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CLINICAL TRIAL REPORT

Effect of Ciprofol on Postoperative Delirium in Elderly Patients Undergoing Hip Surgery: A Randomized Controlled Trial

Zhen Chen[1], Ying-Ying Liu[1], Qian Hu[1], Jia-Sheng Wang[1], Rui-Yang Cao[1], Su-Ting Yu[2], Feng Lu[3,4], Mao-Lin Zhong[3,4], Wei-Dong Liang[3,4], Lifeng Wang[3,4]

[1]The First Clinical Medical College of Gannan Medical University, Ganzhou, Jiangxi, People's Republic of China; [2]Guangdong Provincial People's Hospital Ganzhou Hospital, Ganzhou, Jiangxi, People's Republic of China; [3]Department of Anesthesiology, First Affiliated Hospital of Gannan Medical University, Ganzhou, Jiangxi, People's Republic of China; [4]Ganzhou Key Laboratory of Anesthesiology, The First Affiliated Hospital of Gannan Medical University, Ganzhou, Jiangxi, People's Republic of China

Correspondence: Lifeng Wang, Department of Anesthesiology, First Affiliated Hospital of Gannan Medical University, 128 Jinling Road, Golden Development Zone, Ganzhou City, Jiangxi Province, 341000, People's Republic of China, Email wwwanglifeng@126.com

Purpose: As a novel intravenous anaesthetic, ciprofol is widely used in clinical practice. However, its potential association with postoperative delirium (POD) is unclear. Silent information regulator factor 3(SIRT3) could regulate mitochondrial function, initiate mitochondrial autophagy, and has played an important role in maintaining normal neuronal cell function. This trial aimed to explore the effect of ciprofol on the pathogenesis of POD and whether SIRT3 had a correlation with the pathogenesis of POD.

Patients and methods: One hundred fourteen elderly patients scheduled for elective hip joint surgery were included in this randomized controlled, double blind study. The patients were randomly assigned at a 1:1 ratio to either the ciprofol group (Group C, induction of anaesthesia with 0.3 mg/kg ciprofol) or the propofol group (Group P, induction of anaesthesia with 1.5 mg/kg propofol). On postoperative days 1 and 3, the 3D-CAM scale was used to assess whether POD occurred in both groups of patients.

Results: No statistically significant difference was observed in the general condition of the patients in the two groups. Within the first 3 days after surgery, the incidence of POD was lower in Group C than in Group P (5.5% vs 20%; $P = 0.022$). At 1 min of administration, ciprofol had less circulatory effects and a lower incidence of injection pain, but a higher incidence of muscle twitching than propofol. On postoperative day 1, SIRT3 expression was greater in Group C than in Group P ($P = 0.028$). Additionally, SIRT3 expression was found to be correlated with POD. The serum SIRT3 level on postoperative day 1 had an area under the receiver operating characteristic (ROC) curve of 0.8540 ($P < 0.001$), with a detection threshold of 1.565 ng/mL, yielding a sensitivity of 0.820 and a specificity of 0.900.

Conclusion: In this study, we found that ciprofol was associated with a lower incidence of POD and had a minimal impact on circulatory function. SIRT3 expression and POD were correlated. A serum SIRT3 level less than 1.565 ng/mL on postoperative day 1 may indicate a likelihood of POD, highlighting its potential diagnostic value.

Keywords: postoperative delirium, ciprofol, total hip arthroplasty, silent information regulator factor 3

Introduction

Postoperative delirium (POD) is an acute confusional state characterized by fluctuations in attention and consciousness, disorientation, memory impairment, perceptual disturbances, and cognitive disarray. It is one of the most common postoperative complications in elderly patients.[1,2] POD not only prolongs the hospital stay, reduces long-term quality of life, and increases the socioeconomic burden but also may lead to death.[3,4] POD may be associated with factors such as age, ASA classification, level of education, hypoalbuminemia, surgical trauma, and intraoperative hypotension;[5,6] however, its exact pathogenesis remains unclear. Recent studies revealed that neuroinflammation,[7] oxidative stress,[8] and mitochondrial dysfunction[9] may be key mechanisms underlying the development of POD. Exploring the

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pathogenesis of and risk factors for POD as well as implementing early interventions targeting these factors is highly valuable for reducing the incidence of POD.

Owing to the aging of the population, hip joint diseases are becoming increasingly prevalent. Hip arthroplasty has been shown to improve quality of life of elderly patients with hip disorders.[10] Currently, approximately one million hip replacement surgeries are performed worldwide each year, a number that may double over the next 20 years.[11] Patients undergoing such procedures are predominantly elderly, and postoperative delirium (POD) is highly prevalent among hip replacement patients, especially on the third postoperative day, with an incidence ranging from 28% to 61%.[12,13] This may be associated with factors such as significant blood loss, intraoperative circulatory instability, extensive surgical trauma, and postoperative pain.[14]

