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ORIGINAL RESEARCH

Effect of Intravenous Esketamine on Rebound Pain Following Single-Shot Brachial Plexus Block in Patients Undergoing Shoulder Arthroscopic Surgery: A Prospective, Randomized, Placebo-Controlled Study

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Purpose: Rebound pain (RP) often occurs after the resolution of peripheral nerve blocks. Studies suggest that perineural esketamine prolongs block duration and reduces RP incidence. This study aimed to determine whether intravenous esketamine reduces RP incidence following single-shot interscalene brachial plexus block (ISBPB) in shoulder arthroscopic surgery.
Patients and methods: In this randomized controlled trial, 200 patients scheduled for shoulder arthroscopy received ultrasound-guided single-shot ISBPB preoperatively and were randomized to receive either intravenous esketamine (0.5 mg/kg bolus + 0.25 mg/kg/h infusion) or placebo. Primary outcomes included RP incidence, onset time, duration, and pain scores. Secondary outcomes included block duration, postoperative pain scores, and hemodynamic parameters (heart rate [HR], mean arterial pressure [MAP]).
Results: The incidence rates of rebound pain (RP) were comparable between groups, with no significant differences in RP duration or pain scores ($P>0.05$). However, the Numeric Rating Scale at rest (NRS-R) scores at 8h, 12h, and 24h postoperatively were significantly higher in the C-group compared to the E-group ($P<0.05$). Hemodynamic stability was superior in the E-group during immediately post-administration (T4) to skin incision (T8), with higher MAP at T6–T10 ($P<0.05$). Sensory/motor block onset and duration showed no intergroup differences ($P>0.05$). Adverse events (dizziness, nausea) were comparable, with one transient hallucination in the E-group.
Conclusion: Patients undergoing arthroscopic rotator cuff repair under combined single-shot interscalene brachial plexus block and general anesthesia exhibit a rebound pain incidence of approximately 25%. Intravenous administration of esketamine (0.5 mg/kg bolus followed by continuous infusion at 0.25 mg/kg/h) during the operation failed to significantly reduce the incidence of rebound pain post-block ($P>0.05$). However, it demonstrated significant reductions in pain scores at 8h, 12h, and 24h postoperatively ($P<0.05$), with enhanced hemodynamic stability observed from anesthetic induction to pre-incision periods. No severe adverse events were reported.
Keywords: esketamine, rebound pain, interscalene brachial plexus block, rotator cuff tear

Introduction

Arthroscopic rotator cuff repair is frequently associated with moderate to severe postoperative pain,[1] and the sources of pain are multi-factorial: ischemic pain from intraoperative capsular distension, periosteal irritation induced by anchor implantation, and peripheral neural sensitization mediated by inflammatory mediators (eg PGE2, IL-6).[2–4] Inadequate pain control during the initial 48 hours postoperatively not only significantly impedes long-term pain resolution but also correlates with increased complications, including joint stiffness and chronic regional pain syndrome.[5] Evidence has demonstrated that single-shot interscalene brachial plexus block (ISBPB) significantly enhances postoperative analgesia

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in patients undergoing shoulder arthroscopy, effectively reducing opioid requirements and minimizing postoperative nausea and vomiting.[6,7] While continuous ISBPB delivers sustained analgesia in comparison to single-shot techniques, it necessitates catheter insertion and maintenance—thereby introducing additional procedural steps and potential risks relative to the single-injection approach. Consequently, single-shot ISBPB is widely regarded as the most common method for postoperative pain management in shoulder arthroscopy, and is the core of postoperative multimodal analgesia and preventive analgesia strategies.[8–10]

Emerging evidence has increasingly recognized a phenomenon termed "rebound pain (RP)", characterized by a rapid escalation in pain intensity following the resolution of peripheral nerve blocks. Barry et al operationally defined RP as a transition from mild pain (NRS≤3 to severe pain NRS≥7) within 24 hours post-block.[11] Unlike persistent postoperative pain, rebound pain (RP) represents a transient phenomenon typically manifesting within 12–24 hours after nerve blockade[12] and persisting for 2–6 hours. Studies report an RP incidence of 41.9–49.6% in patients undergoing upper limb surgery under interscalene brachial plexus block (ISBPB).[11,13,14] The emergence of RP substantially undermines the clinical benefits of regional anesthesia, including enhanced pain control and reduced opioid consumption, thereby necessitating urgent preventive strategies.

There are several proposed pathophysiological mechanisms that may explain rebound pain following peripheral nerve block. These include the "gate control failure effect" (where abrupt resolution of blockade leads to explosive transmission of previously suppressed nociceptive signals) and concurrent peripheral sensitization induced by inflammatory mediators (eg, substance P, bradykinin) and central sensitization mediated by excessive NMDA receptor activation.[15–17]

In this context, esketamine—the S-enantiomer of ketamine that selectively antagonizes NMDA receptors, theoretically mitigates central sensitization by blocking glutamatergic signaling, thereby potentially reducing rebound pain following nerve blockade. Prolonging the duration of nerve blockade has been demonstrated to mitigate RP incidence. As an adjuvant for ISBPB, esketamine has been demonstrated to prolong ISBPB duration through perineural administration while significantly decreasing rebound pain incidence after block resolution.[13,18,19] However, perineural esketamine remains an off-label application, with no formal safety trials conducted to date. Given the ethical and regulatory challenges in pursuing such trials, the long-term safety profile of perineural esketamine remains unestablished.

Esketamine exhibits potent analgesic and anesthetic properties, coupled with anti-hyperalgesic, anti-inflammatory, and neuroprotective properties.[20,21] Low-dose intravenous esketamine may synergize with regional analgesic techniques to modulate postoperative pain intensity[22] and is recommended in expert consensus guidelines for inclusion in perioperative multimodal analgesia regimens as an NMDA receptor-targeting agent. This study aimed to evaluate whether intravenous esketamine reduces the incidence of RP following single-shot ISBPB in patients undergoing arthroscopic rotator cuff repair.

