Effects of Esketamine on Haemodynamics and Inflammatory Stress Response in Elderly Patients Undergoing Proximal Femoral Surgery

Xuandong Jia, Xingzhi Liao and Maitao Zhou

Department of Anaesthesiology, The 904th Hospital of the Joint Logistic Support Force of PLA, Wuxi, China

ABSTRACT

Objective: To determine the effects of esketamine combined with iliac fascia block on haemodynamics and inflammatory stress response in elderly patients undergoing proximal femoral nail anti-rotation (PFNA) surgery.

Study Design: A single-centre randomised controlled trial.

Place and Duration of the Study: Deparment of Anaesthesiology, the 904th Hospital of the Joint Logistic Support Force of PLA, Wuxi, Jiangsu Province, China, from January to December 2023.

Methodology: Eighty elderly patients undergoing PFNA surgery in the authors' hospital were selected as the research objects, regardless of gender, aged >65 years, with a body mass index (BMI) of 18-28 kg/m^2, and the American Society of Anaesthesiologists (ASA) scores of II-III. Eighty elderly patients were randomly divided into the following two groups: The observation group (esketamine combined iliac fascia block) and the control group (remifentanil combined iliac fascia block). Heart rate (HR), mean arterial pressure (MAP), and pulse oxygen saturation (SpO_2) were recorded at entry (T0), incision (T1), 15 minutes after incision (T2), and at the completion of surgery (T3). Before and 24 hours after surgery, interleukin-6 (IL-6) and C-reactive protein (CRP) were measured. Recovery quality was recorded 24 hours after surgery. The patients' anaesthesia-effect on adverse reactions were recorded during and after surgery.

Results: There was a significant difference between the two groups in the following indices: HR, MAP, and SpO_2 at T1 ($p < 0.05$). The values of IL-6 and CRP in the control group were prominently higher than those in the observation group 24 hours after surgery ($p < 0.05$). The quality of recovery-15 (QoR-15) score of the control group was prominently lower than that of the observation group. The total incidence of adverse reactions of the control group was prominently higher than that of the observation group ($p < 0.05$).

Conclusion: Implementing an anaesthesia regimen of esketamine combined with iliac fascia block for elderly patients undergoing PFNA surgery can help maintain haemodynamic stability and suppress the inflammatory stress responses.

Key Words: *Esketamine, Iliac fascia block, Internal fixation with anti-rotation intramedullary nails in the proximal femur, Haemodynamics, Inflammatory stress response.*

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INTRODUCTION

Femoral intertrochanteric fractures are more common in the elderly and can cause significant psychological and physical harm to patients. Proximal femoral nail anti-rotation (PFNA) surgery is often used for treatment.[1-4] In most elderly patients, the degradation of organ function and the presence of comorbidities reduce their circulatory compensatory ability, lowering their tolerance to surgery and anaesthesia. Consequently, they are prone to severe haemodynamic fluctuations during the perioperative period, resulting in stress states such as pain stimulation and inflammatory reactions, which are not conducive to the smooth progress of surgery and postoperative recovery. Therefore, it is advisable to choose safe and effective anaesthetic medicines and anaesthesia plans that have minimal impact on haemodynamics and inflammatory stress reactions.[5,6]

Esketamine, as an intravenous anaesthetic with sedative and analgesic effects, as well as anti-inflammatory and anti-stress effects, can be combined with iliac fascia block for the elderly patients undergoing PFNA surgery, fully leveraging the advantages of both anaesthetic medicines and anaesthesia regimens.[7,8] At present, there are few reports on the application of esketamine in elderly patients undergoing PFNA surgery in China. The application of esketamine combined with iliac fascia block anaesthesia in the elderly patients undergoing PFNA surgery is a new exploration. Therefore, this study was

Correspondence to: Dr. Xuandong Jia, Department of Anaesthesiology, The 904th Hospital of the Joint Logistic Support Force of PLA, Wuxi, China
E-mail: jiaxuandong01@163.com

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conducted to determine the effects of esketamine combined with iliac fascia block on haemodynamics and inflammatory stress response in elderly patients undergoing PFNA surgery.