Ciprofol is a novel intravenous anaesthetic independently developed in China. Its molecular structure is based on propofol, with the introduction of a cyclopropyl group, which enhances its affinity for γ-aminobutyric acid type A ($GABA_A$) receptors. The potency of ciprofol is approximately 4 to 5 times greater than that of propofol. Compared with propofol, ciprofol offers several advantages, including greater potency, a lower incidence of injection pain, and minimal effects on the circulatory and respiratory systems.[15] It may also exhibit neuroprotective effects.[16,17] The mechanisms underlying these effects include reductions in oxidative stress, inflammatory responses, and antiapoptotic actions, as well as an increase in aerobic glycolysis in astrocytes.[18–20]

Silent information regulator factor 3 (SIRT3) is a nicotinamide adenine dinucleotide (NAD^+)-dependent deacetylase involved in mitochondrial metabolic processes, including energy production, the tricarboxylic acid cycle, and oxidative stress regulation.[21] SIRT3 plays a critical role in processes such as tumorigenesis and aging.[22,23] Studies have shown that the activation of SIRT3 can reduce the incidence of postoperative delirium (POD) and provide significant neuroprotective effects. The mechanisms underlying these effects involve improvements in mitochondrial dysfunction, reductions in neuroinflammation and oxidative stress, and the activation of autophagy through the AMPK/mTOR pathway.[24–26] SIRT3 could regulate the deacetylation of manganese superoxide dismutase (MnSOD) by inhibition of NLRP3 production in vivo and reduces the levels of inflammatory factors and oxidative stress.[27,28] Meanwhile, SIRT3 deficiency upregulates the expression of inflammation-related proteins, including NLRP3, caspase-1, P20 and IL-1β.[29] The naturally occurring SIRT3 agonist trilobatin has also been shown to reduce CNS inflammation and exert neuroprotective effects, accompanied by inactivation of the TLR4/NF-κB pathway.[30] However, clinical evidence supporting these findings is lacking.

Thus, the aim of this study is to observe the incidence of postoperative delirium (POD) in elderly patients after hip replacement surgery under anaesthesia with ciprofol and to explore whether ciprofol can reduce the incidence of POD in this population. An additional aim of this study is to preliminarily investigate whether there is an association between SIRT3 expression and POD and explore whether a reduction in SIRT3 expression predict POD.

Methods

Study Design

This study is a prospective, double-blind, randomized controlled trial approved by the Ethics Review Committee of the First Affiliated Hospital of Gannan Medical University (Ethical Approval No. LLSC-2024009). The trial was registered with the Chinese Clinical Trial Registry on January 31, 2024 (ChiCTR2400080542). The study was conducted in adherence to the principles outlined in the Declaration of Helsinki, and informed consent was obtained from all patients or their legal representatives.

Randomization was performed using SPSS 27.0 software. The study participants were assigned numbers corresponding with the order in which they were enrolled, and the random seed 20240131 was set. The RV.Uniform function in SPSS was used for random number generation. The SPSS Visual Binning function was then used to divide the samples into two equally sized groups on the basis of the random numbers generated.

Each group allocation was placed in an opaque envelope, with the corresponding number (1–114) written on the outside. The sealed envelopes were handed to the researchers. Researchers who were not involved in the trial were responsible for the randomization process. After the participants were enrolled, they were sequentially numbered, and the corresponding numbered envelope was opened. Participants were then assigned to their respective groups and

anaesthetized with the medication corresponding with the number in the envelope. The anaesthesiologist responsible for administering the medication did not participate in any other aspect of the trial but was solely responsible for managing intraoperative drug usage. Another blinded anaesthesiologist recorded various data during the procedure. The same lead surgeon performed all the surgeries. Patients, other healthcare team members, and the research personnel responsible for patient recruitment, data collection, and follow-up assessments were unaware of the group assignments. In the case of an emergency, the doctor or researcher may reveal the patient's assigned group and remove the patient from the study to ensure their safety.

Study Population

The inclusion criteria were as follows: 1. Elderly patients who had indications for hip replacement surgery and consented to elective surgery; 2. were aged between 60 and 80 years; 3. were classified as American Society of Anaesthesiologists (ASA) physical status I–III; 4. had a body mass index (BMI) between 18 and 28 kg/m²; 5. could speak Mandarin and had no barriers to communication, such as an education level greater than 9 years; 6. had a preoperative Mini-Mental State Examination (MMSE) score ≥ 26 points; and 7. had no significant abnormalities in cardiac, pulmonary, hepatic, or renal function.

The exclusion criteria were as follows: 1. Patients with a history of cognitive impairment, dementia, or delirium before surgery. 2. Patients with severe depression, schizophrenia, or other psychiatric or neurological disorders, or those who have used antipsychotic or antidepressant medications. 3. Patients who use anti-inflammatory drugs, corticosteroids, or other hormonal medications or have a history of alcohol or drug dependence. 4. Patients with severe visual, auditory, or speech impairments that prevent them from completing the tests. 5. Patients who are allergic to propofol or ciprofol.

