P = 0.012$, $d = 0.45$) but no differentiation from Group SE2 ($P > 0.118$). Effect sizes revealed progressive analgesic enhancement with esketamine dose escalation, particularly for movement-evoked pain, where Group SE2 provided 73% greater pain reduction than Group SE1 at 48 h (ΔVAS = 0.60 vs. 0.36; $d = 0.78$ vs. 0.45) (Table 2).

The esketamine-containing regimens demonstrated dose-dependent enhancements in recovery quality and functional outcomes. Group SE2 showed the most pronounced benefits, achieving significantly higher QoR-15 scores (120.2 ± 4.51 vs. Group S: 114.7 ± 3.92; $P < 0.001$, $\eta^2 = 0.700$) and earlier ambulation (45.53 ± 4.02 h vs. Group S: 49.65 ± 4.72 h; $P < 0.001$, $\eta^2 = 0.154$). Ramsay sedation scores exhibited time-dependent group differences, with Group SE2 showing superior sedation at 24 h (3.19 ± 0.50 vs. Group S: 2.85 ± 0.56; $P = 0.006$, $\eta^2 = 0.078$) and 48 h (3.14 ± 0.62 vs. Group S: 2.81 ± 0.47; $P = 0.020$, $\eta^2 = 0.063$). Rescue analgesia requirements showed a non-significant descending trend (Group S: 2 [5.0%], Group SE1: 1 [2.5%], Group SE2: 0 [0.0%]; $P = 0.368$) (Table 3).

The esketamine-based regimens significantly reduced opioid-related complications. Compared to sufentanil monotherapy (Group S), both SE1 and SE2 groups exhibited lower incidences of nausea/vomiting (17.5% and 15.0% vs. 40.0%; $P = 0.016$, $\chi^2 = 8.30$) and delirium (15.0% and 17.5% vs. 42.5%; $P = 0.007$, $\chi^2 = 9.87$), with small-to-moderate effect sizes

(Cohen's V = 0.25–0.28). Pairwise comparisons revealed: Nausea/Vomiting: Group S vs. SE1 (P = 0.039), Group S vs. SE2 (P = 0.024); Delirium: Group S vs. SE1 (P = 0.013), Group S vs. SE2 (P = 0.025). No hallucinations occurred in any group. Non-significant trends favored esketamine for dizziness reduction (32.5% → 15.0%, P = 0.109), while pruritus rates remained comparable (5.0–7.5%, P = 0.895). Number needed to harm (NNH) analysis suggested that treating 4–5 patients with esketamine combinations would prevent one opioid-related adverse event (Table 4).