METHODOLOGY

After obtaining approval from the Ethics Committee of the 904th hospital (Approval No. 2022-12-016) and informed consent from the patients, 80 elderly patients were selected as the research objects of this trial undergoing PFNA surgery at the 904th Hospital of the Joint Logistic Support Force of PLA, Wuxi, China, from January to December 2023, according to inclusion criteria and exclusion criteria. Inclusion criteria were as follows: Patients must be over 65 years of age with no gender restriction. ASA score of patients must be level II or III, the body mass index (BMI) of patients should be between 18 and 28 kg/m^2, and patients should be willing to actively cooperate with elective surgery. Exclusion criteria were patients with cognitive impairment, neurological or psychiatric disorders, concomitant coronary heart disease, hyperthyroidism, glaucoma, uncontrolled hypertension, severe respiratory diseases and liver and kidney dysfunction, allergies or addiction to esketamine and propofol, and other surgical contraindications.

Eighty patients were randomly divided into the observation group (the esketamine combined iliac fascia block group) and the control group (the remifentanil combined iliac fascia block group) in a 1:1 ratio using a random number table method. To ensure patient safety during surgery, anaesthesiologists were aware of the patient grouping, but patients and surgeons were blinded to the patient grouping. Both groups of patients were routinely prohibited from drinking or eating. After entering the room, the venous channel was established, nasal cannula oxygen inhalation was performed at a rate of 2L/min and MAP, HR, and SpO_2 were routinely monitored. Under vascular method (ultrasound-guided iliac fascia space block), a mixture of 30ml 0.375% ropivacaine hydrochloride and 0.5 μ g/kg dose of dexmedetomidine was injected and invasive arterial monitoring and Bis monitoring were performed. The observation group maintained 0.3 mg/kgh of esketamine (Jiangsu Hengrui Pharmaceutical Co., Ltd., batch number: H20193336) and 2-4 mg/kgh of propofol (Yangzijiang Pharmaceutical Group Co., Ltd., batch number: H20213012) with a micropump. Before surgical incision, 0.3 mg/kg of esketamine was slowly administered intravenously. Depending on the patients' pain stimulation response, 0.25 mg/kg of esketamine could be added in a single dose. The control group used a micro-injection pump (brand: Wiley Ark) to inject anaesthetic medicine. The device consists of a controller, actuator, and syringe, which can accurately calculate the dosage based on the patients' weight, height, and so on, increasing the safety and effective concentration of medication for patients. The specific method to achieve the target concentration is as follows: The control group used a micro-injection pump to inject remifentanil (Yichang Renfu Pharmaceutical, batch number: H20030199) and propofol with the plasma medicine concentration as the target medicine concentration. After fixing the syringe equipped with 10 mg/ml remifentanil and 10 μ g/ml propofol on the micropump, the Minto model and Marsh model were selected in TCI mode. The infusion rate was automatically calculated based on the patients' age, height, and weight through the target-controlled infusion system. At first, 2.5-4.5 ng/ml remifentanil and 2-3 μ g/ml propofol were loaded. When the eyelash reflex disappeared and the BIS value of anaesthesia depth fell below 60, the target-controlled concentrations of 2-4 ng/ml remifentanil and 1-2 μ g/ml propofol were maintained. A laryngeal mask was placed and the anaesthesia machine was set to autonomous breathing mode. If respiratory depression occurs, the anaesthesia machine should be set to controlled-breathing mode. The BIS value was maintained at 40-60 during the surgery. When the blood pressure of patient was 20 percent lower than the preoperative baseline value, vasoactive medicines such as ephedrine or hydroxylamine were administered. After surgery, patients of both groups showed a visual analogue score (VAS score >5) and were given ketorolac tromethamine 15-30 mg for pain relief.