Methods

This prospective, randomized, double-blind study was conducted in accordance with the Declaration of Helsinki. The protocol received ethical approval from the Ethics Committee of Affiliated Li Huili Hospital of Ningbo University (Approval No. KY2023SL386-01) and was prospectively registered in the Chinese Clinical Trial Registry (Registration No. ChiCTR2400081449) prior to the commencement of patient enrollment.

Recruitment

Prospective enrollment included patients aged 18–80 years scheduled for elective arthroscopic rotator cuff repair under combined single-shot ISBPB and general anesthesia between February 2024 and August 2024. Written informed consent was obtained from all participants. Exclusion criteria comprised: contraindications to regional anesthesia (eg coagulopathy, local infection); chronic pain disorders requiring long-term analgesics; severe cardiopulmonary, neurological, or psychiatric disorders; contraindications to esketamine (eg intracranial hypertension, poorly controlled or untreated hypertension, hyperthyroidism); hypersensitivity to local anesthetics; uncontrolled diabetes mellitus; peripheral neuropathy or injury; pregnancy or suspected pregnancy; and perioperative administration of corticosteroids (eg dexamethasone sodium phosphate).

Preoperative Assessment

On the day preceding surgery, preoperative pain intensity at the surgical site was assessed using the Numeric Rating Scale (NRS; 0 = no pain, 10 = worst imaginable pain) under both resting and movement-evoked conditions. A comprehensive medication history, including recent analgesic use, was documented. Patients completed the abbreviated Central Sensitization Inventory (CSI-9) to evaluate somatic and emotional symptoms associated with central sensitization, with a CSI Part A score ≥20 strongly indicative of probable central sensitization. Additionally, the Pain Catastrophizing Scale (PCS) was administered to quantify pain-related negative cognitive-emotional responses (rumination, magnification, and helplessness). Neuropathic components of surgical site pain were screened using the Douleur Neuropathique 4 questions (DN4) questionnaire.

Study Intervention

Patients were randomized into two groups using a computer-generated randomization table: the control group (C-group, normal saline) and the experimental group (E-group, esketamine). Prior to study entry, sealed opaque envelopes containing group assignments were opened. Study medications were prepared by personnel not involved in the trial and administered using unmarked syringes to ensure blinding.

Intraoperative and Postoperative Treatments

Following establishment of peripheral intravenous access in the Preoperative preparation room, single-shot ISBPB was performed under ultrasound guidance by an anesthesiologist blinded to group allocation and proficient in regional anesthesia techniques. All patients received 20 mL of 0.375% ropivacaine. Sensory and motor blockade assessments were conducted at 2-minute intervals for 30 minutes post-procedure. Testing was discontinued upon confirmation of complete sensory-motor blockade, with the onset time recorded. Cases demonstrating persistent pain perception or preserved voluntary muscle strength at 30 minutes post-block were classified as block failures and excluded from analysis to maintain methodological rigor and data integrity. Sensory testing was performed

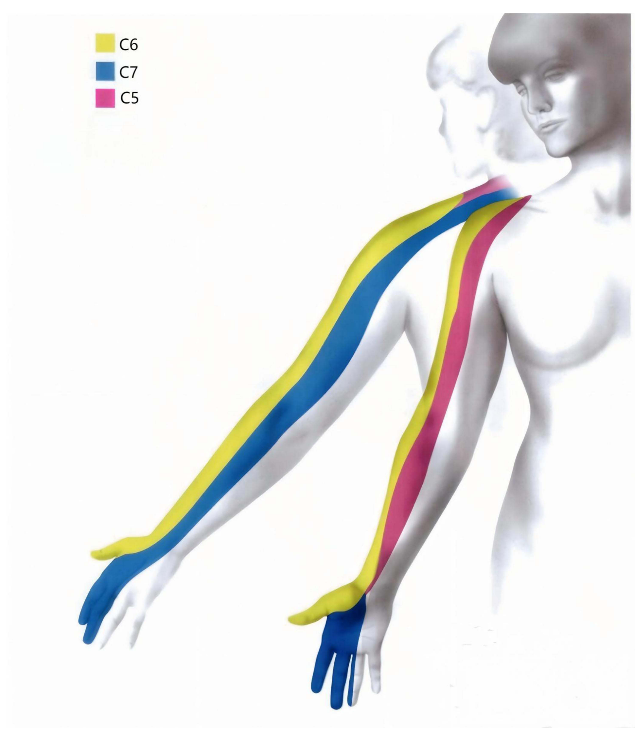

Figure 1 Dermatomal distribution following interscalene brachial plexus block.

Table 1 Sensory and Motor Blockade Assessment Scale

	0 Score	1 Score	2 Score	3 Score
Sensory Blockade	Intact pain and touch sensation	Diminished pain with intact touch	Absent pain with preserved touch	Absent pain and touch sensation
Motor Blockade	Normal muscle strength: Preserved elbow flexion, arm elevation, and grip	Partial weakness: Elbow flexion/arm elevation possible without resistance; weakened grip	Complete paralysis: Inability to flex elbow, elevate arm, or make fist	

using a 25-gauge needle, with dermatomal distributions illustrated in Figure 1. Motor blockade was evaluated via modified Bromage scale. Scoring criteria for sensory and motor blockade are detailed in Table 1.

Upon entering the operating room, all patients underwent general anesthesia with rapid sequence induction using intravenous propofol (1.5~2 mg/kg), sufentanil (0.2~0.3 μg/kg), and rocuronium (0.6 mg/kg), followed by endotracheal intubation and mechanical ventilation. Anesthesia maintenance was managed at the discretion of the attending anesthesiologist, and sufentanil and rocuronium were administered as needed based on the surgical situation. After adjusting the patient's position (60° lateral decubitus with 30° posterior tilt), Group E received a two-stage administration protocol:① Intravenous bolus of 0.5 mg/kg esketamine (dilute with physiological saline to 10mL). ② Continuous intraoperative infusion of 50 mL esketamine (concentration: 1 mg/mL) at a rate of 0.25 mL/kg/h, which was discontinued 10 minutes before the end of surgery. The C-group received equivalent volumes of normal saline (10 mL bolus + 50 mL infusion at 0.25 mL/kg/h).