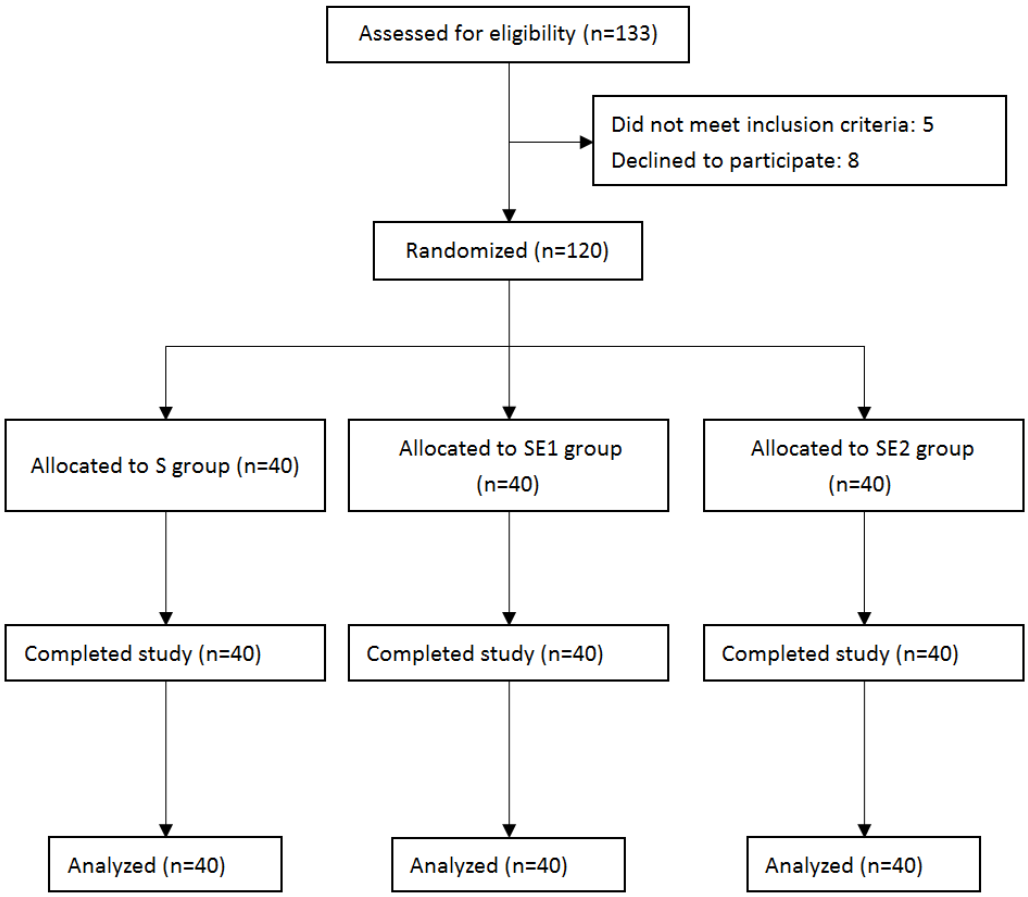

Figure 1. *CONSORT flow diagram for the study.*

Table 1. *Baseline demographic and clinical characteristics.*

Variable	S Group (n=40)	SE1 Group (n=40)	SE2 Group (n=40)	*p*-value
Age (years)	73.8 ±7.6	75.5 ±8.3	72.2 ±7.9	0.181
Female (n, %)	22 (55.0%)	25 (62.5%)	20 (50.0%)	0.526
Height (cm)	157.9 ±6.8	159.1 ±7.1	156.8 ±6.5	0.322
Weight (kg)	55.2 ±7.5	56.8 ±8.2	54.5 ±6.9	0.380
ASA classification (n, %)				0.705
ASA 1	8 (20.0%)	5 (12.5%)	6 (15.0%)	
ASA 2	26 (65.0%)	28 (70.0%)	24 (60.0%)	
ASA 3	6 (15.0%)	7 (17.5%)	10 (25.0%)	
Hypertension (n, %)	24 (60.0%)	28 (70.0%)	25 (62.5%)	0.623
Diabetes (n, %)	17 (42.5%)	13 (32.5%)	15 (37.5%)	0.652
Operation time (min)	94.5 ±13.8	89.2 ±12.9	91.7 ±14.1	0.212

Variable	S Group (n=40)	SE1 Group (n=40)	SE2 Group (n=40)	*p*-value
Intraoperative blood loss (ml)	305 ±56	320 ±47	300 ±52	0.203

Data are presented as mean ±standard deviation (continuous variables) or number (%) (categorical variables).
Group definitions: S Group: Sufentanil 2 μg/kg. SE1 Group: Sufentanil 1.5 μg/kg + Esketamine 1 mg/kg. SE2 Group: Sufentanil 1 μg/kg + Esketamine 2 mg/kg.
Continuous variables: One-way ANOVA. Categorical variables: Chi-square test or Fisher's exact test.