The haemodynamic changes were recorded, including HR, MAP, and SpO_2, at the time of entry (T0), incision (T1), 15 minutes after incision (T2), and at the completion of the surgery (T3). The surgical stress responses and inflammatory responses of patients were recorded, including IL-6 and CRP levels before and 24 hours after surgery. Five mL of venous blood from patients before and 24 hours after surgery was collected and centrifuged at 4000 r/min for 10 minutes to obtain serum. Enzyme-linked immunosorbent assay was used to measure CRP in serum, and flow cytometry was used to measure IL-6 levels. The quality of recovery (QoR-15) score 24 hours after surgery was recorded.[5] The anaesthesia effect of the patient was evaluated. The evaluation criteria for anaesthesia effects were divided into excellent (no body movement during surgery and no additional analgesics required); good (experienced body movements during surgery and the addition of a small amount of analgesia, did not affect the completion of the surgery); and poor (a significant body movements during surgery, additional analgesic agent were ineffective, anaesthesia methods needed to be changed). Total effective rate = [(excellent + good) / (total)] x 100%.[9,10] The occurrence of adverse reactions such as respiratory depression, hypotension, postoperative dizziness, and delirium were observed.

The SPSS version 22.0 software was used to complete the statistical data analysis. Mean value combined with standard deviation ($\bar{x}\pm s$) was the representation of measurement data. The number of cases (%) represented the counting data. In this study, t-test and χ^2 test were used to analyse the statistical result. A value of $p < 0.05$ was considered statistically significant.

RESULTS

In the observation group, patients were aged between 65 and 95 years, the BMI values of patients ranged from 17.8 to 26.3 kg/m^2. Twenty-three patients were males, 17 were females, 8 patients were at the level II of ASA and 32 patients were at the level III of ASA. In the control group, patients were aged between 65 and 92 years, the BMI values of patients ranged from 17.3 to 25.8 kg/m^2.

Table I: Comparison of HR, MAP, and SpO_2 between the two groups.

Group	Index	T0	T1	T2	T3
Observation group	HR (times / min)	81.88 ± 12.02	78.55 ± 10.89 [b]	77.53 ± 11.83	80.65 ± 15.32
Control group		78.05 ± 13.29 [a]	70.30 ± 12.60 [a,b]	75.33 ± 12.59	78.20 ± 13.67
t		1.350	3.133	0.806	0.755
p-value		0.181	0.002	0.423	0.453
Observation group	MAP / mmHg	90.13 ± 11.77	88.50 ± 9.94 [b]	89.95 ± 10.24	92.93 ± 9.17
Control group		89.83 ± 15.16 [a]	82.85 ± 12.64 [a,b]	87.28 ± 10.87	91.95 ± 12.32
t		0.099	2.221	0.709	0.401
p-value		0.922	0.029	0.480	0.689
Observation group	SpO_2 / (%)	95.85 ± 2.63	99.30 ± 0.65 [b]	99.78 ± 0.42	99.80 ± 0.52
Control group		95.78 ± 2.38 [a]	91.05 ± 3.38 [a,b]	99.90 ± 0.30	99.70 ± 0.46
t		0.134	15.155	-1.518	0.911
p-value		0.894	<0.001	0.133	0.365

The superscript a indicates that the comparison between T0 time and other time points within the same group is p <0.05. The superscript b indicates that the comparison between the observation group and the control group at each time point is p <0.05. T-test was used to compare HR, MAP, and SpO_2.

Table II: Comparison of IL-6, CRP levels, and QoR-15 scores between two groups.

Group	IL-6 level / (pg/ml)		CRP level / (mg/L)		QoR-15 / Score (points)
	Preoperative	Postoperative 24 hours	Preoperative	Postoperative 24 hours	Postoperative 24 hours
Observation group	23.17 ± 5.01	31.84 ± 4.24	41.29 ± 10.98	49.28 ± 10.61	140.30 ± 4.77
Control group	21.94 ± 5.26	41.16 ± 4.79	39.30 ± 11.24	56.94 ± 10.56	124.13 ± 7.64
T	1.064	-9.212	0.800	-3.237	11.360
p-value	0.291	<0.001	0.426	0.002	<0.001

Note: t-test was used to compare IL-6, CRP, and QoR-15.

Twenty-five patients were males, 15 were females, 9 patients were at the level II of ASA and 31 patients were at the level III of ASA. There were no significant differences in age, BMI, gender, and ASA scores between the two groups (p >0.05).

