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CLINICAL TRIAL REPORT

Comparison Between Low-Dose Esketamine and Dexmedetomidine on Postoperative Recovery Quality Among Patients Undergoing Humeral Trauma Surgery in Interscalene Brachial Plexus Block: A Randomized, Double-Blind, Controlled Trial

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Purpose: Patients with humeral fracture often suffer from post-traumatic neuropsychiatric sequelae, which can cause immense anxiety or fear and worsen recovery. In this report, we examined the effect of low-dose esketamine versus dexmedetomidine on postsurgical recovery among patients who underwent humerus surgery with interscalene brachial plexus block.

Patients and Methods: In this prospective, randomized, controlled study, 141 patients aged 18 to 65 years who underwent humerus reduction and internal fixation were recruited. Patients were randomly assigned to two groups: esketamine (Group E: received 0.2 mg/kg (i.v.) esketamine administration, with subsequent continuous 0.15mg/kg/h infusion); dexmedetomidine (Group D: received 10-min 0.8μg/kg dexmedetomidine infusion, with 0.4ug/kg/h maintenance infusion). All infusions were terminated at closure of surgical incisions. Our major endpoint was the Quality of Recovery-40 (QoR-40) score on postoperative day 1 (POD-1). The secondary outcomes were QoR-40 POD-3, the intraoperative modified observer's assessment of alert/Sedation (MOAA/S) scores at 5 min (T1) and 10 min (T2) post i.v. administration, at operation initiation (T3), at 10 min interval (T4), 30 min interval (T5) post operation, and at the end of operation (T6), Numeric Rating Scale (NRS) at POD-1, additional postoperative analgesic usage and hospital stays. In addition, we analyzed safety indices, such as hemodynamic profile, postoperative nausea and vomiting, adverse events (AEs) involving the central nervous system.

Results: The QoR-40 scores on POD-1 for Group E were substantially elevated relative to Group D. The T4 and T5 MOAA/S scores of Group D were lower relative to Group E. In comparison to Group E, Group D exhibited reduced T1 and T2 Mean arterial pressure (MAP) and T1-T6 Heart rate (HR). Lastly, we observed no marked alteration in other postsurgical AEs between the two patient cohorts.

Conclusion: Continuous low-dose esketamine infusion seems safely and tolerably, it significantly improves the postoperative recovery quality among patients with ASA I or II receiving elective humeral trauma surgery.

Keywords: esketamine, dexmedetomidine, quality of postoperative recovery, QoR-40, Humeral trauma surgery

Introduction

Traumatic injury is of serious global concern. Emerging evidences revealed that traumatic injury is often accompanied with post-traumatic neuropsychiatric sequelae, namely, anxiety, depression, hyperarousal, sleep disruption, nightmares

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and pain, which severely impact patient postoperative quality of life.[1,2] According to the Global Burden of Disease report completed in 2019, orthopaedic trauma incidences have risen by 70% since 1990s. Following lower limb fractures, upper limb fractures are the second leading form of new fractures,[3] among which humeral fractures are relatively high and are linked to significant postoperative pain requiring multimodal analgesia.[4,5] Orthopedic management is typically done with interscalene brachial plexus block owing to its high efficacy, reduced hospital duration, diminished hospital costs and lack of general anesthesia associated complications.[6] Unfortunately, patients who only received brachial plexus nerve block often experience anxiety and fear.

Emerging evidence revealed that moderate sedation/analgesia usage can elevate patient tolerance during unpleasant or lengthy interventions by alleviating anxiety, discomfort, and pain. According to 2018 American Society of Anesthesiologists (ASA) moderate procedural sedation and analgesia recommendations, dexmedetomidine and esketamine are both effective as intraoperative sedation and analgesia.[7] Dexmedetomidine specifically targets α2-adrenergic receptor and induces sedation and analgesia.[8] One meta-analysis reported that i.v. dexmedetomidine can significantly enhance postoperative quality of life among adult patients.[9] Compared with esketamine, dexmedetomidine has augmented sedation failure, high rates of hypotension and bradycardia.[10,11] In addition, dexmedetomidine has a slower onset (10–15min), while esketamine acts within as little as 30 seconds.[12] More recently, increasing clinical investigations report considerable efficacy and safety of low-dose esketamine. A recent study showed that subanesthetic dose of esketamine (0.15–0.3 mg/kg/h) can improve the sedative and analgesic effects during liposuction surgery.[13] Clinical report showed that intraoperative intravenous esketamine can improve the QoR-40 scores in breast surgery patients.[14] Till date, there are no reports on the potential superiority of esketamine over dexmedetomidine among trauma patients receiving humeral fracture surgery. Herein, we investigated the effects of low-dose esketamine on the early recovery of patients undergoing elective humeral fracture surgery.

