Drug Design, Development and Therapy

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CLINICAL TRIAL REPORT

Effect of Fospropofol Disodium on Perioperative Neurocognitive Function in Elderly Patients Undergoing Total Hip Arthroplasty

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Objective: This study aimed to compare the effects of fospropofol disodium and propofol on perioperative neurocognitive function in elderly patients undergoing total hip arthroplasty (THA), evaluating the non-inferiority of fospropofol disodium in preventing or reducing perioperative neurocognitive disorders (PND) and exploring optimal clinical anesthesia strategies.

Methods: A total of 180 elderly patients (aged 65~80 years) scheduled for THA between November 2022 and November 2024 were randomly assigned to the fospropofol disodium group (Group F, n=90) or the propofol group (Group P, n=90). Cognitive function was assessed preoperatively (1 day before surgery) and postoperatively (1, 3, 7 days, and 1 month) using the Modified Mini-Mental State Examination (MMSE), 3-Minute Diagnostic Interview for Confusion Assessment Method (3D-CAM), Digit Span Test (DST), Verbal Fluency Test (VFT), and Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE). The incidence of postoperative cognitive dysfunction (POCD) and delirium (POD), hemodynamic parameters, and adverse events were compared between the two groups.

Results: No significant differences were observed between the two groups in the incidence of POCD ($p>0.05$) or POD ($p>0.05$) at any postoperative time point. At the time point of 10 minutes after bone cement implantation (T4), the heart rate of patients in the Group F was higher than that of Group P ($p < 0.0001$). At the time of discharge from the PACU, the heart rate of patients in the Group F was lower than that of the Group P ($p = 0.037$). Group F exhibited higher mean arterial pressure (MAP) at the beginning of the operation ($p=0.022$) and a longer extubation time and waking time ($p < 0.001$) but had significantly lower incidences of injection pain ($p=0.018$) and postoperative nausea and vomiting ($p=0.037$). Binary logistic regression identified age as an independent risk factor for PND [OR=1.149, $p=0.006$], while preoperative MMSE score was a protective factor [OR=0.693, $p = 0.002$].

Conclusion: Fospropofol disodium may be a viable alternative in settings where injection pain and PONV are primary concerns, provided that hemodynamic stability is actively managed in elderly THA patients, with non-inferior efficacy in preventing PND compared to propofol and fewer adverse effects. Age and preoperative cognitive function are critical predictors of PND, warranting careful consideration in perioperative management.

Keywords: fospropofol disodium, propofol, perioperative neurocognitive disorders, total hip arthroplasty

Introduction

Perioperative neurocognitive disorders (PND), encompassing postoperative cognitive dysfunction (POCD) and delirium (POD), represent significant complications affecting elderly surgical patients, with reported incidence rates ranging from 10% to 60% following major elective noncardiac surgery like total hip arthroplasty (THA), which manifests high-risk

Received: 5 July 2025
Accepted: 9 September 2025
Published: 12 September 2025

factors of PND such as bone cement implantation, hemodynamic instability and pain.[1,2] These conditions are associated with prolonged hospitalization, increased healthcare costs, and higher mortality rates, posing substantial challenges to postoperative recovery and long-term quality of life. As China's population ages rapidly – with projections indicating that individuals aged ≥60 years will exceed 400 million by 2035 – optimizing anesthetic strategies to mitigate PND has become an urgent clinical priority.

Common hip diseases in the elderly include femoral neck fracture, femoral head necrosis, and other hip joint pathologies, which seriously affect the quality of daily life of patients. Total hip arthroplasty (THA) is a widely used surgical method in orthopedics in recent years, and studies have shown that it has significant clinical effects in the treatment of these hip diseases. However, elderly patients undergoing total hip arthroplasty face multiple risk factors such as advanced age, pain, anesthesia, and surgical trauma, and the incidence of PND ranges from 16% to 45%.[3,4]