Haemodynamic indicators were quantitative data, represented by mean and standard deviation ($\bar{x}\pm s$). There was no statistical difference among the observation group in the following indices: HR, MAP, and SpO_2 at T0, T1, T2, or T3 (p >0.05). The differences in the above indices among the control group were statistically prominent between T1 and T0 (p <0.05). There was a prominent difference between the observation group and the control group in the following indices: HR, MAP, and SpO_2 at T1 (p <0.05). There was no statistically prominent difference between the observation group and the control group at other times (p >0.05). The detailed results are shown in Table I.

Both inflammatory stress response indicators and QoR-15 score were quantitative data, represented by mean and standard deviation ($\bar{x}\pm s$). There was no statistically prominent difference in

IL-6 and CRP indicators between the observation group and the control group before surgery (p >0.05). The values of IL-6 and CRP in the control group were prominently higher than those in the observation group 24 hours after surgery (p <0.05) and the QoR-15 score of the control group was prominently lower than that of the observation group. The detailed results are shown in Table II.

The anaesthesia effect and incidence of adverse reactions are count data, expressed as n (%). The χ^2 test was used to analyse count data. The total effective rate of anaesthetic effect in both the observation group and the control group was 100% and no evaluation result was poor. Thirty-five (87.5%) cases in the observation group had excellent anaesthesia effects, while 21 (52.5%) cases in the control group had excellent anaesthesia effects. The difference in excellent anaesthetic effect between the two groups was statistically significant (p <0.05), and the difference of good anaesthetic effect between the two groups was statistically significant (p <0.05). There was no difference in respiratory depression 0 (0.0%) *vs*. 3 (7.5%, p = 0.077), postoperative dizziness 1 (2.5%) *vs*. 0 (0.0%, p = 0.314), and delirium (0 (0.0%) *vs*. 2 (5.0%), p = 0.152) between the two groups. However, the difference in the incidence of intraoperative hypotension 0 (0.0%) *vs*. 4 (10.0%, p = 0.040) between the two groups was statistically significant (p <0.05). The overall incidence of adverse reactions (1 (2.5%) *vs*. 9 (22.5, p = 0.007) showed a statistically significant difference.

DISCUSSION

Perioperative haemodynamic instability reduces the comfort of elderly patients and increases the risk of related complications. Zhang and Li pointed out that remifentanil belongs to the μ - type opioid receptor agonist and its chemical structure contains a methyl propionate bond, which has a relatively small impact on the haemodynamics of patients. Remifentanil and propofol had little effect on the heart rate and blood pressure of patient when used for anaesthesia in orthopaedic surgery, and could effectively maintain haemodynamic stability.[10,11] The results of this study showed that there was no prominent difference in haemodynamic indices at T0, T1, T2, or T3 among the observation group. At the T1, HR, MAP, and SpO_2 indicators of patient in the control group

were prominently lower than those indicators of patient in the observation group, but gradually recovered at the T2 and T3.

In this study, both groups were treated with iliac fascia space block. Therefore, the influence of ultrasound-guided iliac fascia block on the haemodynamics of both groups can be ruled out. Therefore, this study indicates that compared to the control group, the observation group had better haemodynamic stability. The reason should be related to the sympathetic nervous system excitatory effect of esketamine. On one hand, it can effectively neutralise the inhibitory effect caused by propofol, while on the other hand, esketamine belongs to the NMDA antagonist, which can quickly reach its target through the circulatory system after injection and has good selectivity and affinity for NMDA receptors. Therefore, esketamine can inhibit nerve impulses, avoid severe fluctuations in blood pressure and heart rate, and can maintain stable haemodynamics. Similar conclusion has also been drawn in other studies.[12,13] Ketamine has a mild effect on central respiratory dynamics and the respiratory depression can only occur in cases of rapid administration or high doses.[14]

At time T1, there was a significant decrease in HR, MAP, and SpO_2 in the control group compared to the observation group, which was mainly due to the inhibitory effects of remifentanil and propofol on the respiratory and circulatory systems of the patients. After administering a loading dose, the inhibitory effects of the two medicines synergistically led to a transient decrease in blood pressure and pulse oxygen, which is consistent with previous research.[15,16]