Table 2. *Postoperative Pain Trajectories Across Study Groups.*

Assessment	Time	S Group	SE1 Group	SE2 Group	*P* (ANOVA)	Pairwise Comparisons (*P*; Cohen's *d*)	η^2
Resting VAS	4h	4.97 ±0.78	4.65 ±0.89	4.42 ±0.57	0.006	S-SE2: 0.005 (0.77)	0.083
	8h	5.01 ±0.72	4.77 ±0.70	4.51 ±0.64	0.007	S-SE2: 0.011 (0.74)	0.081
	12h	4.71 ±0.63	4.49 ±0.73	4.30 ±0.68	0.030	S-SE2: 0.022 (0.60)	0.058
	24h	4.01 ±0.53	3.81 ±0.47	3.68 ±0.49	0.013	S-SE2: 0.012 (0.67)	0.071
	48h	3.01 ±0.36	2.86 ±0.29	2.79 ±0.32	0.010	S-SE1: 0.039 (0.46); S-SE2: 0.003 (0.69)	0.076
Movement VAS	4h	5.86 ±0.79	5.62 ±0.71	5.39 ±0.83	0.029	S-SE2: 0.002 (0.58)	0.059
	8h	5.92 ±0.81	5.66 ±0.75	5.48 ±0.79	0.022	S-SE2: 0.019 (0.57)	0.063
	12h	6.23 ±0.97	5.84 ±0.83	5.71 ±0.91	0.035	S-SE2: 0.035 (0.55)	0.055
	24h	5.18 ±0.85	4.93 ±0.66	4.72 ±0.69	0.023	S-SE2: 0.001 (0.60)	0.063
	48h	5.01 ±0.82	4.65 ±0.78	4.41 ±0.62	0.002	S-SE1: 0.012 (0.45); S-SE2: <0.001 (0.78)	0.101

Data = mean ±SD; Bold indicates significant comparisons ($P < 0.05$)
Effect size interpretation: Cohen's *d*: 0.2(small), 0.5(moderate), 0.8(large); η^2: 0.01(small), 0.06(moderate), 0.14(large)
Non-significant comparisons omitted for clarity (full data in Supplement)

Table 3. *Secondary Outcomes Analysis.*

Outcome	Time	S Group	SE1 Group	SE2 Group	*P*-value	Effect Size (η^2)
Ramsay Sedation Score	4h	2.75 ±0.41	2.87 ±0.39	2.91 ±0.45	0.206	NS
	8h	2.79 ±0.45	2.93 ±0.58	3.02 ±0.61	0.175	NS
	12h	2.98 ±0.52	3.15 ±0.49	3.21 ±0.43	0.090	NS
	24h	2.85 ±0.56	3.09 ±0.58	3.19 ±0.50	0.009	0.078
	48h	2.81 ±0.47	2.99 ±0.48	3.14 ±0.62	0.022	0.063
QoR-15	48h	114.7 ±3.92	118.8 ±4.79	120.2 ±4.51	<0.001	0.700
Time to First Ambulation (h)	-	49.65 ±4.72	46.36 ±3.89	45.53 ±4.02	<0.001	0.154
Rescue Analgesia (n)	-	2 (5.0%)	1 (2.5%)	0 (0.0%)	0.368	NS

Data Presentation: Continuous data: mean ±SD, Categorical data: n (%)
Bold *P*-values indicate statistical significance ($P < 0.05$)

Table 4. *Postoperative Adverse Events Within 48 Hours.*

Adverse Event	S Group (n=40)	SE1 Group (n=40)	SE2 Group (n=40)	*P*-value	Significant Pairwise Comparisons (*P*-value; Cohen's V)
Nausea/Vomiting	16 (40.0%)	7 (17.5%)	6 (15.0%)	0.016	S-SE1: 0.039 (V=0.26); S-SE2: 0.024 (V=0.28)
Hallucination	0 (0.0%)	0 (0.0%)	0 (0.0%)	N/A	Not applicable
Pruritus	3 (7.5%)	2 (5.0%)	2 (5.0%)	0.895	NS
Delirium	17 (42.5%)	6 (15.0%)	7 (17.5%)	0.007	S-SE1: 0.013 (V=0.28); S-SE2: 0.025 (V=0.25)
Dizziness	13 (32.5%)	8 (20.0%)	6 (15.0%)	0.109	NS

Data = n (%)
Bold indicates statistical significance ($P < 0.05$)

4. Discussion

Our randomized controlled trial demonstrates that combining esketamine with reduced-dose sufentanil for patient-controlled intravenous analgesia (PCIA) significantly improves postoperative pain control and functional recovery in elderly patients undergoing total hip arthroplasty (THA), while concomitantly reducing opioid-related adverse events. These findings align with emerging evidence supporting multimodal analgesia strategies and extend the clinical utility of *N*-methyl-D-aspartate (NMDA) receptor antagonists in geriatric perioperative care.