Materials and Methods

Research Design and Subjects

This prospective, double-blind, RCT was approved by Xuzhou Central Hospital (XZXY-LK-20231029-0168) and registered with the Chinese Clinical Trial Registry prior to patient recruitment (ChiCTR2300077248). The study adhered to the Declaration of Helsinki and its latter amendments. We also acquired written informed consent from all individuals prior to the initiation of the study. Lastly, this study strictly abided by the Consolidated Standards of Reporting Trials (CONSORT) reporting criteria for RCT.

This investigation was conducted between November 25, 2023, and August 31, 2024, at the Xuzhou Central Hospital, concluding with the final follow-up of the last patient. In total, we examined 141 patients who received elective humeral trauma surgery, between 18 and 65 years of age, with the ASA physical status stratification between I and II (I being healthy patient and II being patient with mild systemic disease). The following patients were excluded from analysis: allergy to any medication used in this study; esketamine contraindications, namely, glaucoma, large vessel aneurysm, and so on; severe cardiopulmonary, hepatic, and renal impairment; cognitive decline or history of psychiatric or neurological disorders; preoperative atrioventricular block or bradycardia; and lastly, refusal to participate in study or fail to complete the questionnaire.

Randomization and Blinding

Eligible participants were randomly assigned in a 1:1 ratio to either the esketamine group (Group E) or the dexmedetomidine group (Group D) using computer generated randomization sequence (Figure 1). To confirm blinding, group allocations were sealed in numbered envelopes, before delivery to an anesthesia nurse who was not linked to the investigation. The anesthesia nurse prepared the study drugs according to group assignment and provided esketamine or dexmedetomidine.

Patients, responsible anesthesiologists and the investigator who was responsible for patient recruitment, data collection, and follow-up assessments were blinded to group assignment. In the event of an emergent situation, such as an unanticipated and precipitous decline in a subject's clinical condition, responsible anesthesiologists are authorized to alter

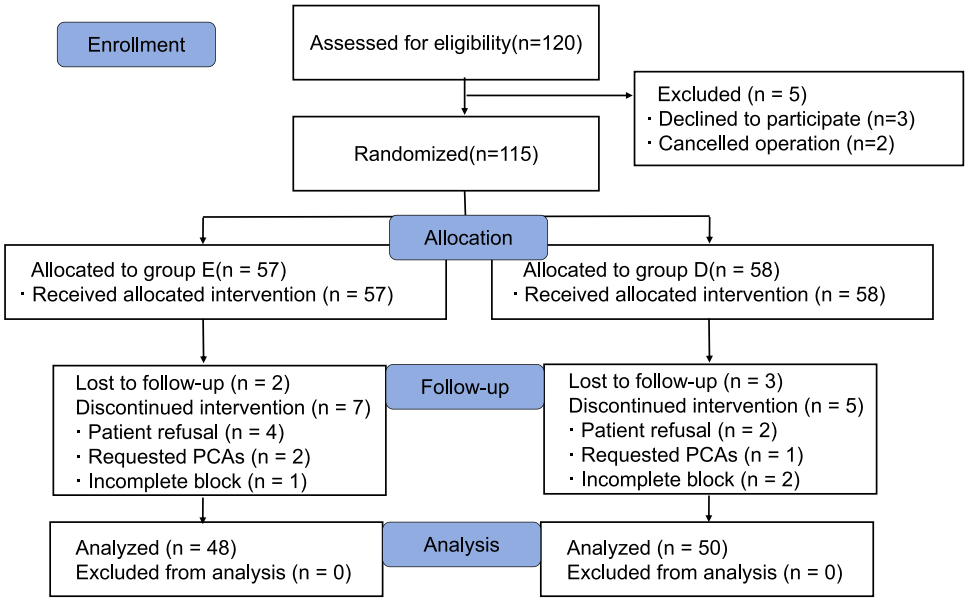

Figure 1 CONSORT illustration depicting the patient selection process. Group E esketamine-treated patients, Group D dexmedetomidine-treated patients.

or cease the administration of the investigational agent. The protocol of blinding may be breached solely in instances where it is demonstrably necessary for clinical management purposes.