The criteria for withdrawal from the study were as follows: 1. Patients or their legal representatives who requested withdrawal from the study during the observation period. 2. Patients or their legal representatives who refused to cooperate postoperatively. 3. Patients with an intraoperative blood loss volume > 800 mL or who required hospitalization for more than 3 months. 4. Patients whose surgeries exceeded 3 hours or who experienced severe adverse events, such as severe allergic reactions, during surgery.

Procedures

Patients fasted for 6 h and were not allowed to drink for 2 h before surgery, and no preanaesthetic medication was administered. After entering the operating room, peripheral venous access was established, and monitoring of blood pressure (BP), electrocardiogram (ECG), heart rate (HR), pulse oximetry (SpO2), respiratory rate (RR), and the Narcotrend index (NI) was performed. Under local anaesthesia, radial artery puncture was performed for arterial catheterization for invasive arterial blood pressure monitoring and blood gas analysis. All patients in both groups received femoral nerve block (15 mL of 0.375% ropivacaine) and lateral femoral cutaneous nerve block (5 mL of 0.375% ropivacaine) under ultrasound guidance. The sensory block level was assessed 15 minutes later, and upon sufficient blockade, anaesthesia was induced.

Anaesthesia was induced on the basis of standard body weight calculations, and slow intravenous injections were administered. Ciprofol is 4–5 times more potent than propofol; therefore, we used the lowest dose of the equivalent.[31] Group C received ciprofol 0.3 mg/kg, and Group P received propofol 1.5 mg/kg. Once an adequate depth of anaesthesia was achieved, sufentanil 0.5–1.0 μg/kg and rocuronium 0.6–1.0 mg/kg were administered. After the muscles were adequately relaxed, endotracheal intubation was performed under direct laryngoscopic guidance. After intubation, the ventilation parameters were adjusted as follows: tidal volume, 6–8 mL/kg; respiratory rate, 12–16 breaths/min; I:E ratio, 1:2; and oxygen flow, 2 L/min. Immediately thereafter, maintenance drugs were infused: for Group P, propofol 4–6 mg/(kg h) and remifentanil 0.05–0.2 μg/(kg min); for Group C, ciprofol 0.8–1.2 mg/(kg h) and remifentanil 0.05–0.2 μg/(kg min). The infusion rates of propofol, ciprofol, and remifentanil were adjusted according to the NI, maintaining the NI between 40 and 60 and the end-tidal carbon dioxide pressure (PetCO2) at 35–45 mmHg. Intermittent doses of rocuronium were given to maintain muscle relaxation. If the patient's intraoperative blood pressure decreased by more than 20% from baseline, 6 mg of ephedrine was administered intravenously. If the heart rate dropped below 50 beats per minute, 0.5 mg of atropine was administered intravenously. At the end of the surgery, propofol, ciprofol, and remifentanil were discontinued, and 4 mg of ondansetron was administered intravenously for postoperative antiemesis. If POD was diagnosed postoperatively, haloperidol (5 mg) was administered intramuscularly.

All patients received patient-controlled intravenous analgesia (PCIA) postoperatively. The PCIA formula was as follows: sufentanil 2 μg/kg + ondansetron 12 mg + 0.9% sodium chloride, prepared to a total volume of 100 mL.

Remedial measures: Given that all the patients enrolled were elderly, benzodiazepines were not used to reduce the risk of increasing the incidence of POD.[32] Only intravenous anaesthetics, ciprofol and propofol, were used for anaesthesia induction. If the NI did not fall below 60 within 1 minute of ciprofol or propofol injection, a remedial dose of sedatives was administered: for Group C, 0.1 mg/kg ciprofol was given; for Group P, 0.5 mg/kg propofol was given. If, after the remedial dose, the NI still did not fall below 60, a second remedial dose was given until the desired depth of anaesthesia was achieved.

Endpoints

Primary Outcome Measure: The incidence of postoperative delirium (POD) within the first 3 days after surgery. Patients were screened for POD on postoperative day 1 (D1) and postoperative day 3 (D3) using the 3D-CAM scale. This scale is an improvement of the CAM and consists of 10 evaluator-rated items, 10 observer-rated items, and 2 selective items, with each item being classified as "correct" or "incorrect." These 22 items are categorized into 4 features: feature 1—acute changes or fluctuations in mental status; feature 2—attention deficits; feature 3—changes in level of consciousness; and feature 4—disorganized or confused thinking. A diagnosis of delirium is made if the patient is positive for Feature 1 and Feature 2, along with any positive result from Feature 3 or Feature 4.

Secondary Outcome Measures: Mean arterial pressure (MAP), heart rate (HR), and Narcotrend index (NI) values recorded at the following time points: upon entry into the operating room (T0), 1 minute after drug administration (T1), 2 minutes after drug administration (T2), 3 minutes after drug administration (T3), after intubation (T4), after position change (T5), at the start of surgery (T6), and at the end of surgery (T7). The frequency of remedial sedative doses and the time taken to reach the appropriate depth of anaesthesia were recorded. The number of times that ephedrine and atropine were administered intraoperatively was also noted. On D1 and D3, patients were followed up to inquire about the occurrence of adverse events, including nausea, vomiting, and pain.