The observed dose-dependent analgesic enhancement with esketamine corroborates the neurophysiological role of *N*-methyl-D-aspartate (NMDA) receptors in central sensitization and wind-up phenomena [17]. By antagonizing these receptors, esketamine likely attenuated postoperative hyperalgesia, particularly for movement-evoked pain, where Group SE2 achieved a 73% greater reduction in pain intensity compared to Group SE1 at 48 h. This mechanism complements μ-opioid receptor activation by sufentanil, reflecting the documented analgesic synergy between these agents [18, 19]. As the *S*-enantiomer of ketamine, esketamine exhibits enhanced anesthetic and analgesic potency with a more favorable adverse effect profile than racemic ketamine. Its multimodal mechanisms involve non-competitive NMDA receptor antagonism, activation of μ- and δ-opioid receptors, and modulation of descending nociceptive pathways through increased synaptic availability of norepinephrine and serotonin [20]. A recent meta-analysis by Yao et al. confirmed that esketamine-sufentanil combinations reduce 24-hour visual analog scale (VAS) scores by 1.3 points (95% CI: −1.6 to −1.0) compared to sufentanil monotherapy, aligning with our findings (Cohen's d = 0.55–0.78 vs. pooled d = 0.65 in Yao et al.) [19]. Collectively, these data underscore esketamine's potential to optimize postoperative pain management via patient-controlled intravenous analgesia (PCIA) following total hip arthroplasty (THA), primarily through its multimodal pharmacological actions.

The SE2 regimen demonstrated a 50% reduction in sufentanil consumption, which correlated with a 62.5% decrease in postoperative nausea/vomiting (PONV) (40% vs. 15%, P = 0.016) and a 64.7% reduction in postoperative delirium (POD) incidence (42.5% vs. 15%, P = 0.007). These findings extend prior observations on esketamine's neuroprotective properties by revealing its dual role in mitigating opioid-related complications and neuroinflammation [21]. Notably, the magnitude of benefit exceeded predictions from the Apfel risk model for pure opioid-sparing effects, suggesting additional protection against neuroinflammation-driven complications via esketamine's anti-inflammatory actions, including TNF-α suppression and microglial activation inhibition [11, 22]. This safety profile aligns with Yao et al.'s meta-analysis, which reported a 52% reduction in PONV risk (RR = 0.48, 95% CI: 0.35–0.66) with perioperative esketamine [19]. Importantly, the absence of increased psychomimetic effects (hallucinations: 0–2.5% across groups) at 2 mg/kg esketamine reflects its superior NMDA receptor selectivity (Ki = 0.3 nM vs. 1.4 nM for R-ketamine) [5], corroborating Meng et al.'s findings in geriatric hip arthroplasty patients, where 2.5 mg/kg esketamine reduced nausea/vomiting by 62% without exacerbating neuropsychiatric risks compared to sufentanil monotherapy [23]. The SE2 group demonstrated significantly accelerated time to first walk (45.5 h vs. 49.7 h in Group S; Cohen's d = 0.95) and enhanced recovery quality (QoR-15 score: 120.2 vs. 114.7; d = 1.28), aligning with ERAS targets for THA rehabilitation [24]. In the study of song et al, it was also found that sufentanil combined with esketamine could significantly shorten the first walking time after total hip replacement compared with sufentanil alone [25]. Critically, the SE2 group's movement-evoked VAS scores remained below the 4.5 threshold recommended by international consensus for unre-

stricted physiotherapy [26]. This pain control level may reduce hospitalization duration by 1.2–1.8 days, as mobility-restricted patients with VAS >4.5 exhibit prolonged bedrest-related complications (e.g., pneumonia, DVT) [27]. The superior QoR-15 scores in SE2 likely reflect both improved analgesia (resting VAS <3.0) and reduced opioid-induced side effects (e.g., sedation, ileus), consistent with Xue et al.'s findings that esketamine-based analgesia elevated QoR-15 scores versus sufentanil monotherapy [28]. In summary, esketamine achieves multimodal synergistic effects through NMDA receptor antagonism, anti-inflammatory modulation, and opioid-sparing actions. Its combination with low-dose sufentanil offers a superior risk-benefit profile for postoperative pain management in elderly THA patients, balancing enhanced analgesia with minimized neuropsychiatric and gastrointestinal complications.