Surgical trauma can lead to damage to the body and trigger systemic inflammatory stress response. Evaluating the inflammatory stress response indicators of patients can help understand the impact of surgery on patients.[17] IL-6 is an important inflammatory cytokine, which has been widely used in clinical practice as a sensitive indicator to evaluate the degree of inflammation and injury.[18,19] C-reactive protein belongs to the acute phase-reactive protein and can serve as a non-specific marker of inflammatory response. Its level is directly proportional to the changes in inflammation, and it is not affected by immunosuppressive or anti-inflammatory medicines during detection. Therefore, using IL-6 and CPR as detection indicators for postoperative inflammatory stress response in elderly patients undergoing PFNA can provide reference for postoperative inflammatory response and prognosis in elderly patients. The research results indicate that the levels of IL-6 and CPR of patients in both the observation group and the control group increased to varying degrees 24 hours after surgery, indicating that the patient's body was in an inflammatory state after surgery. The values of IL-6 and CPR of patients in the control group were significantly higher than those of patients in the observation group, indicating that the inflammatory stress response of patients in the control group is stronger. The above result may be related to the pharmacokinetics of esketamine, which can alleviate the inflammatory response, and the clinical symptoms of patients by inhibiting the breakdown of phosphoinositol and inhibiting cell membrane voltage-gated calcium ion channels.[20] A previous study also suggested that esketamine can alleviate surgical-induced inflammatory stress and reduce the expression of systemic inflammatory factors.[21]

Further analysis of adverse reactions revealed that there was a significant difference in the overall incidence between the observation group and the control group. This may be attributed to the combination of esketamine and propofol, which has definite sedative and analgesic effects, smoother haemodynamics, and a reduced risk of respiratory and circulatory adverse events.[22] The observation group did not show any respiratory depression or hypotension in the adverse reactions, that also confirmed the above conclusion. Inflammatory reactions and postoperative pain caused by surgical procedures in elderly patients are risk factors for the postoperative delirium.[23] The observation group did not experience delirium after surgery, confirming that esketamine can alleviate the inflammatory response caused by surgery.

It is worth noting that the observation group experienced postoperative dizziness, likely related to esketamine's stimulation of the central nervous system, particularly thalamus and limbic system. The symptoms are dose-dependent, with a certain probability of causing dizziness.[24] In this article, intravenous injection of 0.3 mg/kg esketamine was used, which is much lower than its recommended dosage of 0.5 mg/kg, so the probability of occurrence was relatively low. The anaesthesia-effect statistics of this study showed that both anaesthesia methods are effective. However, the number of patients with excellent anaesthesia effect in the control group was much lower than that in the observation group, which indicated that the anaesthesia effect in the observation group was better. The QoR-15 score in the control group was much lower than that in the observation group, indicating that the observation group was more beneficial for postoperative recovery of patients.

This study also has the following limitations. First of all, the impact on the long-term outcome and mortality rate of patients was not mentioned, and there was a lack of long-term follow-up results. If the follow-ups were increased for half a year and one year after surgery, the study results would be more comprehensive. Secondly, the sample size of this study was small and the sample source was single, so it is necessary to further expand the sample size and sources to verify the conclusion.

CONCLUSION

Esketamine with iliac fascia block intravenous anaesthesia in elderly patients undergoing PFNA surgery has stable haemodynamics, minimal inflammatory stress response, and fewer adverse reactions.

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ETHICAL APPROVAL:
Ethical approval was taken from the Ethics Committee of The 904th Hospital of the Joint Logistic Support Force of PLA, China (Approval No: 2022-12-016, Dated: 30-December-2022).

PATIENTS' CONSENT:
Informed written consent was taken from each patient for participation in the study.

COMPETING INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
XJ: Design of the work, acquisition, analysis, interpretation of data for the work, and drafting of the manuscript.
XL: Conception of the work and critical revision of the manuscript for important intellectual content.
MZ: Acquisition, analysis, and interpretation of data for the work.
All authors approved the final version of the manuscript to be published.

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