Serum Biomarker Measurements: Peripheral blood samples (4 mL) were collected from patients at T0, D1, and D3, centrifuged at 4000 × g for 10 minutes, and the serum was stored at −80°C. Serum SIRT3 levels were measured at T0, D1, and D3 using enzyme-linked immunosorbent assay (ELISA) kits produced by Bioswamp Life Science Lab, Wuhan, China. The absorbance at 450 nm was measured using a microplate reader. A standard curve was constructed with the concentration of standard samples on the x-axis and optical density (OD) values on the y-axis. The concentration of SIRT3 in each serum sample was calculated by comparing its OD value to the OD value of known standards. All analyses were repeated and quantified according to the manufacturer's protocol, and the mean value was used for analysis. All the serum samples were processed by the same laboratory technician every three months.

Statistical Analysis

This experiment is a randomized controlled trial, with the control group being the propofol group (Group P) and the experimental group being the ciprofol group (Group C). The primary outcome measure of this study was the incidence of postoperative delirium (POD) in patients. According to previous studies, the incidence of POD in elderly patients who underwent orthopaedic surgery under propofol anaesthesia was 27%,[33] whereas the incidence of POD in elderly patients anaesthetized with ciprofol was 7%.[16] Setting both $\alpha = 0.05$ and $\beta = 0.2$, with an equal number of patients in both groups, the minimum sample size required for each group was 52 patients according to calculations using PASS 15 statistical software. Considering a 10% loss to follow-up rate, 57 patients were required per group, for a total of 114 patients.

Data were analysed and processed using SPSS 27.0 statistical software. For normally distributed continuous data, values are expressed as means ± standard deviations, and independent sample t tests were used for intergroup comparisons. Nonnormally distributed continuous data are presented as medians (interquartile ranges), and Mann–Whitney *U*-tests were used for intergroup comparisons. Categorical data are expressed as frequencies (percentages), and chi-square or Fisher's exact tests were used for intergroup comparisons. Repeated measures analysis of variance was used to compare haemodynamic parameters (MAP, HR) and serum biomarkers (SIRT3) at different time points, with Bonferroni correction applied. A P value <0.05 indicated statistical significance.

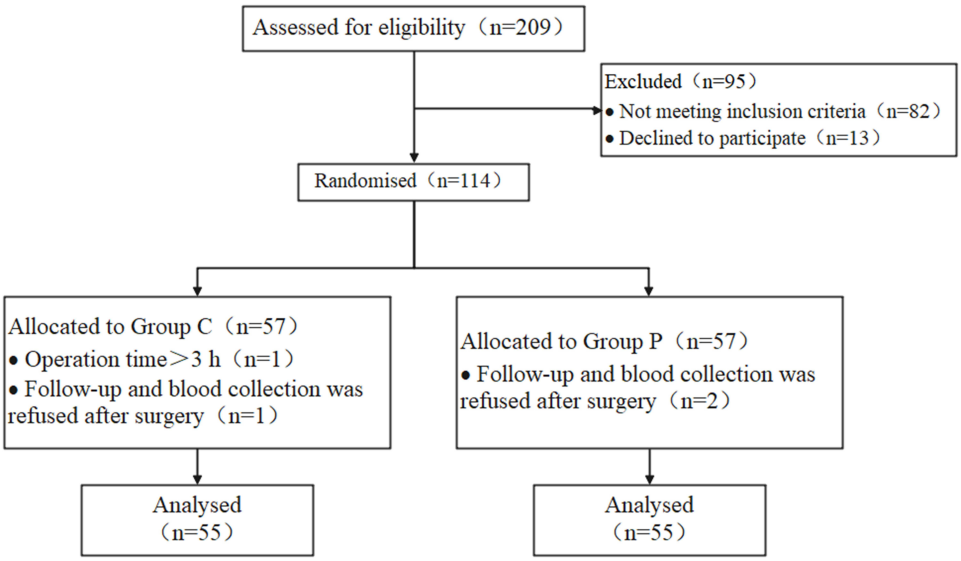

Figure 1 Flow chart.

Results

Baseline Measurements

A total of 209 patients were recruited, and 114 patients were enrolled and randomly assigned to two groups. One patient was excluded because of a surgery duration >3 hours, and three patients withdrew from the study because they refused postoperative follow-up and blood sampling (Figure 1). Ultimately, data from 110 patients were analysed. There were no statistically significant differences between the two groups in terms of age, sex, BMI, ASA classification, preoperative MMSE score, surgery duration, or intraoperative blood loss volume ($P > 0.05$) (Table 1).