All patients underwent standardized arthroscopic rotator cuff repair, including subacromial decompression, rotator cuff tendon debridement, and suture anchor fixation for partial- or full-thickness tears.

Postoperatively, patients were placed in a shoulder immobilizer sling and an abduction pillow, with the shoulder positioned in 30–40° of internal rotation and 20° of abduction. An individualized rehabilitation protocol was then initiated based on the extent of the tear, tendon quality, and surgical specifics. All patients received standardized multimodal analgesia: Intravenous parecoxib 40 mg administered before the end of surgery. Postoperative oral tramadol 100 mg every 12 hours combined with intravenous parecoxib 40 mg. Rescue analgesia with pethidine as required.

Outcome Measures

Preoperative resting and movement-evoked (R/M) pain intensities were assessed using the NRS (0:no pain; 1~3:mild pain; 4~6:moderate pain; 7~10:severe pain). Scores from the CSI-9, PCS, and DN4 questionnaires were documented. Hemodynamic parameters, including heart rate (HR) and mean arterial pressure (MAP), were recorded at predefined intervals: T1: Operating room admission; T2: Pre-intubation; T3: Post-intubation; T4: immediately post-administration; T5: 3 minutes post-administration; T6: 5 minutes post-administration; T7: 10 minutes post-administration; T8: skin incision; T9: 30 minutes into surgery; T10: surgical completion.

Anesthesia duration, surgical time, and intraoperative sufentanil consumption were documented. Sensory and motor block onset times, total block duration, and NRS scores at block resolution were recorded. Postoperatively, patients completed pain logs upon sensation returned to the arm (indicating nerve block resolution) or surgical site pain onset. Follow-up NRS scores at rest were collected in the post-anesthesia care unit (PACU) and at 2h, 4h, 6h, 8h, 12h, 24h, and discharge.

Rebound pain (RP) was defined as a transition from mild pain (NRS ≤ 3) to severe pain (NRS ≥ 7) within 24 hours post-ISBPB. Patients were instructed to log pain intensity if ISBPB failed to suppress surgical pain or if they perceived inadequate pain control by ISBPB (eg sudden pain intensification). Adverse events (eg dizziness, visual hallucinations, nausea/vomiting) were systematically documented.

Statistical Analysis

A priori power analysis was performed using GPower 3.1. Based on prior studies indicating a 40%-50% rebound pain incidence after ISBPB, we hypothesized a 50% reduction with esketamine (α=0.05, β=0.2). The calculated sample size was 172 patients; 200 were enrolled to accommodate a 10% dropout rate.

Data analysis was performed using SPSS Statistics version 25.0 (IBM Corp, Armonk, NY, USA). Normally distributed continuous variables were expressed as mean±standard deviation, and compared between groups using the independent samples *t*-test. Intergroup differences across multiple time points were evaluated using repeated-measures analysis of variance (ANOVA). Non-normally distributed continuous variables were reported as median and interquartile range (IQR) and analyzed with non-parametric tests (Mann–Whitney U or Kruskal–Wallis test as appropriate). Categorical variables were summarized as frequencies or percentages (%) and compared using the chi-square test or Fisher's exact test. Ordinal data were analyzed via the Wilcoxon rank-sum test. A two-tailed $P < 0.05$ was considered statistically significant.

Results

This study enrolled 200 patients undergoing rotator cuff repair surgery. After excluding cases with invalid or incomplete data, 187 patients (Group E: n=94; Group C: n=93) were included in the final analysis. The participant flow chart is shown in Figure 2. The two groups demonstrated comparable baseline characteristics, including demographic variables, preoperative Numerical Rating Scale (NRS) scores at rest and during movement (R/M), anesthesia duration, operative time, intraoperative sufentanil consumption, CSI-9 scores, PCS scores, and DN4 neuropathic pain scores. Detailed comparisons are presented in Table 2.

Changes in HR and MAP

Compared to the C-group, the E-group demonstrated more stable mean arterial pressure (MAP) fluctuations during the period from immediately post-administration (T4) to skin incision (T8), a hemodynamic profile likely attributable to the sympathomimetic properties of esketamine. Furthermore, at T6, T7, T8, T9, and T10 timepoints, MAP values in the E-group were significantly higher than those in the C-group ($P < 0.05$), as detailed in Figure 3.