Monitoring

Prior to surgery, all patients underwent an 8-h fast from solids and a 2-h fast from clear fluids. Peripheral venous access was established after they entered the operating room. Subsequently, we closely monitored the vital signs via pulse oximetry (SpO2), electrocardiogram (ECG), heart rate (HR), and noninvasive blood pressure (NBP) measurement. Patients received 5 L/min oxygen via face mask.

Anesthesia Protocol

To ensure the consistency of medication administration, both groups received the same administration route. Group E received intravenous injection 0.2mg/kg esketamine diluted to 10 mL, followed by 20 mL normal saline over 10 minutes, and then an infusion of 0.15mg/kg/h esketamine until incision closure. Group D received an injection of 10 mL normal saline, followed by an infusion of 0.8μg/kg dexmedetomidine diluted to 20 mL over 10 minutes, and then an infusion of 0.4ug/kg/h dexmedetomidine until skin closure. All pumps are covered with opaque paper to ensure blindness for other personnel.

An ultrasound-guided interscalene brachial plexus block was conducted following the initial 10-min of i.v. administration. All ultrasound-guided blocks were performed by a team of senior anesthesiologists with extensive experience in regional anesthesia. Patients were laid supine, with their heads turned to the opposite side. After standard sterile preparation, a 3.5 MHz linear array transducer (EDGE® ultrasound machine, Sonosite Inc USA) was used to identify the brachial plexus between the anterior and middle scalene muscles. Under real-time ultrasound guidance, a short-bevel needle (25-gauge, 5 cm) was inserted toward the brachial plexus using in-plane technique with a lateral-to-medial direction. A slight withdrawal confirmed the absence of blood or air, after which 15 mL of 0.5% ropivacaine was administered. The sensory blockade efficacy was assessed using pinprick tests along the musculocutaneous, radial, median, and ulnar distribution at 5 min intervals until an effective blockade, i.e, complete absence of pinprick sensation, was established. In case the patient experienced pain in the surgical location, additional analgesics were introduced or we switched to a different anesthetic method, and the patient was excluded from the study altogether.

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Postoperative Management

Hemodynamic parameters, including NBP, HR, and SpO2 were monitored and documented till surgery termination. Adverse events (AEs) were defined as bradycardia (HR < 50 bpm), hypertension (systolic blood pressure (SBP) >140 mmHg or >20% rise in baseline value), hypotension (SBP < 90 mmHg or a > 20% decline from baseline value) and respiratory depression (pulse oxygen saturation <93% or respiratory rate <8 beats/min), and were provided with i.v. atropine 0.5 mg, urapidil 10–25mg, and ephedrine 5–10 mg, respectively. Patients were given an i.v. administration of 50 mg flurbiprofen during incision closure, and they received i.v. 30 mg ketorolac administration every 8 h for one day postoperation. If the NRS scores ≥4, rescue dose of 5mg oxycodone hydrochloride was given.

Outcome Measurements

The major endpoint was the postoperative day 1 (POD-1) QoR-40 score. The score was based off a questionnaire that evaluated 5 aspects of patient recovery: physical comfort (12 queries), emotional status (9 queries), physical independence (5 queries), psychological support (7 queries), and pain (10 queries). Individual items presented a 5-point rating (1 = none of the time, 2 = some of the time, 3 = usually, 4 = most of the time, 5 = all of the time), and the summation score was between 40 and 200 points. All participants received a detailed description of all questions the day before surgery.