Table 1 Comparison of General Data and Intraoperative Variables Between the Two Groups

Characteristics	Group C(n=55)	Group P(n=55)	*P*-Value
Age(year)	61(60, 63)	62(61, 67)	0.084
Sex			0.849
Male	27(49.1%)	28(50.9%)	
Female	28(50.9%)	27(49.1%)	
Height(cm)	160.58±9.2	160.98±7.8	0.806
Weight(kg)	58.92±7.9	59.57±9.4	0.694
BMI(kg/m^2)	22.86±2.7	22.94±2.7	0.873
ASA			0.340
II	51(92.7%)	48(87.3%)	
III	4(7.3%)	7(12.7%)	
Preoperative MMSE score			0.541
26	20(36.4%)	23(41.8%)	
27	25(45.5%)	26(47.3%)	
28	10(18.2%)	6(10.9%)	
Operation time(min)	84.05±17.8	89.45±18.9	0.126
Blood loss (mL)	200(200, 250)	200(200, 250)	0.603

Notes: Values are n (%) or mean ± SD.
Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index.

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Table 2 Comparison of the Incidence of Postoperative Delirium

POD incidence, n(%)	Group C(n=55)	Group P(n=55)	*P*-value
D1	2(3.6%)	8(14.5%)	0.047*
D1 to D3	1(1.8%)	3(5.5%)	0.618
Total	3(5.5%)	11(20%)	0.022*

Notes: Values are n (%), Pearson Chi-Square and Fisher precision tests were used. vs Group C *P<0.05.

Primary Outcomes

Our study revealed that within the first 3 days after surgery, the overall incidence of postoperative delirium (POD) in Group C was lower than that in Group P (P = 0.022). On postoperative day 1, the incidence of POD in Group C was significantly lower than that in Group P (P = 0.047). However, there was no significant difference in the incidence of POD between the two groups from postoperative day 1 to day 3 (P = 0.618) (Table 2).

Secondary Outcomes

At T0, there were no statistically significant differences in the MAP or HR between the two groups. One minute after induction (T1), the MAP and HR in Group P were significantly lower than those in Group C (Figure 2). Moreover, during surgery, the number of patients in Group C who required ephedrine was significantly lower than that in Group P (23 vs 42, P < 0.001) (Table 3). At T0, there were no significant differences in the NI values between the two groups. At T1, T2, T5, and T7, the NI values were significantly different between the two groups. The NI values in Group C were higher than those in Group P at 1 minute and 2 minutes after drug administration (Figure 3). Anaesthesia was successfully induced in all patients (100% success rate), but the time to reach an adequate depth of anaesthesia in Group C (97.27 ± 43.1 seconds) was significantly longer than that in Group P (63.45 ± 35.1 seconds) (P < 0.001). During induction, 17 patients (30.9%) in Group C required one additional dose of ciprofol, and 8 patients (14.5%) required two additional doses. In contrast, 22 patients (40.0%) in Group P required one additional dose of propofol, and 4 patients (7.3%) required two additional doses. However, the differences in the number of additional sedative doses between the two groups were not statistically significant (Table 4).

We also observed some complications during and after surgery. During anaesthesia induction, 8 patients (14.5%) in Group C experienced muscle tremors, whereas only 2 patients (3.6%) in Group P experienced muscle tremors (P = 0.047). Thirteen patients (23.6%) in Group P experienced injection pain, whereas no patients in Group C reported

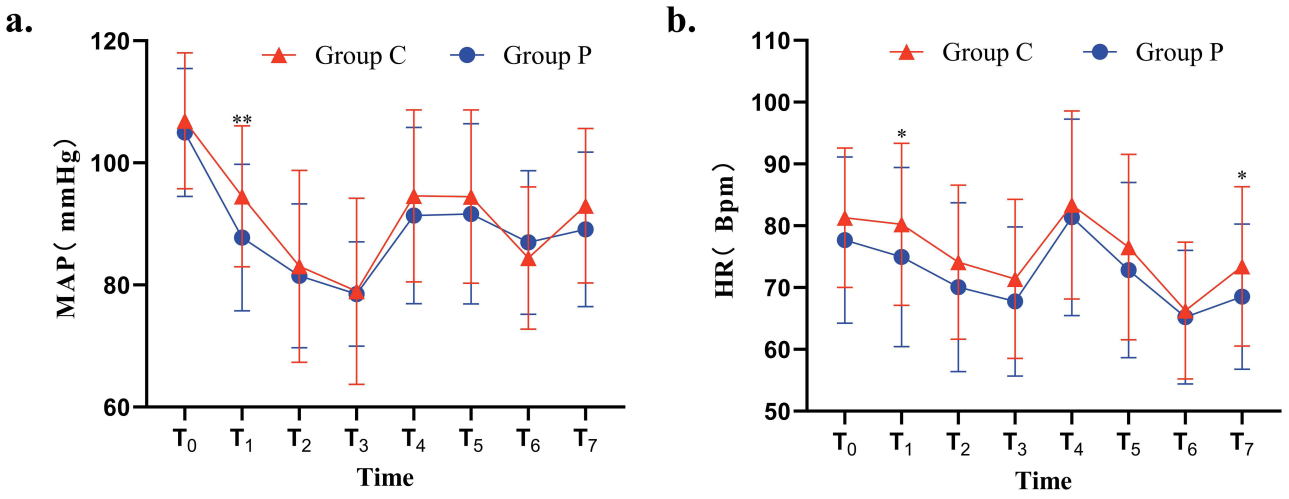

Figure 2 MAP (**a**) and HR (**b**) at different time points in the two groups. vs Group C *P<0.05, **P<0.001.