Propofol, also known as 2,6-diisopropylphenol, a widely used intravenous anesthetic, exerts its effects through GABA-γ receptor modulation to produce a sedative effect.[5] While demonstrating neuroprotective potential through anti-inflammatory properties,[6] its lipid emulsion formulation carries risks including injection pain, hyperlipidemia, and propofol infusion syndrome[7] due to its use of fat emulsion as a special dosage form. Fospropofol disodium, a water-soluble precursor drug for propofol, significantly enhances the water solubility of the drug by converting the carbon hydroxyl group of propofol into a methyl phosphate group, addresses these limitations through enzymatic conversion to active propofol while avoiding lipid-related complications.[8] After entering the body, disodium phosphopropofol is gradually decomposed by alkaline phosphatase (ALP) catalyzed to produce pharmacologically active metabolites such as propofol, phosphate and formaldehyde. These metabolites are able to rapidly distribute and equilibrate in the neural tissues and thus exert anesthetic effects.[8] Compared with the fat emulsion form of propofol, the lyophilized powder form of fospropofol disodium is effective in reducing the risk of allergy and microbial contamination of hyperlipidemia caused by fat emulsion. At the same time, the drug has a lower probability of triggering injection site pain and postoperative nausea and vomiting (PONV), and a lower degree of inhibition of the patient's respiratory and circulatory systems.[9,10] The results of Phase II and Phase III clinical trials have shown that compared to propofol, intravenous fospropofol disodium induces general anesthesia in patients, with no significant difference in performance in terms of degree of sedation and patient satisfaction, and no serious adverse should.[11] Studies have shown that a comparison of the effects of fospropofol disodium with propofol for induction and maintenance of sedation in mechanically ventilated patients in the intensive care unit showed that fospropofol disodium had a milder inhibitory effect on the circulatory system of the patients.[12] Emerging evidence suggests comparable sedative efficacy with improved hemodynamic stability and reduced adverse effects,[13] yet its impacts on neurocognitive outcomes remain underexplored. So, propofol is a benchmark, its prodrugs have not been successful until fospropofol, and crucially, no prior study has directly compared the neurocognitive outcomes of fospropofol disodium and propofol in a model of PND. Our work therefore aims to fill a specific gap by investigating whether the clinically desirable pharmacokinetic differences of fospropofol translate to a meaningful difference in neurocognitive outcomes post-operatively.

Current understanding of PND pathophysiology implicates multifactorial mechanisms including neuroinflammation, blood–brain barrier disruption, and neurotransmitter dysregulation.[14,15] Advanced age emerges consistently as the predominant risk factor, with preoperative cognitive status serving as a critical predictor.[14] So, this study investigates whether fospropofol disodium demonstrates non-inferiority to propofol in PND prevention among elderly THA patients, while simultaneously evaluating its safety profile and hemodynamic effects. Our hypothesis posits that fospropofol's metabolic characteristics – particularly phosphate generation during conversion – may confer additional neuroprotective benefits beyond conventional propofol. The clinical significance of this investigation lies in its potential to: 1) establish evidence-based guidelines for anesthetic selection in vulnerable elderly populations, 2) reduce PND-associated morbidity through pharmacological optimization, and 3) provide mechanistic insights into the relationship between anesthetic metabolism and cognitive outcomes. By employing comprehensive neuropsychological testing at multiple postoperative intervals, this study aims to generate robust data to inform perioperative decision-making in aging surgical populations.

Materials and Methods

Ethical Approval

The study was approved by the Ethics Committee of the First Hospital Affiliated to the University of Science and Technology of China (Anhui Provincial Hospital) (Ethics Approval No. 2022KY Lun Audit No. 099) and has completed registration with the China Clinical Trial Registry (Registration No. ChiCTR2200061893).

Sample Size Calculation

Studies have shown that the incidence of cognitive dysfunction in elderly patients undergoing major non-cardiac surgery is approximately 40%. Based on this, we assumed that the incidence of PND in the propofol group was 40%. Sample size calculations were performed using the PASS 15.0 software, with the non-inferiority cutoff set at 20%, and the initial sample size was calculated to be 150 cases. Considering the possible difficulties in postoperative follow-up and the expected shedding rate of about 20%, the total number of subjects in the experimental group included in the study was 180, which were divided into two groups of 90 cases each according to the ratio of 1:1. The sample size of the control group was set at a ratio of 2:1 between the test group and the control group, which was 45 cases. The total number of subjects was 225.