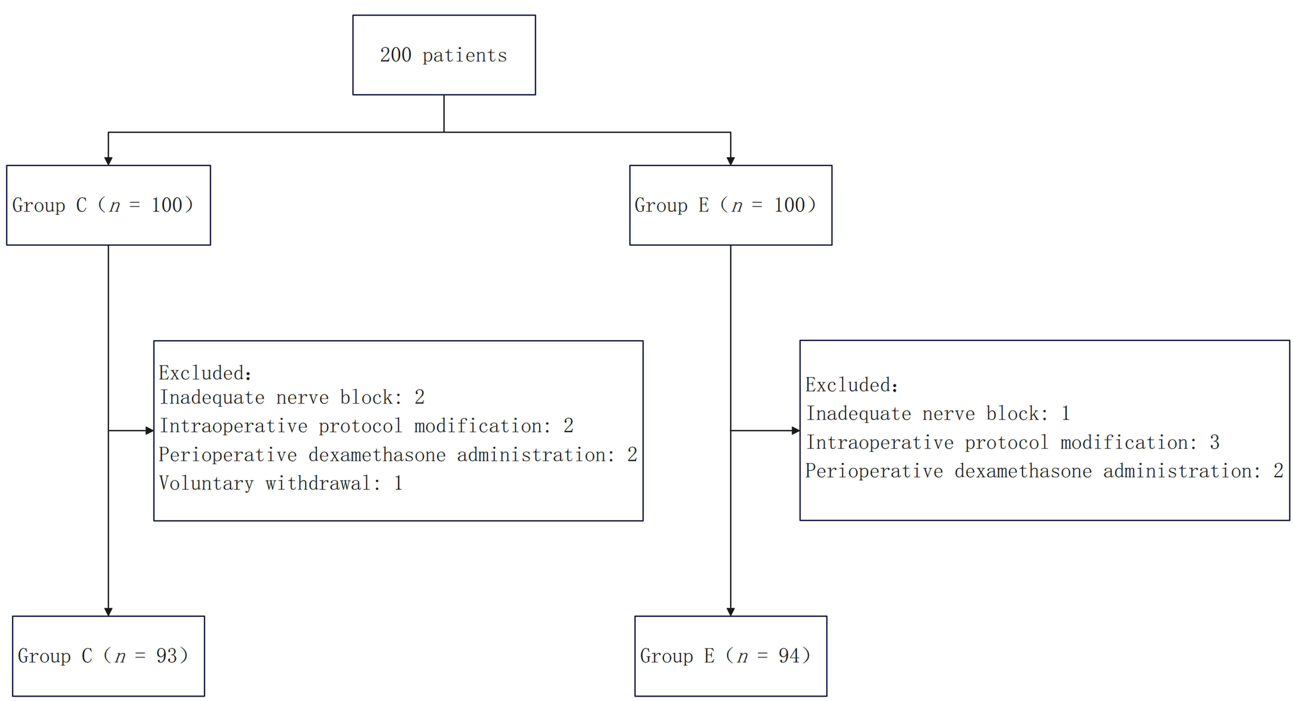

Figure 2 Participant flow diagram.

Table 2 Perioperative Data and Characteristics of Patients

		Group C (*n*=93)	Group E (*n*=94)
Age (y)		59.40±10.08	60.65±11.59
Female/male		28/65	35/59
BMI (kg/m^2)		23.71±4.44	24.09±2.30
ASA physical status (I/II)		32/61	30/64
Preoperative NRS score	Rest (R)	0.00 (0.00, 2.00)	0.00 (0.00, 2.00)
	Movement (M)	5.00 (3.00, 6.00)	5.00 (4.00, 6.00)
Duration of anesthesia (min)		64.89±34.60	63.28±23.08
Duration of operation (min)		52.92±34.25	51.09±21.43
Intraoperative sufentanil dosage (μg)		20.28±4.83	20.61±3.69
CSI-9 score			
Mild central sensitization (0—9)		89 (95.7%)	93 (98.9%)
Moderate central sensitization (10—18)		4 (4.3%)	1 (1.1%)
Severe central sensitization (19—36)		0 (0.0%)	0 (0.0%)
PCS score			
No significant pain-related distress (0—37)		92 (98.9%)	90 (95.7%)
Significant pain catastrophizing tendencies (38—52)		1 (1.1%)	4 (4.3%)
DN4 score			
The neuropathic component of pain was deemed less probable (0—3)		92 (98.9%)	94 (100%)
Definite neuropathic characteristics (4—10)		1 (1.1%)	0 (0.0%)

Duration of Sensory and Motor Block

No statistically significant intergroup differences were observed in sensory and motor block onset times, H1–H2 interval, H2–H3 interval, or total block duration ($P > 0.05$). Full comparative analyses are presented in Table 3 and Figure 4.

Changes in NRS-R at Different Time Points

No statistically significant differences in NRS-R scores were observed between the two groups at postoperative PACU, 2h, 4h, 6h, or discharge timepoints ($P > 0.05$). However, patients in the C-group exhibited significantly higher NRS-R scores compared to the E-group at 8h, 12h, and 24h postoperatively ($P < 0.05$), as detailed in Table 4 and Figure 5.

Comparison of Incidence, Duration, and Pain Scores of Rebound Pain

Postoperative follow-up revealed comparable incidence rates of rebound pain (RP) between the C-group (17 cases) and E-group (15 cases), with no statistically significant intergroup differences ($P > 0.05$). Both groups exhibited comparable rebound pain duration and pain scores. Episodes predominantly manifested approximately 35 minutes after block resolution with nocturnal clustering, as detailed in Table 5 and Figure 6.

Side Effects Assessment

In the PACU, dizziness was reported in 4 patients in the C-group and 6 patients in the E-group, with no statistically significant intergroup difference ($P > 0.05$). Similarly, the incidence of nausea and vomiting was comparable between groups (C-group: 6 cases vs E-group: 4 cases; $P > 0.05$). Notably, one patient in the E-group experienced transient postoperative hallucinations, which resolved following intervention. Detailed adverse event profiles are summarized in Table 6.