Table 3 Comparison of the Use of Vasoactive Drugs Between the Two Groups

Vasoactive Agents	Group C(n=55)	Group P(n=55)	*P*-value
Ephedrine, n(%)	23(41.8%)	42(76.4%)	<0.001***
Nitroglycerin, n(%)	2(3.6%)	3(5.4%)	1.000
Atropine, n(%)	5(9.1%)	8(14.5%)	0.376
Esmolol, n(%)	0(0.0%)	0(0.0%)	1.000

Notes: vs Group C ***P<0.001.

injection pain ($P < 0.001$). There were no significant differences between the two groups in terms of postoperative nausea and vomiting ($P > 0.05$) (Table 5).

We also compared the SIRT3 expression levels in the two groups at different time points. On postoperative day 1, the serum SIRT3 levels in Group C were higher than those in Group P ($P < 0.05$) (Figure 4a). However, on postoperative day 3, there was no significant difference in the serum SIRT3 level between the two groups ($P > 0.05$) (Figure 4a). The ROC curve for serum SIRT3 levels on postoperative day 1 showed an area under the curve (AUC) of 0.8540 ($P < 0.001$), with a threshold of 1.565 ng/mL, corresponding to a sensitivity of 0.820 and a specificity of 0.900 (Figure 4b). The ROC curve for postoperative day 3 had an AUC of 0.8703 ($P > 0.05$) (Figure 4c). We believe that levels of SIRT3 less than 1.565 ng/mL measured on postoperative day 1 may be of value in the diagnosis of POD.

Discussion

In this study, the clinical data of 114 elderly patients who underwent hip fracture surgery were analysed, and both ciprofol and propofol were found to be safe for anaesthesia induction and maintenance during such surgeries. We observed that the incidence of postoperative delirium (POD) was lower with ciprofol than with propofol, and there was less impact on haemodynamics during surgery, along with a lower incidence of injection pain. Additionally, ciprofol did not increase the incidence of postoperative complications.

Propofol is the most common intravenous anaesthetic used during the perioperative period, and it has been shown to reduce the incidence of POD to some extent.[34,35] The potential mechanisms include a reduction in inflammatory cytokine production, attenuation of tumour necrosis factor-α (TNF-α) effects on the blood–brain barrier, and inhibition of hippocampal neuronal apoptosis.[36–38] In a previous study, propofol was found to promote type 1 inositol triphosphate receptor (InsP3R-1) activation, which in turn induced mitochondrial autophagy to provide cytoprotection.[39] SIRT3 exerts

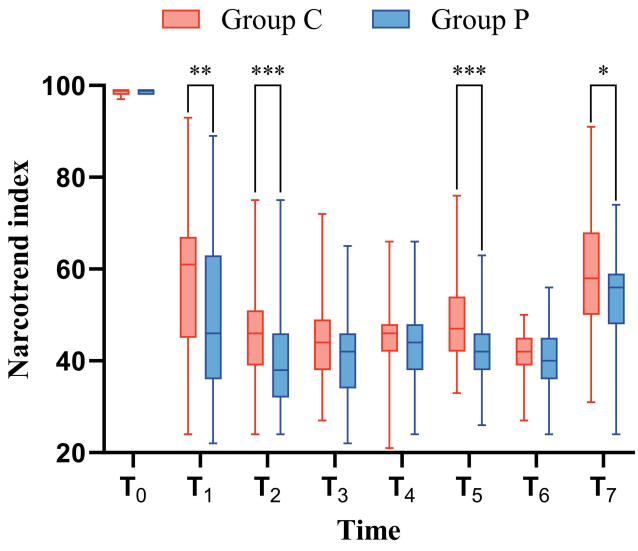

Figure 3 Narcotrend index values at different time points in the two groups. vs Group C *P<0.05, **P<0.01, ***P<0.001.

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Table 4 Comparison of Induction Time and Number of Additional Sedatives Administered

Measurement	Group C(n=55)	Group P(n=55)	*P*-Value
Induction time (second)	97.27±43.1	63.45±35.1	<0.001***
Sedatives additional dose, n(%)			0.369
0 times	30(54.5%)	29(52.7%)	
1 times	17(30.9%)	22(40.0%)	
2 times	8(14.5%)	4(7.3%)	

Notes: vs Group C ***P<0.001.

