Effects of Small-Dose Esketamine on Postoperative Analgaesia and Sleep Quality in Patients with Total Hip Replacement

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ABSTRACT

Objective: To determine the effect of esketamine in patient-controlled analgaesia after hip replacement on postoperative pain and improve sleep quality in patients.

Study Design: Randomised double-blind study.

Place and Duration of the Study: Department of Anaesthesiology, The First Affiliated Hospital of Guangxi Medical University, from March 2021 to May 2022.

Methodology: The research enrolled 72 patients who were subjected to unilateral complete hip replacement surgery utilising jointly administered universal and peripheral nerve-obstructing anaesthetics. A randomised numeric table method was used to allocate patients to either the F-D group (fentanyl combined with dexmedetomidine, n = 34) or the Es-D group (esketamine combined with dexmedetomidine, n = 38). The key outcome indicators included the time to first administration of rescue analgaesic, the dose of rescue analgaesics, and postoperative sleep quality.

Results: Baseline characteristics did not differ between the two groups. The time until postoperative analgaesic rescue medication was considerably shorter for those in the Es-D group ($p < 0.05$). In addition, the Es-D group used significantly fewer rescue analgaesics ($p = 0.01$). The PSQI score and unpleasant responses (PONV, dizziness, nightmare) did not significantly differ between the two groups ($p < 0.05$). Nevertheless, urine retention occurred in four patients in group F-D but not in group Es-D ($p < 0.05$).

Conclusion: Esketamine produced better analgaesia than fentanyl with fewer side effects after surgery. However, no improvement was observed in sleep quality.

Key Words: *Arthroplasty, Postoperative analgaesia, Esketamine, Sleep quality, Patient-controlled analgaesia.*

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INTRODUCTION

Around half of the patients undergoing total hip arthroplasty report experiencing intermediate-to-intense degrees of post-operative pain, which may lead to movement restrictions and sleep disturbances for the patient in the early stages of recovery. Moreover, prolonged lying down significantly increases the risk of deep vein thrombosis and fatal cardiovascular events such as pulmonary embolism.[1] While opioids are extensively employed to treat acute pain because of their extremely effective pain-relieving properties, they are also associated with various adverse effects, including but not limited to nausea, vomiing, dizziness, and urinary retention.[2] Thus, opioid-free postoperative analgaesia has gained popularity as a substitute.

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Ketamine, having been used for ages as an anaesthesia and analgaesic, has recently gained widespread interest in pain treatments. Research has proven that small doses of ketamine are able to reduce acute pain by inhibiting both NMDA and non-NMDA receptors, with fewer side effects.[3] In addition, it has also been proven to lessen opioid tolerance and diminish hyperalgaesia. In co-administration with opioids for analgesia, ketamine allows a lower opioid dosage while improving analgaesia and significantly reducing the side effects associated with opioids.[4]

Currently, esketamine is mainly used for anxiety and depression,[5] with little knowledge of its application in perioperative analgaesia. The introduction of esketamine in patient-controlled analgaesia was hypothesised to decrease the dose of adjunctive analgaesics and improve sleep quality without increasing the side effects. The study was conducted to determine the pain-relieving effectiveness of esketamine in patients with total joint arthroplasty.

METHODOLOGY

A randomised, double-blind prospective study was conducted between March 2021 and May 2022 in the Department of Anaes-

thesiology at the First Affiliated Hospital of Guangxi Medical University, China. GPower 3.1 was utilised to calculate the required sample size. The minimum sample size was determined to be 70 (one-tailed, effect size d = 0.8, α = 0.05, 1-β = 0.95). The study was approved by the First Affiliated Hospital of Guangxi Medical University's Clinical Ethics Committee (2021, KY-E-001). The study was registered with the Chinese Clinical Trials Registry (Registration Code: ChiCTR2100043649). Individuals between the ages of 18 and 70 years who were scheduled to have selective arthroplasty of the hip were enrolled. Exclusion criteria were bilateral total hip replacement, reoperation, major organ disease, including heart disease, hepatic and renal failure. Patients with severe psychiatric disorders, insomnia, or contraindications to medications such as propofol, esketamine, and lidocaine were also excluded. Additionally, patients addicted to opioids or taking long-term opioids for pain were also excluded. Prior to the induction of general anaesthesia, all patients underwent an iliac fascia block and a lateral femoral cutaneous nerve block. All patients received PCA device training and Pittsburgh Sleep Quality Index (PSQI) education. The validated Chinese version of the PSQI questionnaire was used to assess preoperative sleep quality.[6] The PSQI is an anonymous survey with 19 items that rate the quality of sleep of the patients. The total number ranges from 0 (best sleep quality) to 21 (worst sleep quality).[7]

All patients had standard ECGs, non-invasive BP, pulse oximetry, and bispectral index monitoring across the whole perioperative period. Anaesthesia was induced using propofol (2.5–3.5 ug/ml), remifentanil (2.5–3.5 ng/ml), and cisatracurium (0.2–0.3 mg/kg). TCI anaesthesia (isoproterenol 2.5 ~ 3.0 ug/ml and remifentanil 2.5 ~ 3.5 ng/ml) was used to maintain anaesthesia. If the patient had a VAS ≥4 in the recovery room, 1 mg/kg of tramadol was given intravenously.