Our secondary endpoint included the POD-3 QoR-40 score, intraoperative hemodynamic alterations, such as, MAP and HR at baseline (T0), 5 min (T1), 10 min (T2) post administration, at operation initiation (T3), 10 min (T4), 30 min (T5) post-operation, and at the end of operation (T6); the intraoperative MOAA/S (A scoring scale used to evaluate a patient's behavioral response to stimulation). The MOAA/S score ranges from 5(fully alert) to 0(completely sedated) Table S1 and NRS scores (A tool used to assess the level of pain). Pain intensity is measured on a scale from 0 to 10, where 0 represents no pain and 10 represents the most intense pain. Figure S1 at POD1; additional postoperative analgesic usage; hospitalization duration; intra- and postoperative AEs, namely, decreased oxygen saturation, respiratory depression, hemodynamic instability, postoperative nausea and vomiting (PONV, Table S2) postoperative shivering, nightmares, hallucination, dizziness and agitation.

Sample Size Calculation and Statistical Analyses

The appropriate sample size was determined in PASS version 15.0 via analysis of the results of our pilot study. The average QoR-40 scores of Groups E and D were 179.1 and 173.0 and the standard deviations (SDs) were 8.37 and 9.76, with an α of 0.05, β of 0.1, and 48 patients were required per cohort. Considering a dropout rate of 20%, we included 120 individuals in this study.

All statistical analyses were conducted using SPSS software version 26.0 and GraphPad Prism version 10.0. For continuous data, the Shapiro–Wilk test and histograms were used to assess the distribution of data. Data with normal distribution were examined via two independent sample *t*-test, and provided as mean ± SD. Variables with non-normal distribution were assessed via the Mann–Whitney U-test and are expressed as median (interquartile range). Lastly, Categorical data were examined via the chi-squared ($\chi 2$) and Fisher's exact tests and are presented as absolute numbers (%). Repeated normally distributed variables (MAP, HR) were examined using analysis of covariance (ANCOVA), baseline MAP and HR used as covariates to more accurately assess the impact of groups on the results. The sphericity was evaluated through Mauchly's test, if violated, the Greenhouse–Geisser correction was employed for degrees of freedom adjustment. Lastly, a generalized estimating equation (GEE) was employed for the analysis of repeated abnormally distributed variables (QoR-40, MOAA/S). Two-tailed *p*-value <0.05 were considered as statistically significance.

Results

Patients Demographics and Clinical Profiles

The study details are summarized in Figure 1. In total, 115 patients who chose to receive elective humeral trauma surgery were recruited in this study. Among them, 98 patients (48 from Group E and 50 from Group D) completed the study, and

17 patients were eliminated from analysis due to the following reasons: 5 were lost to follow-up, 3 requested patient-controlled analgesia (PCA), 6 failed to complete the questionnaire, and 3 received incomplete motor and sensory block.

Preoperative use of analgesic or sedative medications was documented. Patients routinely received 0.3g oral acetaminophen every 8h. If the NRS scores ≥4, they received 50mg tramadol hydrochloride tablet every 6 h. Patients who requested management of poor sleep quality received 0.4mg oral alprazolam. No other differences were present in the baseline characteristics or intraoperative data between the two cohorts (p>0.05) (Table 1).

Recovery Quality (QoR-40) Score Alterations

Alterations in the QoR-40 score over time are summarized in Table 2. We conducted a GEE comparing both patient cohorts in overall QoR-40 on PODs 1 and 3 after correcting the effect of baseline QoR-40 (Table 2). There was an interaction between time and group (p<0.001). The QoR-40 on POD-1 was substantially high among Group E versus D (p<0.001), which indicates a significant improvement in postoperative recovery. The estimated QoR-40 differences on POD-1 between both cohorts was 6.91 (95% CI 4.48,9.35), and no marked difference was evident in QoR-40 on POD 3 (p=0.299). In case of the five dimensions, Group E exhibited marked enhancement in physical comfort and emotional status on POD1 relative to Group D (p<0.001, p=0.014). No substantial difference was found in the remaining dimensional QoR-40 scores (p > 0.05) (Table S3).