Table 5 Comparison of Complications Between the Two Groups

Adverse Reaction	Group C(n=55)	Group P(n=55)	*P*-Value
Muscle tremors	8(14.5%)	2(3.6%)	0.047*
Injection pain	0(0.0%)	13(23.6%)	<0.001***
PONV			
D1	38(69.1%)	35(63.6%)	0.545
D3	12(21.8%)	5(9.1%)	0.065

Notes: vs Group C *P<0.05, ***P<0.001.
Abbreviation: PONV, postoperative nausea and vomiting.

its anti-inflammatory effects mainly through the regulation of mitochondrial autophagy.[40] The anti-inflammatory effects of propofol may have some link to SIRT3. Ciprofol and propofol are structurally similar and may have similar functions, but the specific mechanism by which cyclobenzaprine is associated with mitochondrial autophagy is unclear. However, propofol often leads to dose-dependent hypotension, causing significant haemodynamic fluctuations that may increase the risk of postoperative complications such as renal dysfunction, myocardial injury, and even mortality.[41,42] Ciprofol, on the other hand, has a safe therapeutic window (0.15–0.9 mg/kg), a low incidence of injection pain, and minimal cardiovascular effects.[43] In previous studies, researchers recommended a 0.3 mg/kg dose of ciprofol for elderly patients.[44] However, this may be a relatively low starting dose, as we excluded the use of benzodiazepines to avoid their potential impact on POD. As a result, some elderly patients in our study did not achieve an ideal depth of anaesthesia with a 0.3 mg/kg dose of ciprofol, and remedial doses were administered during the procedure. While a 0.3 mg/kg dose is considered relatively safe, a dose of 0.4 mg/kg may also be a safe option when using ciprofol alone. This finding aligns with that of another study, although the risk of hypotension may be slightly higher with a 0.4 mg/kg dose.[45] However, as this study did not specifically investigate this topic, no definitive conclusions can be drawn.

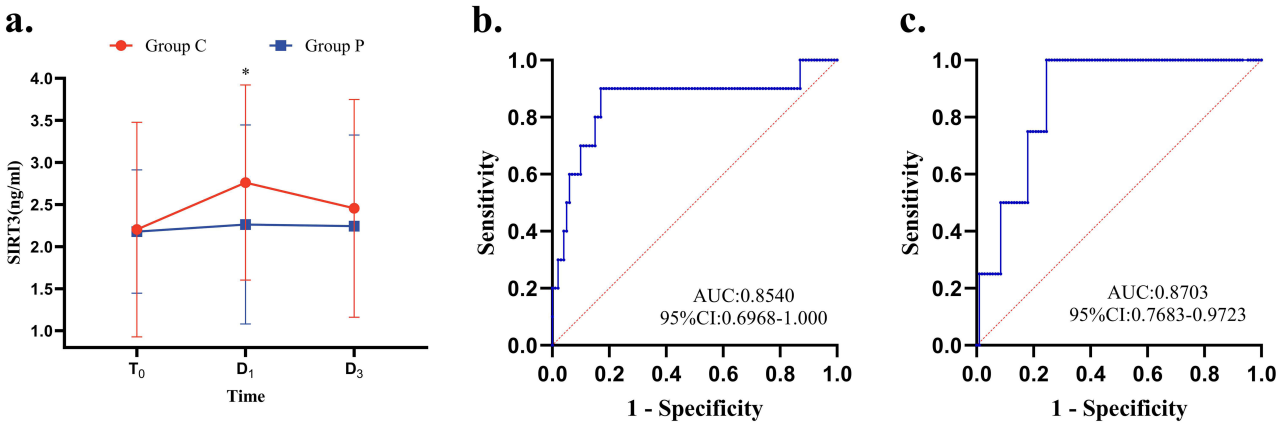

Figure 4 Changes in the expression of SIRT3 over time (**a**) and ROC curves of SIRT3 level and POD ((**b**) day 1, (**c**) day 3) vs Group C *P<0.05.

Our study revealed that, after anaesthesia induction, both groups of patients experienced varying degrees of decreases in MAP and HR. However, with ciprofol, the reduction in MAP and HR was less pronounced, and the patients' haemodynamics were more stable This finding is consistent with that of previous research.[46] This suggests that ciprofol has a smaller circulatory suppressive effect, which may be due to its greater potency compared to propofol, allowing for lower clinical doses and resulting in lower plasma drug concentrations. Consequently, the effects on receptors or channels related to circulatory suppression are smaller. Furthermore, the metabolites of ciprofol are pharmacologically inactive, which may also contribute to its lesser impact on circulation.

Injection pain is one of the most common adverse reactions associated with propofol. The incidence of injection pain associated with propofol is approximately 70%.[47] Injection pain can lead to patient anxiety, distressing memories, and decreased satisfaction.[48] The pain may be caused by two mechanisms: free propofol directly stimulating nociceptors in the vein wall or its active component activating the kallikrein-kinin system upon contact with the vascular endothelium, leading to the release of bradykinin. The intensity of pain is positively correlated with the aqueous concentration of the drug.[48,49] In our study, 23.6% of patients in the propofol group experienced injection pain, whereas no injection pain was reported in the ciprofol group, indicating a significant difference in incidence, possibly because the introduction of a cyclopropyl group into ciprofol increases its lipophilicity and hydrophobicity, resulting in its much lower aqueous concentration compared to propofol.[50] Second, the clinical dosage of ciprofol is usually lower than that of propofol, causing less irritation to the vessel wall.[43]

The onset time for propofol is approximately 30 seconds to 1 minute.[51] However, ciprofol has a longer onset time. In our study, we observed that with ciprofol, the NI value decreased more gradually, with an average onset time of 97s, than with propofol, which was only 63s. The possible reason for this is that ciprofol has high lipophilicity and a low aqueous concentration, making its active component release slower. Therefore, in clinical practice, when it is not possible to monitor anaesthetic depth, the administration of muscle relaxants is recommended at least 2 minutes after ciprofol administration to avoid the feeling of suffocation or near-death due to the efficacy of muscle relaxants appearing prior to sedation.