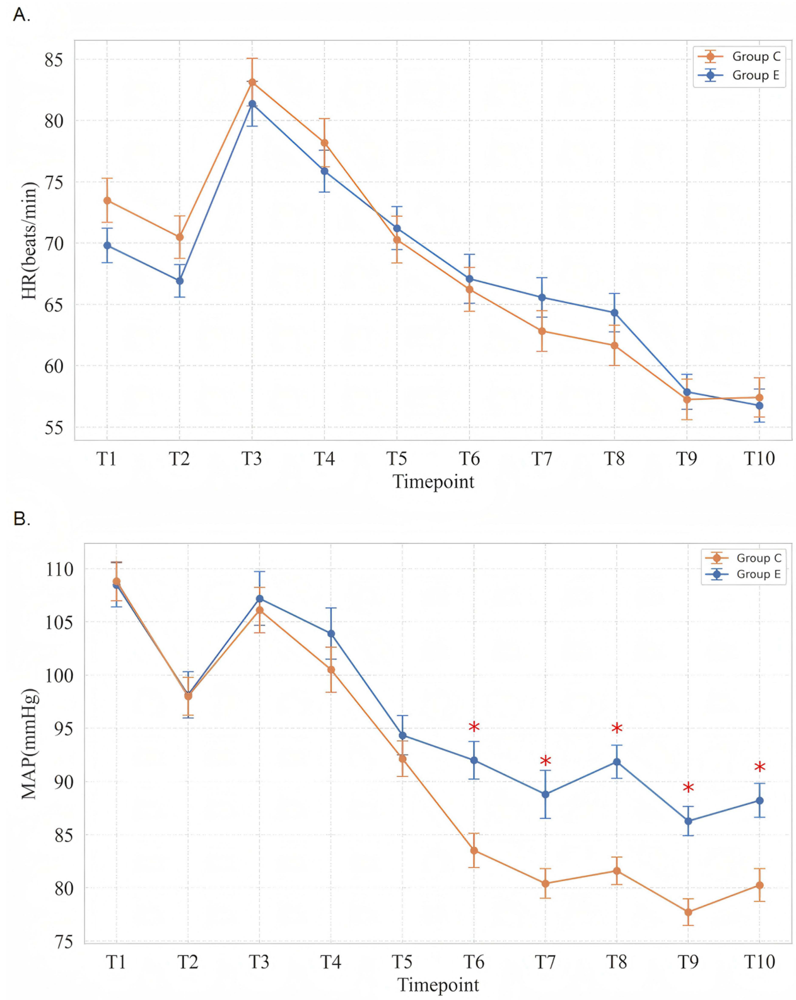

Figure 3 (**A** and **B**) Trends of the hemodynamic data and during the peri-intubation period. *Indicates that compared with group C, *P*<0.05.

Discussion

RP is prevalent after ISBPB resolution, occurring more frequently in younger patients, females, orthopedic surgeries, and those not receiving perioperative dexamethasone.[11] Touil et al reported a 47% RP incidence in ambulatory patients undergoing upper limb surgery under axillary brachial plexus block,[14] while Barry et al identified RP in 49.6% of ambulatory surgical patients receiving preoperative peripheral nerve blocks.[11] Similarly, Zhu et al observed a 41.89% RP incidence in patients undergoing unilateral upper limb fracture open reduction and internal fixation under supraclavicular brachial plexus block.[13]

Table 3 Intergroup Differences in Sensory and Motor Block Onset and Duration

	Onset Time of Sensory block (min)	Onset Time of Motor block (min)	PNB Duration (min)		
			H1-H2 (min)	H2-H3 (min)	Total Duration (min)
Group C (*n*=93)	7.49±1.29	8.24±0.89	425.13±113.60	220.02±84.19	641.30±174.02
Group E (*n*=94)	7.12±1.36	9.15±1.55	469.39±154.64	219.57±79.92	688.96±217.42

Notes: Comparison between the two groups, *P*>0.05. H1-H2: Time interval between the time of the end of the block (H1) and the beginning of the onset of the paresthesia reported by the subject (H2); H2-H3: Time interval between the time of beginning of the occurrence of paresthesia reported by the subject (H2) and finally the onset of pain at surgery site (H3).

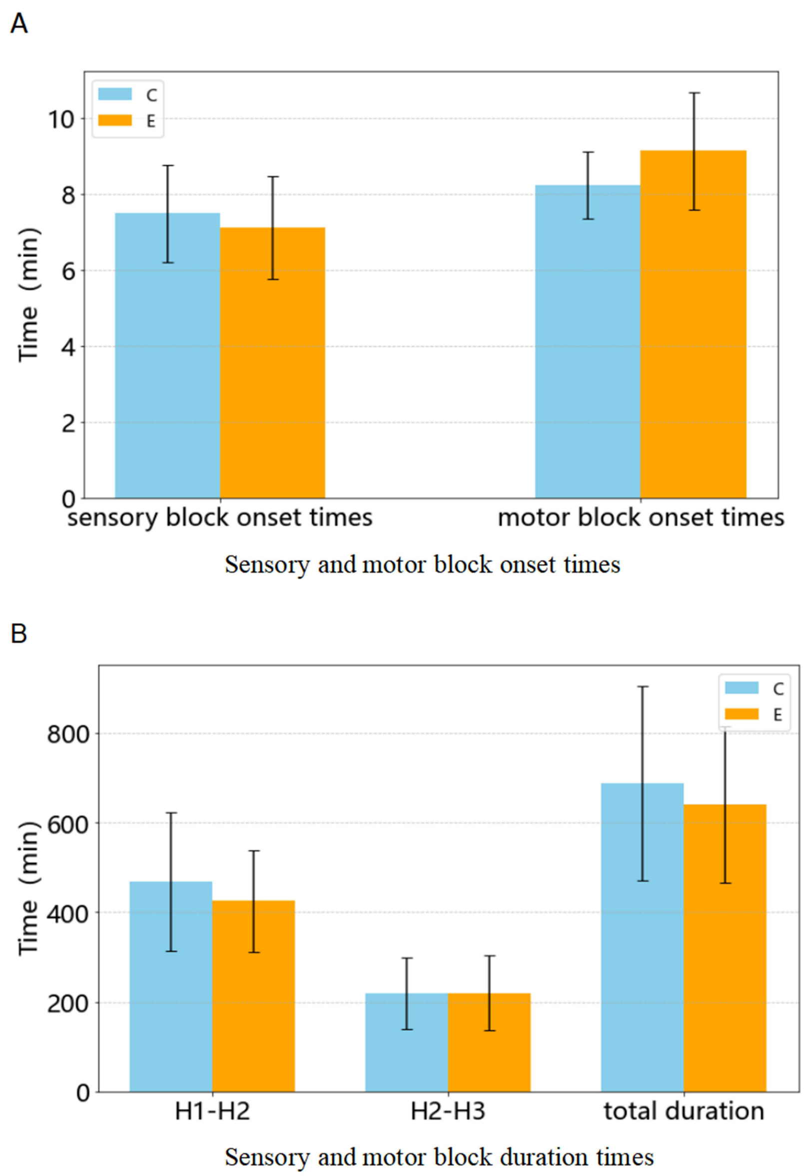

Figure 4 Sensory and motor block onset and duration. (**A**) Sensory and motor block onset times. (**B**) Sensory and motor block duration times. H1-H2: Time interval between the time of the end of the block (H1) and the beginning of the onset of the paresthesia reported by the subject (H2); H2-H3: Time interval between the time of beginning of the occurrence of paresthesia reported by the subject (H2) and finally the onset of pain at surgery site (H3).