Postoperative patient-controlled analgaesia was given to all participants. Fentanyl 0.7g (14 ug/h), dexmedetomidine (100 ug), and tropisetron (10 mg) were diluted to 150 ml with 0.9% saline for the F-D group. Esketamine 100mg (2 mg/h), dexmedetomidine 100 mg, and tropisetron 10 mg were diluted in 150 ml of 0.9% sodium for the Es-D group. PCA settings were adjusted for a background dosage of 3 ml per hour, a single 3 ml treatment, and a 30-minute hold. All patients received 0.2 g of celecoxib (twice daily) to reduce pain and an ice pack at the site of the surgery. Individuals with pain (VAS score ≥4) received intramuscular tramadol 50–100 mg to alleviate pain. In this study, 10 mg of i.v. Morphine was considered equivalent to 100 mg of i.v. Tramadol.

The statistical analyses were done using SPSS 26.0 (SPSS, Inc., Chicago, Illinois, USA). The Kolmogorov-Smirnov test determined data normality. In addition, a Student's t-test or Wilcoxon Signed-Rank test was performed for continuous variables. Results were reported as mean ± standard deviation (SD) using an Independent student's t-test for normally distributed data. The non-normally distributed data were compared with Mann-Whitney U test, medians, and IQRs. Comparisons between groups were made using the non-parametric rank-sum test. Counts were provided as numbers (n) and percentages (%). A 0.05 significance level was used for each hypothesis.

RESULTS

The trial included 77 patients, two of whom declined, one patient dropped out mid-study, and two patients failed inclusion criteria, leaving 72 patients for final enrolment.

Table I describes patient demographics and baseline variables. The two groups did not show any notable disparities in terms of patient demographics and baseline data. Table II depicts the postoperative data including VAS score, cumulative dose of analgaesics, PSQI score, and adverse events.

DISCUSSION

This randomised controlled trial demonstrated superior analgaesia with esketamine compared with fentanyl, with clinically and statistically significant differences between groups. Poor pain management has been linked to increased rates of postoperative complications, delayed ambulation, and persistent pain.[8]

Table I: Patient demographics and baseline variables.

Variables	Group Es-D n= 38 (52.8%)	Group F-D n = 34 (47.2%)	p-value°
Male / Female, n	27/11	24/10	0.96
Age (year)	54 (46, 63)	51 (39, 61)	0.40
BMI (kg/m²)	23.5 ± 3.1	23.1 ± 3.6	0.57
ASA (II/III/IV)	3 /33 /2	3 / 28 / 3	0.13
Blood loss (ml)	200 (100, 200)	200 (100, 250)	0.55
Length of surgery (min)	88 (67, 110)	76 (68, 98)	0.25
Length of anaesthesia (min)	131 (112, 160)	125 (103, 140)	0.16
Extubation time from surgery end (min)	26 (18, 32)	28 (16, 34)	0.59
Propofol cumulative dosage (mg/(kg·h)	5.1 ± 1.1	5.2 ± 1.11	0.44
Remifentanil cumulative dosage (ug/(kg·h)	5.1 ± 1.3	5.7 ± 1.8	0.1
Baseline measurements			
SpO_2 (%)	99 (98, 99)	99 (98, 100)	0.62
Heart rate	72 (65, 79)	75 (67, 83)	0.6
MAP (mmHg)	97 (86, 109)	100 (96, 113)	0.17
LOS, days	4 (3, 5)	4 (3, 4)	0.06

°Chi-square or Fisher's exact test (categorical variables), t-test (continuous variables), Wilcoxon rank-sum test. Values are presented as median [IQR], mean ± SD or n (%). ASA: American Society of Anaesthesiologists, BMI: Body mass index, MAP: Mean arterial pressure, LOS: Length of hospital stay after surgery.

Table II: Postoperative data on pair score, analgaesia, and adverse events.

Variables	Group Es-D n = 38 (52.8%)	Group F-D n = 34 (47.2%)	p-value[o]
VAS*			
Within 24h, resting	1 (0, 2)	2 (1, 3)	0.08
Within 24h, moving	2 (1, 4)	4 (3, 5)	0.001*
Within 24h-48h, resting	2 (0, 3)	3 (2, 4)	0.018*
Within 24h-48h, moving	3 (2, 4)	4 (3, 5)	0.017*
First-time analgaesic use (h)	21 (10, 33)	11 (8, 23)	0.04*
Cumulative dose of analgaesics			
Morphine equivalent within 48 hours (mg)	5 (0, 15)	10 (10, 25)	0.01*
0~24h (mg)	5 (0, 10)	10 (5, 12.8)	0.02*
24~48h (mg)	5 (0, 10)	7.5 (5, 10)	0.03*
PSQI score**			
Before surgery	7 (4, 9)	6 (4, 9)	0.58
After surgery			
0~24	11 (6, 13)	8 (4, 11)	0.08
24~48h	9 (5, 12)	7 (3,10)	0.1
Adverse events			
PONV	6 (15.7%)	8 (14.7%)	0.40
Dizzy	8 (21%)	4 (12.5%)	0.29
Urine retention	0	4 (12.5%)	0.03*
Nightmare	4 (10.5%)	6 (18.7%)	0.38
LOS[$], days	4 (3, 5)	4 (3, 4)	0.06