Perioperative Hemodynamic Alterations

MAP alterations over the study period are presented in Figure 2a. According to Mauchly's test, we revealed violation of the sphericity assumption (W = 0.084, p<0.001). Thus, we corrected the degrees of freedom using the Greenhouse–

Table 1 Clinical Characteristics and Demographics of Patients

	Group E (n=48)	Group D (n=50)	*P*-value
Sex (M/F)	28/20	27/23	0.666
ASA PS (I/II)	23/25	18/32	0.232
Age (yr)	55.5(48.5–60.0)	55.0(49.0–59)	0.989
BMI (kg/m^2)	24.1±2.6	24.0±2.2	0.937
Surgery time (min)	78.0(72.0–81.5)	75.0(72.0–83)	0.536
Regional block time (min)	13.0(10.0–14.0)	14.0(11.0–15.0)	0.094
Type of surgery			0.722
Proximal humeral fracture	14	12	
Midshaft humeral fracture	25	28	
Distal humeral fracture	11	10	
Preoperative Pain score (NRS; 0–10)	3.0(2.0–3.0)	2.0(1.0–3.0)	0.559
Preoperative medication			
Acetaminophen	48	50	NA
Tramadol hydrochloride	15	18	0.673
Alprazolam	10	8	0.607
Preoperative HADS	5.5(4.0–7.0)	6.0(4.0–7.0)	0.142

Notes: Values are provided as patient number, mean ± SD or median (IQR). Group E: esketamine-treated patients, Group D: dexmedetomidine-treated patients, Surgery time: duration between skin incision to the end of skin suture. Regional block time: duration between skin disinfection to end of drug injection.
Abbreviations: ASA PS, American Society of Anesthesiology physical status; BMI, body mass index; HADS, hospital anxiety and depression scale.

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Table 2 Comparison of QoR-40 Scores Between the Two Patient Cohorts at Varying Time Points

	Preoperative	Postoperative Day 1	Postoperative Day 3
Group E (n=48)	175.0(169.3–179.8)	172.0(168.5,176.8)	183.0(178.0–187.0)
Group D (n=50)	176.0(169.0–179.3)	164.5(161.5,170.0)	181.5(177.0–184.0)
Difference (95% CI)	−0.28(−3.30,2.50)	6.91#(4.48,9.35)#	1.10#(−0.98,3.18)#
Wald χ^2 value	0.010	30.90#	1.10#
p	0.920	*<0.001	0.299

Notes: Data (non-normal distribution) are provided as median (IQR). Group E: esketamine-treated patients, Group D: dexmedetomidine-treated patients, #Analyzed with a generalized estimate equation following baseline QoR-40 adjustment, *$p<0.05$.
Abbreviation: CI confidence interval.

Geisser estimates of sphericity (e). The main effect of the group and the interaction effect between time and patient cohort reached significance (F = 11.39, $p = 0.001$, and F = 38.86, $p<0.001$, respectively). MAP was elevated at T1 and T2 compared to Group D ($p<0.05$).

HR alterations over time are presented in Figure 2b. On the basis of Mauchly's test, we revealed violation of the sphericity assumption (W = 0.095, $p<0.001$). Thus, we corrected the degrees of freedom using the Greenhouse–Geisser estimates of sphericity (e). We uncovered marked significant between time and patient grouping (F = 13.99, $p<0.001$, and F = 74.26, $p<0.001$, respectively). Relative to Group E values, HR was diminished at T1-T6 ($p<0.05$).

Intraoperative MOAA/S Score Alterations

Table 3 reveals intraoperative MOAA/S score alterations. We conducted generalized estimated equation (GEE) to evaluate the T1-T6 MOAA/S scores of both patient cohorts. The estimated T4 and T5 MOAA/S differences were 0.46 (95% CI 0.21, 0.71, $p<0.01$) and 0.91 (95% CI 0.77,1.05, $p<0.01$), respectively. No obvious difference was observed in the MOAA/S score at other time points ($p>0.05$).