In contrast, the RP incidence in our study (approximately 25%) was notably lower than these reported rates. This discrepancy may be attributed to the following factors: ① Analgesic adherence: unlike ambulatory cohorts with suboptimal compliance and limited access to professional pain management guidance,[23] our hospitalized patients received standardized analgesic supervision. ② Demographic differences: our cohort predominantly comprised older patients with rotator cuff tears, a population inherently at lower RP risk due to age-related declines in pain sensitivity and elevated pain thresholds.[12] ③ Intraoperative anti-inflammatory intervention: intra-articular administration of compound betamethasone and sodium hyaluronate prior to skin closure mitigated postoperative inflammatory responses and pain intensity. ④ Multimodal analgesic protocol: a perioperative regimen combining intravenous parecoxib 40 mg and oral tramadol 100 mg provided effective analgesic bridging, thereby suppressing RP incidence.[24] Admassie et al[25] demonstrated that patients receiving postoperative analgesics such as opioids and NSAIDs exhibit a significantly lower incidence of rebound pain following the resolution of peripheral nerve blocks. ⑤ Procedural Heterogeneity: Variations in surgical site and operative technique, block type, and baseline pain profiles may further explain divergent RP rates

Table 4 Postoperative NRS-R Score of Two Groups at Different Time Points[M (P_{25}, P_{75})]

	Time Points	Group C	Group E
NRS-R score	PACU	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)
	2h	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)
	4h	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)
	6h	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)
	8h	1.00 (1.00, 2.00)	1.00 (0.50, 1.00)*
	12h	3.00 (2.00, 4.00)	2.00 (1.00, 3.00)*
	24h	2.00 (0.50, 3.00)	2.00 (0.00, 3.00)*
	Discharge	1.00 (0.00, 2.00)	0.00 (0.00, 1.00)

Note: *Indicates that compared with group C, $P<0.05$.

across studies. Rebound pain significantly undermines the clinical benefits conferred by nerve blockade, representing a critical challenge that demands prioritization in postoperative pain management strategies.

The pathogenesis of rebound pain after peripheral nerve block is multifactorial and not yet fully elucidated. In a rodent model, rats receiving ropivacaine sciatic nerve blockade exhibited transient thermal hyperalgesia during block resolution compared to placebo-treated controls, though mechanical hypersensitivity was not observed.[26] Notably, surgical incision-induced local inflammatory responses inherently provoke thermal hyperalgesia at the wound site, termed post-incision primary hyperalgesia. The release of inflammatory mediators (eg prostaglandins, cyclooxygenase isoforms [COX-1/COX-2], cytokines, substance P, and neutrophil-derived factors) potentiates peripheral nociceptor sensitization, contributing to postoperative hyperalgesia. Although neural blockade interrupts nociceptive signal transmission from peripheral nerves to the spinal dorsal horn—suppressing pain perception via ascending spinothalamic tracts and subsequent thalamocortical pathways[15] —it fails to mitigate peripheral nociceptor sensitization. Persistent inflammatory cascades allow preservation of nociceptive signaling memory, which becomes activated upon block resolution,[16,17] potentially explaining the emergence of rebound pain.

These mechanistic insights collectively suggest that sole reliance on neural blockade inadequately disrupts the pathophysiological cascade involving peripheral inflammatory responses and central sensitization. This raises a critical inquiry: as an NMDA receptor antagonist, esketamine exerts dual therapeutic effects—suppressing central sensitization while synergistically optimizing postoperative pain management through multimodal analgesic mechanisms. Previous clinical studies have demonstrated that intraoperative administration of high-dose remifentanil in patients undergoing as low-dose ketamine effectively prevents opioid-induced hyperalgesia.[27,28] Importantly, the analgesic efficacy of esketamine has been well-documented across multiple surgical contexts, with accumulating evidence supporting its role in attenuating both acute and sustained postoperative pain. A systematic review addressing perioperative intravenous esketamine for acute postoperative pain management in adults revealed through meta-analysis[29] that subanesthetic

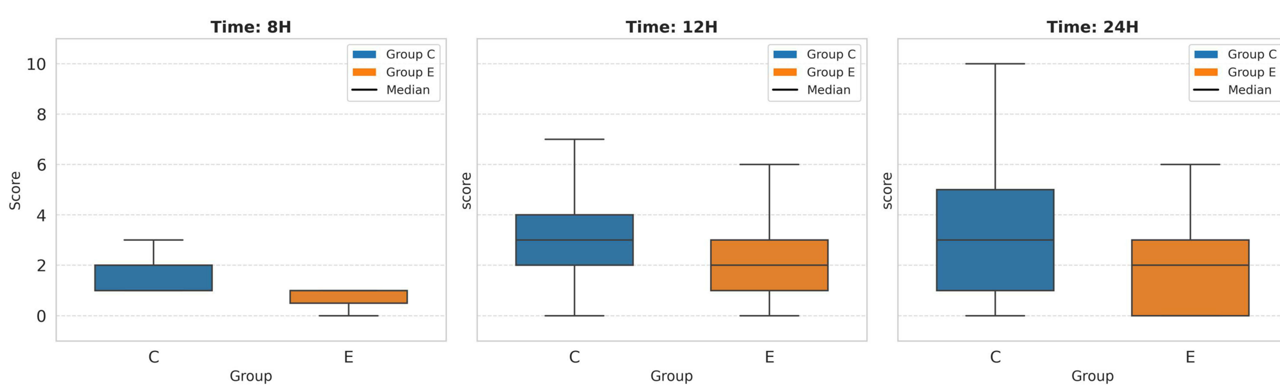

Figure 5 Group comparison at key time points (median highlighted).