*[o]Chi-square or Fisher's exact test (categorical variables), t-test (continuous variables), Wilcoxon rank-sum test. The data points are n (percent) or the median n-inter-quartile range. *VAS: VAS (Visual Analogue Scale) is an 11-point scale with 0 being no pain and 10 being severe.**PSQI: Pittsburgh sleep quality index scores range from 0 (best sleep) to 21 (worst sleep)*: p <0.05. Tramadol converted to i.v. morphine equivalent: morphine (i.v.) 10 mg = tramadol 100mg (i.v.). LOS[$]: Length of hospital stay after surgery.*

Multimodal pain management is effective in relieving postoperative pain and reducing the frequency of acute pain becoming chronic.[9] Postoperative patient-controlled analgaesia (PCA) combined with peripheral nerve block or wound infiltrate and ice compress has demonstrated the highest efficacy in alleviating pain and speeding recovery in joint replacement patients.[10] Ultrasound-guided fascia iliaca block proved effective in blocking nociceptive transmission of femoral and obturator nerves and reducing perioperative pain in patients undergoing hip surgery.[11] In this study, all patients were subjected to a supra-inguinal fascia iliaca compartment block prior to surgery. They also received lateral femoral cutaneous nerve blocks to minimise incisional pain. Postoperatively, PCA was provided for synergistic analgaesic effects.

Opioids are a classic analgaesic effective in relieving pain but are often associated with undesirable effects such as nausea, vomiting, and urinary obstruction.[12] Esketamine, a strong analgaesic produced from ketamine, is regarded as a potential alternative for controlling pain during the perioperative period. Multiple studies have documented the rising utilisation of ketamine for perioperative pain management owing to its excellent analgaesic properties.[13] Low-dose esketamine was found to be effective in relieving the symptoms of people with complex regional pain syndrome.[14] In accordance with previous findings, the results of this study revealed a significantly longer duration until the first use of rescue analgaesia in the low-dose esketamine group (median 21 hours, IQR 10-34 hours) compared to the fentanyl group (median 11 hours, IQR 8-23 hours). These findings indicate the substantial analgaesic efficacy of subanaesthetic-dose esketamine in reducing postoperative opioid requirements. The present study confirmed the superiority of esketamine over fentanyl, as both groups of patients received a uniform regimen of multimodal analgaesia. In a prospective study of the management of pain in patients following scoliosis surgery, Zhang *et al*. reported that small doses of esketamine safely enhanced pain relief.[15] Additionally, Brinck *et al*. examined analgaesic approaches after lumbar fusion surgery, revealing that a continuous esketamine infusion reduced postoperative oxycodone consumption without significant adverse reactions.[16] At present, esketamine's analgaesic mechanism is not clear. Studies suggest that s-ketamine acts analgaesically by antagonising NMDA receptors.[17] Central sensitisation is an activation of NMDAs that causes spontaneous pain and allodynia.[18] Nevertheless, ketamine's analgaesia mechanism requires additional research in reliable animal investigations.

Sleeping is an essential part of the brain's operation. Getting to sleep well has been shown to enhance memory recalling, learning capacity, attention, creativity, and physical recuperation.[19] Ketamine acts as an antidepressant, anxiolyte, and circadian regulator, helping to extend deep sleep and ameliorate perioperative sleep disturbances.[20] In a recent study on analgaesia after scoliosis surgery, Zhang *et al*. revealed that the adjuvant use of small dosages of esketamine and dexmedetomidine promoted subjective sleep quality in patients undergoing this procedure.[15] The present study evaluated the preoperative and postoperative sleep scores in both groups to determine whether esketamine could improve sleep. However, the sleep scores demonstrated no significant differences between both groups. Sleep is likely affected by numerous factors, including pain, environment, hormones, personality, anaesthetic agents, surgical trauma, and lifestyle habits. As such, additional research controlling for these potential confoun-

ders is warranted to further investigate the sleep-promoting effects of esketamine.

CONCLUSION

Subanaesthetic-dose esketamine significantly reduced postoperative analgaesic requirements without increasing adverse events. However, this approach provided no beneficial effects on sleep quality.

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ETHICAL APPROVAL:
Ethical approval was obtained from the Ethics Committee of the First Affiliated Hospital of Guangxi Medical University (2021) (KY-E-001). All procedures were performed according to local guidelines and regulations of Guangxi Medical University First Affiliated Hospital.

PATIENTS' CONSENT:
Informed and written consent was obtained from all the participants included in the study.

COMPETING INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
QW: Conception and design of the work, and writing of the original draft.
SF: Analysis and interpretation of data for the work.
WD: Critical revision of the manuscript for important intellectual content.
CXL: Writing and proofreading, editing, and supervision.
WZH: Agreement to be accountable for all aspects of the work.
All authors approved the final version of the manuscript to be published.

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