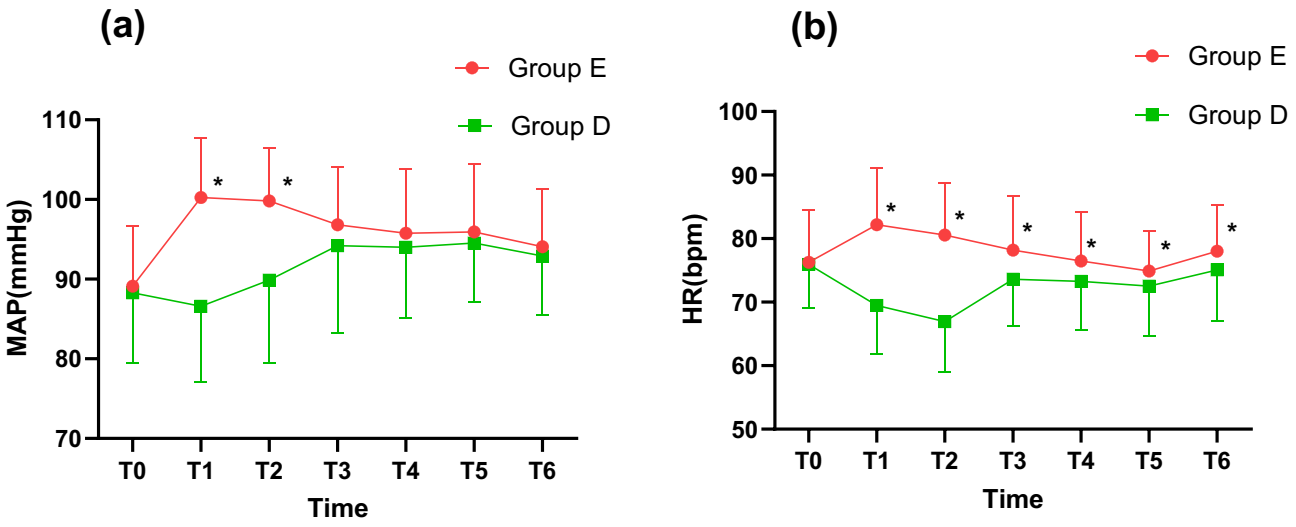

Figure 2 Perioperative hemodynamic parameters. (**a**) MAP alterations, (**b**) HR alterations. Data are provided as mean±standard deviation and data analysis employed ANCOVA. Group E: esketamine-treated patients, Group D: dexmedetomidine-treated patients, T0: baseline, T1: 5 min post i.v. administration, T2: 10 min post i.v. administration, T3: at operation initiation, T4: 10 min post operation, T5: 30 min post operation, T6: at operation termination. *$p < 0.05$.

Table 3 Intraoperative MOAA/S Scores

MOAA/S Scores, Median [IQR]	Group E (n=48)	Group D (n=50)	*P* value
T1	4(4,5)	4(4,5)	0.708
T2	5(4,5)	4.5(4,5)	0.837
T3	5(4,5)	5(4,5)	0.157
T4	5(5,5)	4(3,5)	0.000*
T5	4(4,5)	4(4,4)	0.000*
T6	5(4,5)	5(4,5)	0.136

Notes: T1: 5 mins post i.v. injection, T2: 10 mins post i.v. injection, T3: at operation initiation, T4: 10 min post operation, T5: 30 min post operation, T6: at operation termination. *Represents significance between the two patient cohorts.
Abbreviation: MOAA/S, modified observer's assessment of alert/sedation.

Postoperative Data Assessment

Table 4 list the postoperative data of all participants. In Group E, three subjects experienced nightmares, while one reported dizziness. Their symptoms were temporary and resolved with psychological counseling by the nurse without the use of medication. There were no reports of postoperative shivering, hallucinations or agitation in either group. We also found no marked differences in the PONV and NRS incidences at POD-1, as well as oxycodone hydrochloride usage and hospitalization duration between the two cohorts ($p>0.05$). Furthermore, no significant respiratory AEs were reported in either group post-surgery (Table S4).

Table 4 Postoperative Clinical Information

	Group E (n=48)	Group D (n=50)	*P* value
PONV at POD-1 [n (%)]	2(4.0%)	4(8.0%)	0.678
CNS adverse events			
Postoperative shivering	0	0	NA
Nightmares	3	0	0.243
Hallucination	0	0	NA
Dizziness	1	0	0.490
Agitation	0	0	NA
NRS at POD-1 median [IQR]	4.5(3,5)	4(3,5)	0.865
Oxycodone hydrochloride usage [n (%)]	23(47.9%)	26(52.0%)	0.686
Length of hospital stay (days)	5(4,5)	5(4,5)	0.188

Notes: Data are provided as number (proportion), median (IQR).
Abbreviations: PONV, postoperative nausea and vomiting; CNS, central nervous system; NRS, an 11-point numeric rating scale (0 = no pain, 10 = worst imaginable pain), length of hospital stay: duration between hospital admission and hospital discharge.