Criteria for Inclusion and Exclusion

Inclusion criteria included patients undergoing total hip arthroplasty with age 65~80 years old, ASA grade I-III, right-handed, no history of radiotherapy or chemotherapy and elective total hip arthroplasty. Exclusion criteria included patients with schizophrenia, epilepsy, Parkinson's disease, and myasthenia gravis; patients with communication difficulties due to coma, severe dementia, speech disorders, or those who cannot cooperate due to other diseases; patients with craniocerebral trauma, or other craniocerebral disorders; and patients with anesthesia drug abuse; patients who need to be admitted to ICU for further treatment after surgery due to surgical reasons such as hemorrhage, or those who are still in a hemodynamically unstable state after intraoperative vasoactive drug treatment are excluded because sedative and analgesic drugs may continue to be given during ICU treatment to affect the judgment of PND. Criteria for termination of the study: subjects were terminated if they developed severe allergic reactions, hemorrhagic shock during the study period, or if the patient's family clearly indicated their refusal during the study.

Patients and Double-Blind Design

One hundred and eighty elderly patients aged 65~80 years who underwent total hip arthroplasty at the First Hospital of the University of Science and Technology of China from November 2022 to November 2024 were selected. The participants were divided into experimental and control groups. The experimental group was further subdivided into the propofol group (Group P) and the fospropofol disodium group (Group F), while the control group consisted of elderly family members who did not undergo surgery history. We included the control group to determine the mean baseline cognitive function of elderly patients undergoing this type of surgery, to enable subsequent Z-score analysis, and to exclude any self-learning effects that may exist in the scale. And this group was not included in the results presentation. Prior to the start of the program, random numbers were generated by the program leader using the "Random Number Generation" applet and placed into envelopes one by one. Half an hour before the start of anesthesia, the anesthesiologist received the envelope and obtained the random numbers. The random numbers were group F for odd numbers and group P for plural numbers. Neither the subjects nor the researchers were aware of the groupings (Figure 1).

Anesthesia Methods

Anesthesia Induction

Fospropofol Disodium Group (Group F): Sufentanil is administered at a dose of 0.3~0.4 μg/kg, followed by fospropofol disodium at a dose of 10 ~12 mg/kg; Propofol Group (Group P): Sufentanil is given at a dose of 0.3 ~0.4 μg/kg, followed by propofol at a dose of 1.5~2 mg/kg. Once the Bispectral Index (BIS) value drops below 60, rocuronium at a dose of 0.6~0.9 mg/kg is administered intravenously. After satisfactory neuromuscular blockade is achieved, tracheal intubation