Table 5 Rebound Pain Data of Two Groups

	Group C	Group E
Incidence of rebound pain (%)	24 (25.8%)	23 (24.5%)
Onset time of rebound pain	1:30 (23:07, 02:45)	0:10 (21:45, 00:30)
The time interval from the resolution of the ISBPS to the Onset time of rebound pain (min)	37.08±10.52	33.57±9.2
Duration of rebound pain (min)	150.00±67.08	108.75±39.07
NRS score	8.22±0.67	7.75±2.12

Note: Comparison between the two groups, *P*>0.05.

doses (≤0.5 mg/kg) effectively augmented postoperative analgesia, reducing both pain intensity and opioid requirements. A multicenter retrospective cohort study[30] demonstrated that an intravenous bolus of esketamine (0.075~0.5 mg/kg) pre-incision combined with intraoperative continuous infusion (maintenance rate: 0.25~6.7 µg/kg/min) significantly alleviated postoperative pain and decreased opioid consumption. In opioid-tolerant patients undergoing lumbar fusion surgery, Nielsen et al[31] reported that intraoperative esketamine administration (0.5 mg/kg bolus followed by 0.25 mg/kg/h infusion) reduced 24-hour morphine consumption by 32%, though no significant differences were observed in acute pain scores, nausea, vomiting, or hallucinogenic events. Conversely, Brinck et al[32] found that in opioid-naïve lumbar fusion patients, a pre-incision esketamine bolus (0.5 mg/kg) followed by either low- (0.12 mg/kg/h) or high-dose (0.6 mg/kg/h) infusions significantly lowered NRS scores over 48 hours postoperatively, albeit without reducing oxycodone consumption.

Collectively, esketamine demonstrates antihyperalgesic properties while effectively attenuating postoperative pain intensity and reducing opioid consumption, thus being recommended for preventing and managing rebound pain. Notably, prior studies revealed that single intravenous boluses of ketamine at 0.3 mg/kg[33] or 40 mg[18] failed to reduce rebound pain incidence or severity, potentially attributable to subtherapeutic dosing below the antihyperalgesic threshold. Given esketamine's twofold greater analgesic potency compared to racemic ketamine,[34] equivalent efficacy can be achieved at lower doses. Integrating its pharmacological profile with established dosing paradigms, this study employs a pre-incision intravenous bolus of 0.5 mg/kg (equivalent to 1.0 mg/kg racemic ketamine)—the upper limit of subanesthetic dosing—followed by continuous infusion maintenance at 0.25 mg/kg/h. As demonstrated by Peltoniemi et al[34] this dosing strategy achieves rapid therapeutic plasma concentrations (0.5 mg/kg bolus) followed by steady-state levels (0.25 mg/kg/h infusion), optimizing NMDA receptor antagonism while minimizing neuropsychiatric adverse effects.

Contrary to expectations, this study revealed that intravenous esketamine administration (0.5 mg/kg bolus with 0.25 mg/kg/h maintenance infusion) failed to significantly reduce rebound pain incidence, nor did it affect nerve blockade duration time—findings consistent with previous reports. The impact of esketamine on RP is dependent on the route of administration (perineural rather than systemic). In a study on postoperative pain after anterior cruciate ligament

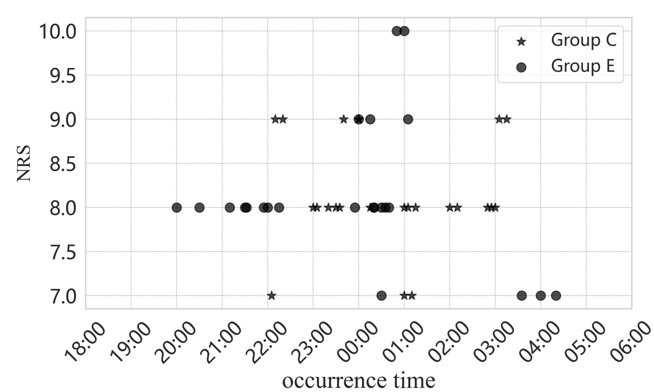

Figure 6 Onset time of rebound pain.

Table 6 Adverse Reactions Between the Two Groups [Cases (%)]

	Dizziness	Headache	Nausea and Vomiting	Hallucination
Group C (*n*=93)	4 (4.3)	0 (0.0)	6 (5.4)	0 (0.0)
Group E (*n*=94)	6 (6.3)	0 (0.0)	4 (4.3)	1 (0.0)

reconstruction, it was found that esketamine as an adjuvant to ropivacaine in peripheral nerve injection prolonged the duration of sensory nerve block, effectively controlled postoperative pain, and reduced the incidence of rebound pain.[18] Similarly, in patients with upper limb fractures, the combination of esketamine and ropivacaine for brachial plexus block effectively prolonged the duration of nerve block and reduced the incidence of rebound pain.[13,19]