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Discussion

Based on our observation, low-dose esketamine (0.2 mg/kg esketamine, with subsequent continuous 0.15mg/kg/h infusion) significantly improved the POD-1 recovery among patients with ASA I or II undergoing elective humeral trauma surgery.

Patients suffering from humeral fracture frequently experience anxiety and pain related to anesthesia and surgery. Procedural sedation and analgesia (PSA), which is aligned with the theory of enhanced Recovery After Surgery (ERAS), is a gold standard practice for alleviating anxiety, discomfort and pain during invasive diagnostic and therapeutic interventions.[15] Being a frequently indicated drug in PSA, the safety and efficacy of esketamine have been reported in multiple investigations.[16,17] Zhu et al[16] demonstrated that 4ug/kg/h esketamine administration partially augmented POD-1 recovery quality among patients undergoing modified radical mastectomy, which is similar to our findings. Lee et al[18] also reported that intraoperative dexmedetomidine enhanced POD-1 QoR among patients undergoing video-guided thoracoscopic surgery. This study found that esketamine is superior to dexmedetomidine in enhancing POD-1 recovery. The estimated QoR-40 difference on POD-1 between the two groups was 6.91 (95% CI 4.48, 9.35), which not only reached statistical significance ($p < 0.05$) but also surpassed the minimal clinically important difference (MCID) threshold of 6.3 points, as reported by Myles et al.[19] Moreover, patients who received esketamine demonstrated significantly better scores in physical comfort and emotional well-being when comparing the five QoR-40 dimensions on POD-1 (Tables 2 and S3).

Physical comfort, which encompasses 12 items, is a critical indicator of postoperative well-being. An elevated physical comfort score on POD-1 reflects effective pain management and suggests a minimal occurrence of adverse effects such as nausea, vomiting, or dizziness. Moreover, it indicates a substantial recovery in appetite and gastrointestinal functions, contributing to overall physical ease.[20] The emotional state score, comprising 9 items, is equally important. A high score in this domain indicates an absence of pronounced anxiety, depression, or emotional lability, highlighting the patients' ability to cope with the stressors of postoperative recovery.[20] The combination of high scores in both physical comfort and emotional state suggests that patients in the esketamine group experienced a high quality of life during their postoperative recovery.[21] This is typically associated with superior clinical outcomes, such as faster discharge, fewer postoperative complications and greater patient satisfaction. The major difference observed in the study may be the specific antidepressant influence of esketamine.[22,23] The underlying mechanism may involve NMDA receptor antagonism, alpha κ and μ opioid receptor (KOR and MOR) antagonism, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) activation, and brain-derived neurotrophic factor (BDNF) upregulation.[23,24]

We also reviewed several pertinent studies examining the impact of varying dosages on postoperative recovery quality. Notably, Xu et al[25] demonstrated that intraoperative intravenous low-dose esketamine (0.25 mg/kg bolus followed by a continuous infusion of 0.12 mg/kg/h) enhanced early postoperative recovery in patients undergoing laparoscopic radical resection of colorectal cancer. Additionally, Zhang et al[26] reported that 0.5 mg/kg/h esketamine infusion improved the quality of postoperative recovery and reduced pain on POD-1. Moreover, the combination of 0.2 mg/kg esketamine with dexmedetomidine was found to be safe for lung tumor percutaneous radiofrequency ablation, offering fewer hemodynamic disturbances, milder respiratory depression, shorter recovery times, and higher radiologist satisfaction due to better sedation depth control.[27] These studies provide valuable insights and reinforce our findings that intravenously administered low-dose esketamine significantly enhances early quality of recovery (QoR) in patients undergoing elective humeral trauma surgery. According to the 9th edition of Miller's Anesthesia,[28] for general anesthesia with esketamine, the minimum required blood concentration had ranged from 0.3 to 1.0 mg/L; however, a blood concentration of ≥0.05 mg/L was sufficient to elevate the pain threshold. The pharmacokinetic characteristics of esketamine in the Chinese population indicated an average half-life of roughly 4 hours, a distribution volume between 5 and 10 L/kg, and a clearance rate (Cl) of approximately 1.08 L/kg/h.[29] In our study, we administered an initial dose of 0.2 mg/kg of esketamine, followed by a continuous infusion at 0.15 mg/kg/h. Given the average weight of patients in the esketamine group was 69.8 kilograms, the steady-state plasma concentration (Css) was calculated using the formula Css = R/Cl, with Cl estimated at around 1.08 L/kg/h and R being the infusion rate, resulting in a Css of 0.139 mg/L in our study. Our pharmacokinetic analysis confirmed that the achieved C□ (0.027 mg/L) was below the typical therapeutic range of 0.3–1.0 mg/L for general anesthesia, indicating a potential underdosing during induction. We observed enhanced