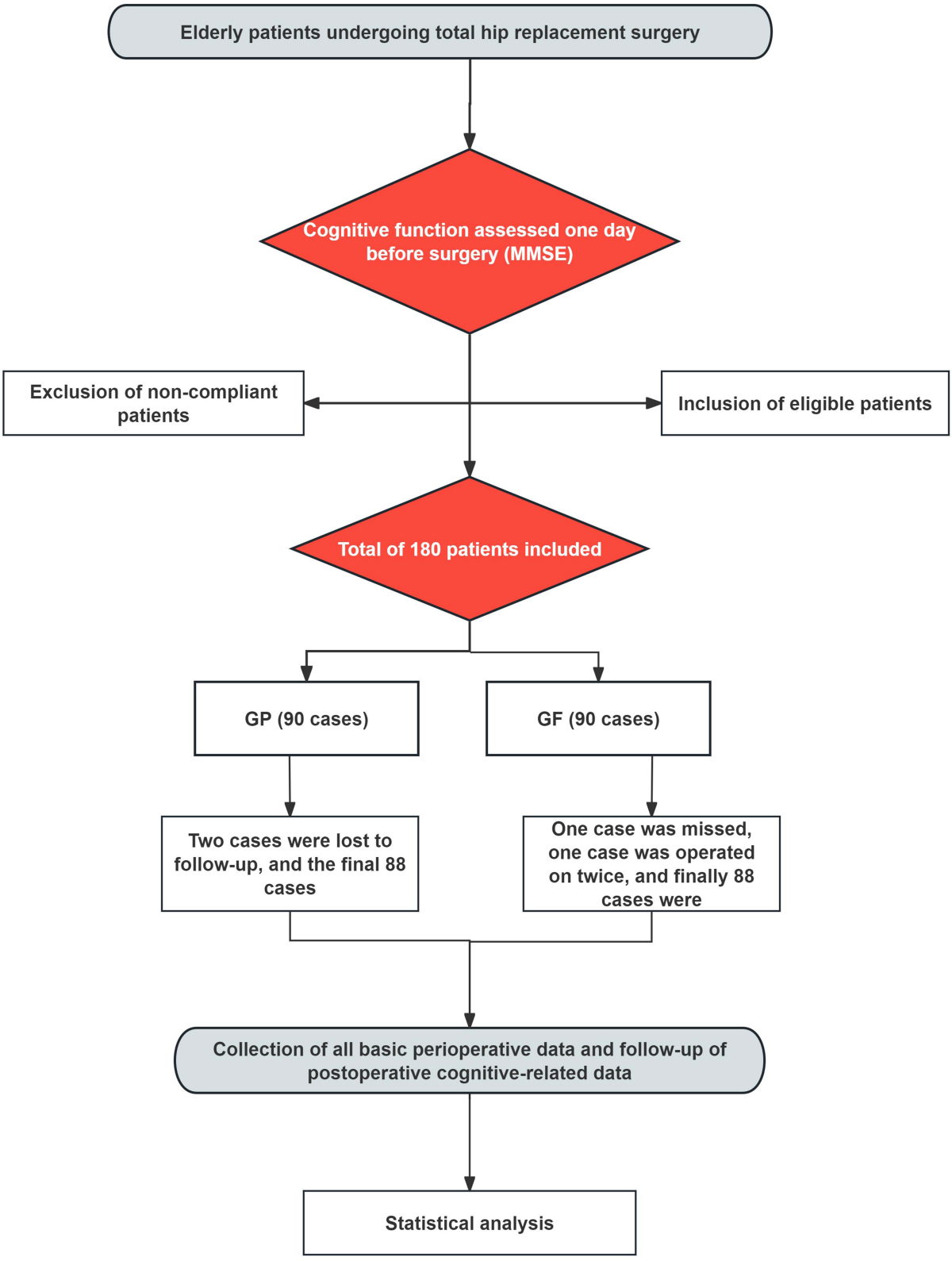

Figure 1 Flowchart of the experiment.
Abbreviations: MMSE, Mini-Mental State Examination; GP, Propofol group; GF, Fospropofol Disodium group.

is performed, the position of the endotracheal tube is confirmed using a stethoscope, the tube is then secured, subsequently the anesthesia machine is connected to initiate mechanical ventilation, and the patient's vital signs are monitored to ensure stability.

Anesthesia Maintenance and Intraoperative Management

For the Fospropofol Disodium Group (Group F), fospropofol disodium is administered via continuous infusion at a rate of 10~15 mg/kg/h, and remifentanil is infused at a rate of 10~15 μg/kg/h. For the Propofol Group (Group P), propofol is infused at a rate of 3 ~ 5 mg/kg/h, while remifentanil is infused at the same rate of 10~15 μg/kg/h. The depth of anesthesia is adjusted appropriately based on BIS monitoring results to ensure that the BIS value is maintained within the optimal range of 40~60.

Data Collection

General Information Collection

Record basic information about the patient (name, age, gender, BMI, ASA classification, history of chronic illness) and valid contact information for the patient or his/her immediate family. Patients were asked about their level of education and noted whether they could cooperate with the completion of the scale, and if they could not, the patient was excluded.

Data Collection During Anesthesia

The perioperative hemodynamic performance of the two groups was recorded in detail and MAP and HR data were monitored at several key time points, including: baseline (T0), immediately after induction of anesthesia (T1), at the beginning of the operation (T2), at the time point of bone cement implantation (T3), at the time point of 10 minutes after bone cement implantation (T4), at the end of the operation (T5), after extubation of the endotracheal tube (T6), after discharge from the PACU (T7). Anesthesia duration time and operation duration time, extubation time and PACU stay time; the dose of vasoactive drugs used during anesthesia and the number of visits were also recorded in both groups.