Our findings delineate a therapeutic window for esketamine in elderly patient-controlled intravenous analgesia (PCIA) protocols: 1 mg/kg (Group SE1): Provided sufficient resting analgesia (resting VAS <3.0) with minimal sedation burden (Ramsay score Δ = 0.12–0.24 vs. Group S). For frail patients (ASA III), this regimen achieved optimal equilibrium between pain control and sedation safety, aligning with European Society of Regional Anaesthesia and Pain Therapy (ESRA) guidelines recommending conservative NMDA antagonist dosing in high-risk surgical populations [27]. 2 mg/kg (Group SE2): Demonstrated superior efficacy for movement-evoked pain management (passive leg elevation VAS <4.5), albeit with moderately elevated sedation scores (Ramsay 3.19 at 24 h vs. 2.85 in Group SE1). Importantly, Group SE2 exhibited a more favorable clinical benefit-risk profile in ASA I–II patients, achieving a 64% relative risk reduction in delirium incidence compared to Group S. Pharmacokinetic studies support this stratification, as elderly patients exhibit 38% lower esketamine clearance due to CYP2B6 polymorphism prevalence [29].

This study has limitations: 1) Lack of direct comparison with regional anesthesia limits definitive efficacy hierarchy conclusions; 2) Sample size precluded subgroup analyses by cognitive status or POD risk factors; 3) Long-term outcomes beyond 48 h were not assessed. Future multicenter trials should integrate continuous nociception monitoring and compare cost-effectiveness versus catheter-based techniques.

5. Conclusion

This randomized controlled trial (RCT) demonstrates that adjunctive esketamine (2 mg/kg) in sufentanil-based patient-controlled intravenous analgesia (PCIA) provides superior movement pain control (48-h movement VAS: 4.41 vs. 5.01; $P < 0.001$) and accelerates functional recovery (time to ambulation: 45.5 h vs. 49.7 h; Cohen's $d = 0.95$) in elderly patients undergoing total hip arthroplasty (THA), while significantly reducing opioid-related complications (nausea/vomiting: 15% vs. 40%; delirium: 15% vs. 42.5%). Future studies should validate the long-term benefits and cost-effectiveness of this regimen.

Abbreviations

THA	Total Hip Arthroplasty
PCIA	Patient-controlled Intravenous Analgesia
VAS	Visual Analogue Scale
RSS	Ramsay Sedation Scale
QoR-15	Quality of Recovery-15
POD	Postoperative Delirium
PONV	Postoperative Nausea and Vomiting
NMDA	*N*-methyl-D-aspartate
POND	Postoperative Neurocognitive Disorders
ASA	American Society of Anesthesiologists
NYHA	New York Heart Association
LVEF	Left Ventricular Ejection Fractions
LMA	Laryngeal Mask Airway
IBP	Invasive Arterial Blood Pressure
BIS	Bispectral Index

Author Contributions

Jia Han: Project administration, Funding acquisition
Xian-Jie Zhang: Conceptualization, Methodology
Wen-Hu Zhai: Investigation
Jian-Sheng Luo: Funding acquisition, Writing- review & editing
Yu-Hang Shou: Investigation, Writing-original draft

Ethics Statement

This study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Deyang People's Hospital (Approval No. KY-2021-04-158-K01). Written informed consent was obtained from all participants following a detailed explanation of study procedures and potential risks. Patient confidentiality was maintained through anonymized data management compliant with China's Personal Information Protection Law.

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Data Availability Statement

The data analyzed during this study can be obtained from the corresponding author on reasonable request.

Conflicts of Interest

The authors declare no conflicts of interest.

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