Although continuous intravenous esketamine infusion did not significantly reduce rebound pain incidence in our study, it demonstrated markedly lower pain scores at 8h, 12h, and 24h postoperatively compared to the control group, indicating its retained utility in postoperative pain management. Esketamine exhibits superior NMDA receptor binding affinity and enhanced analgesic efficacy relative to racemic ketamine. Beyond its noncompetitive NMDA receptor antagonism, esketamine modulates multiple non-NMDA pathways—including opioid, cholinergic, and gamma-aminobutyric acid (GABA) receptor interactions—that collectively contribute to its analgesic profile. These multimodal mechanisms enable esketamine to alleviate postoperative pain and reduce opioid requirements through both NMDA-dependent and independent pathways. Two meta-analyses evaluating perioperative intravenous ketamine for acute postoperative pain management in adults demonstrated that esketamine may reduce postoperative analgesic consumption and pain intensity across variations in surgical type, administration timing, study size, and baseline pain intensity.[29,30] Compared to placebo, esketamine significantly improved resting pain scores at 4h, 12h, and 24h postoperatively,[28] aligning with our findings of its pronounced analgesic impact during the initial 12-hour postoperative window.[28,35]

Esketamine improves clinical outcomes during the perioperative period through dual mechanisms: attenuating post-operative pain via suppression of central sensitization and multimodal receptor synergism, while stabilizing hemodynamics by counteracting anesthesia-induced cardiovascular depression. During anesthesia induction, propofol administration induces vasodilation and exerts significant cardiovascular depressive effects, leading to reductions in cardiac output, cardiac index, stroke index, and systemic vascular resistance. Conversely, tracheal intubation elicits a pronounced stress response manifested by tachycardia and hypertension. The interplay between pharmacological suppression and physiological stress renders the period spanning from the resolution of the intubation-induced stress response to the surgical incision as the phase of greatest hemodynamic instability.[36] Esketamine counteracts these hemodynamic perturbations through its sympathomimetic properties, which stimulate the sympathetic nervous system, enhance endogenous catecholamine release, and inhibit norepinephrine reuptake, thereby mitigating propofol-induced cardiovascular suppression. Numerous studies have demonstrated ketamine's efficacy in stabilizing hemodynamics during induction.[37–39] Esketamine shares pharmacological similarities with racemic ketamine but exhibits approximately threefold greater binding affinity for NMDA receptors. Consequently, its analgesic and anesthetic potency ranges between 2–3 times that of racemic ketamine. Compared to the racemic form, esketamine demonstrates accelerated metabolic clearance and a more favorable adverse effect profile. For anesthetic induction, esketamine requires only half the dose of racemic ketamine while achieving a two-thirds reduction in recovery time. Chen et al demonstrated in a randomized controlled trial that esketamine coadministration maintains hemodynamic stability, reduces hypotension incidence, and elicits negligible psychoactive adverse effects. While esketamine increased heart rate across dosage tiers compared to controls, these differences lacked statistical significance.[40] In our protocol, postural adjustment preceded esketamine administration. The esketamine group (Group E) exhibited significantly higher mean arterial pressure (MAP) than controls (Group C), with superior hemodynamic stability observed from post-administration (T4) through skin incision (T8). Although Group E demonstrated marginally elevated heart rates, the intergroup difference remained non-significant—findings concordant with previous investigations.

Adverse effects associated with esketamine include dizziness, headache, somnolence, nausea/vomiting, hallucinations, elevated intracranial pressure, hypertension, and tachycardia. Prolonged use may lead to ulcerative cystitis, while short-term administration can result in transient urinary incontinence.[41] These adverse events exhibit dose-dependent incidence; however, subanesthetic doses often suffice for effective analgesia, with fewer side effects due to esketamine's rapid metabolic clearance. In a study by Zhu et al, intravenous esketamine demonstrated a significantly higher propensity for hallucinations and a non-significant trend toward increased somnolence compared to perineural administration.[18] A meta-analysis by Riddell et al on low-dose ketamine in painful orthopedic surgeries reported inconclusive evidence regarding nausea and hallucination risks.[21] In our study, no severe adverse events were observed. Both groups exhibited mild, self-limiting dizziness and nausea, which remained within clinically acceptable thresholds and did not impede postoperative recovery. One patient in the E-group experienced transient hallucinations, which resolved promptly following targeted intervention. Collectively, esketamine demonstrated a favorable safety profile in this cohort, coupled with robust analgesic efficacy, particularly during the early postoperative period.

Several limitations of this study should be acknowledged. First, no independent dose-finding study was conducted for esketamine in this research. The dosing regimen was primarily designed based on established experience and recommended doses for esketamine as postoperative adjuvant analgesia documented in existing literature. We adopted the upper limit of the commonly reported subanesthetic dose range, which has been demonstrated to be safe and effective. Second, the quantification method for nerve block duration carries potential bias. In this study, nerve block duration was defined as the sum of the time intervals from sensory onset to perceived sensory recovery in the arm, and from perceived sensory recovery to pain recurrence at the surgical site. However, clinical observation revealed that in some patients, ISBPB regression occurred between midnight and early morning. During this period, patients were in deep sleep, where physiological alterations in pain threshold modulated by the sleep-wake cycle could result in the occurrence of pain insufficient to arouse the patient. This phenomenon may lead to an overestimation of the actual block duration.

Conclusion

In conclusion, among patients undergoing arthroscopic rotator cuff repair under combined single-shot interscalene brachial plexus block (ISBPB) and general anesthesia, intravenous administration of esketamine (0.5 mg/kg bolus followed by a continuous infusion at 0.25 mg/kg/h) failed to reduce the incidence of rebound pain (RP) but significantly lowered postoperative pain scores at 8h, 12h, and 24h. Additionally, patients exhibited enhanced hemodynamic stability during anesthetic induction without severe adverse events. Therefore, esketamine serves as a clinically valuable analgesic adjunct, particularly in the context of postoperative pain management.

Data Sharing Statement

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

The protocol received ethical approval from the Ethics Committee of Affiliated Li Huili Hospital of Ningbo University (Approval No. KY2023SL386-01) and was prospectively registered in the Chinese Clinical Trial Registry (Registration No. ChiCTR2400081449) prior to the commencement of patient enrollment.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests in this work.

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