QoR-40 scores on postoperative day 1, even at this subanesthetic concentration, suggesting potential clinical benefits at lower doses.

Herein, we revealed that HR and MAP were strongly different between the two patient cohorts (Figure 2). Earlier reports suggest that esketamine stimulates the cardiovascular system in a concentration-reliant fashion via its sympathomimetic pathway.[30,31] A study by Zhou et al[32] demonstrated that esketamine upregulated MAP values relative to placebo before and after skin incision. Likewise, we demonstrated that Group E produced elevated T1 and T2 MAP, which remained within 20% of the basal blood pressure relative to Group D. Dexmedetomidine is a robust anesthetic, particularly when combined with a regional nerve block. Its many advantages are preserving airway reflexes, expanding tracheal smooth muscles, and inhibiting the cough response without inducing respiratory depression.[33] Unfortunately, the sympathetic inhibition of dexmedetomidine greatly increases the chances of bradycardia and hypotension.[34,35] Similar to earlier reports,[36] we demonstrated that dexmedetomidine-treated patients had reduced T1-T6 HR relative to esketamine-treated patients. Based on this evidence, low-dose esketamine infusion is potentially effective in stabilizing the intraoperative hemodynamic status.

Recent reports reveal that dexmedetomidine-mediated sedation is very potent among older patients.[12] Herein, we demonstrated that dexmedetomidine significantly reduced the MOAA/S scores in T4 and T5 relative to esketamine, indicating that dexmedetomidine also produces deeper sedation among younger patients. Our data corroborated the data from the Hansol Kim et al study.[37] Notably, although we referred to prior investigations[18,38] and employed a reduced dexmedetomidine dose, we still achieved deeper sedation in Group D, which raises the necessity of additional future discussions on the appropriate and optimal dexmedetomidine dose for clinical use.

Lastly, we observed no obvious alterations in PONV, CNS AEs, or hospitalization duration between the two patient cohorts. Earlier reports suggested that ketamine use is often restricted due to associated AEs of the CNS.[39] In this report, we found no difference in neurological side effects between the two cohorts. One reason is that, esketamine is reported to induce lesser psychotomimetic influences, relative to the racemic mixture and R-isomer.[40] The other is that participants of the current study were administered low-dose esketamine, which has been safely employed in many clinical trials.[41]

This study has several limitations. First, we did not monitor circulating esketamine content. Second, we focused on elective surgical patients with no comorbidities (ASA I–II) and included only a 3-day follow-up, which limits the generalizability of our results and the ability to assess long-term effects. Further research is needed to evaluate esketamine use in elderly patients to confirm the applicability of our findings. Future studies will aim to conduct larger, more diverse trials that build on the current work. Third, the optimal dosage and medication route of esketamine requires further clarification. Although our proposed dosage showed efficacy, it is potentially sub-optimal. Lastly, our sample population was relatively small, and study was conducted at a single-center. Hence, we warrant further multi-center and large population-based studies to validate our findings.

Conclusion

Intravenously administered low-dose esketamine is safe and well tolerated in humeral surgery, it can significantly enhance early QoR among patients with ASA I or II undergoing elective humeral trauma surgery.

Date Sharing Statement

All data generated or analyzed during this study were included in the published article. Further inquiries about the datasets can be directed to the corresponding author on reasonable request. Any information we share will be deidentified.

Ethic Approval and Informed Consent

This study strictly abided by the CONSORT reporting criteria for RCT. The study was ethically endorsed by the Xuzhou Central Hospital (XZXY-LK-20231029-0168) and registered at the Chinese Clinical Trial Registry (ChiCTR2300077248). All subjects provided written informed consent prior to the initiation of the study.

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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 report no conflicts of interest in this work.

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