During the anaesthesia induction phase, we also observed that 8 participants in the ciprofol group developed myoclonus, a phenomenon that has been noted by some researchers.[52] Additionally, a small number of patients exhibited excitation, such as delirium and involuntary movements, during the anaesthesia induction phase. This may also be related to the slower onset time of the ciprofol, causing patients to remain in a shallower state of anaesthesia for a longer period (similar to the excitement stage in Guedel's stages of anaesthesia). This shallow anaesthetic state may cause anxiety in patients, leading to myoclonus and other manifestations. Furthermore, in our study, we observed that approximately 2–3 minutes after intubation, the NI values in Group C were higher than those in e Group P, with some patients' NI exceeding 60, necessitating immediate administration of sedative and anaesthetic drugs. In clinical practice, it is important to maintain the depth of anaesthesia and sedation after induction to avoid intraoperative awareness.

Propofol reduces the incidence of POD. However, in this study, we found a statistically significant difference in the incidence of POD on postoperative day 1 between the two groups: 3.6% in Group C versus 14.5% in Group P ($P < 0.05$). This finding suggests that the use of ciprofol during surgery is associated with a lower incidence of POD, although the exact mechanisms remain unclear.[53] SIRT3 is the only member of the sirtuin family that plays a role in extending the human lifespan and is linked to the onset of neurodegenerative diseases.[54] Recent studies have revealed that SIRT3 can reduce the incidence of postoperative cognitive dysfunction (POCD), with its primary mechanisms including the inhibition of hippocampal neuroinflammation, maintenance of mitochondrial function, and activation of autophagy.[25,26,55] In this study, we measured the expression of SIRT3 in the peripheral blood of both groups at three time points, preoperatively, on postoperative day 1, and on postoperative day 3, and explored the correlation between the onset of POD and SIRT3 expression. We found that the expression of SIRT3 increased postoperatively in both groups, possibly because surgical trauma stimulated the expression of SIRT3, thereby inhibiting the expression of inflammatory cytokines and reducing oxidative stress.[56] The expression of SIRT3 was greater in the ciprofol group than in the propofol group, which may be associated with the lower incidence of POD in this group. To further explore this, we performed univariate logistic regression analysis and found that the expression of SIRT3 in the serum on postoperative day 1 may

have diagnostic value for the occurrence of POD. SIRT3 has potential value for the diagnosis of POD when serum levels fall below 1.565 ng/mL.

This study also has several limitations. First, postoperative delirium (POD) in this study was solely assessed using the 3D-CAM scale, and the use of a single assessment method may introduce some bias, with underestimation of the incidence of POD. Second, we only administered a 0.3 mg/kg dose of ciprofol and was unable to evaluate the clinical effects of higher doses of ciprofol, such as whether it results in a faster onset of anaesthesia or further reduces the incidence of POD. Third, the participants in this study were predominantly aged 60–65 years, with fewer elderly patients aged 75 years and above. As a result, 45.5% of patients in Group C who received a 0.3 mg/kg dose of ciprofol required one or more remedial sedative doses. In contrast, the study by LU,[52] which included patients aged 75 years and older, revealed that a 0.3 mg/kg dose of ciprofol successfully induced anaesthesia in all patients. The age distribution in our study of elderly patients aged 60–80 years was not uniform; thus, the conclusions may not be applicable to the entire elderly population. In addition, this study was a single-centre study that lacked external validation; guidelines are lacking for elderly patients over the age of 80 years. Therefore, we look forward to multicentre, large-sample studies or stratified analyses based on age to guide medication use in all age groups of elderly patients.

Conclusion

In this study, we found that ciprofol could be safely and effectively used for anaesthesia in elderly (aged 60–80 years) hip arthroplasty patients. Ciprofol had a minimal impact on circulatory function, could reduce the use of intraoperative vasoactive drugs, had a low incidence of injection pain, and was associated with a lower incidence of POD. There may be a correlation between SIRT3 expression and the onset of POD. A serum SIRT3 level less than 1.565 ng/mL on postoperative day 1 may indicate a likelihood of POD and serve as a predictor of POD onset.

Data Sharing Statement

Data are available to researchers on request for the purpose of reproducing the results or replicating the procedure by directly contacting the corresponding author.

Ethics Approval

The study was reviewed and approved by the Ethics Committee of the First Affiliated Hospital of Gannan Medical University (No. LLSC-2024009).

Consent Statement

All study participants or their legally authorized representative provided informed consent.

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