Collection of Scores for the Scale

3D-CAM or MMSE (An unauthorized version of the Chinese MMSE was used by the study team without permission, however this has now been rectified with PAR. The MMSE is a copyrighted instrument and may not be used or reproduced in whole or in part, in any form or language, or by any means without written permission of PAR (www.parinc.com)), DST and VFT scale scores were assessed by professional trained staff and strictly recorded for each patient at 1 day preoperatively, 1 day and 3 days postoperatively. Occurrence of delirium during hospitalization. IQCODE scores at 7 days postoperatively and 1 month postoperatively. Z-score method for defining cognitive decline: First, we included a control group at a ratio of 2:1 and calculated the mean and standard deviation of the cognitive scores for the control group. Second, we set the Z-score threshold ($Z \leq -1.5$) to define cognitive impairment; finally, we subtract the mean score of the control group from the experimental group's score and divide by the standard deviation of the control group to assess the presence or absence of cognitive dysfunction in patients. Since the Z-score method was used as an auxiliary assessment tool after the experiment was conducted, and the final results were qualitative data (ie, "yes" or "no"), the analysis results of the Z-score method were not included in the presentation.

Statistical Analysis

Statistical analysis was performed using SPSS 25.0 and GraphPad Prism 9.0 software program. The incidence of PND (including POD and POCD) in the two groups was tested for non-inferiority. Categorical variables were expressed as percentages, and the chi-square test or Fisher's exact test was used to compare the differences between the categorical variables in the two groups. For quantitative data, normality analysis using the Kolmogorov–Smirnov (K-S) test was used. Data that conformed to normal distribution were described using mean ± standard deviation and two independent samples *t*-test was used to compare differences between variables. If quantitative data did not conform to a normal distribution, they were described using the median (interquartile spacing), and the data were analyzed comparatively using the Mann–Whitney *U*-test. Statistical significance between the two sets of data can be considered to exist when $p < 0.05$ in the statistical analysis. ns indicates no significance; * indicates $p < 0.05$; ** indicates $p < 0.01$; *** indicates $p < 0.001$; **** indicates $p < 0.0001$.

Results

Patient Characteristics and Baseline Data

The study included 176 elderly patients THA, with 88 patients randomized to each treatment group (fospropofol disodium vs propofol) after accounting for exclusions. Baseline demographic and clinical characteristics, including age, sex, body mass index (BMI), comorbidities, and preoperative cognitive function scores, were well-balanced between the two groups. The median age was 70 years in both groups, with no significant differences in comorbidities such as hypertension, diabetes, or coronary artery disease. Preoperative cognitive assessments, including the Mini-Mental State Examination (MMSE), Digit Span Test (DST), and Verbal Fluency Test (VFT), also showed comparable scores, ensuring homogeneity between the groups for subsequent outcome comparisons (Table 1).

Table 1 Comparison of General Information

Items	Group P (n = 88)	Group F (n = 88)	*p*
Age (years), median (IQR)	70 (68, 75)	70 (67.25, 72)	0.120
BMI (kg/m2), mean ± SD	23.54±3.20	24.34±3.16	0.099
Sex (n, %)			0.757
Female	53 (60.23%)	55 (62.5%)	–
Male	35 (39.77%)	33 (37.5%)	–
Etiology (n, %)			0.634
Fractures	19 (21.59%)	15 (17.05%)	–
Hip Arthritis	27 (30.68%)	24 (27.27%)	–
Femoral head necrosis	27 (30.68%)	35 (39.77%)	–
Dysplasia	15 (17.05%)	14 (15.91%)	–
Comorbidities			–
HBP	36 (40.91%)	40 (45.45%)	0.543
DM	19 (21.59%)	13 (14.77%)	0.241
CAD	8 (9.09%)	5 (5.68%)	0.387
Cerebral infarction	5 (5.68%)	8 (9.09%)	0.387
ASA classification (n, %)			0.286
II	54 (61.36%)	47 (53.41%)	–
III	34 (38.64%)	41 (46.59%)	–
Level of education			0.276
Illiterate	37 (42.05%)	30 (34.09%)	–
Elementary school	23 (26.14%)	28 (31.82%)	–
Middle school	10 (11.36%)	17 (19.32%)	–
High school	12 (13.64%)	6 (6.82%)	–
University	6 (6.82%)	7 (7.95%)	–
Preoperative scores			

(*Continued*)

Table 1 (Continued).

Items	Group P (n = 88)	Group F (n = 88)	*p*
MMSE	25 (24, 27)	25 (24, 27.75)	0.553
DST (Orthopedic back)	7 (5, 7)	7 (6, 7)	0.104
DST (Reverse back)	2 (2, 3)	2 (2, 3)	0.229
VFT (Semantic)	13 (11, 15)	12 (8, 15)	0.063
VFT (Phonological)	2 (0, 5)	2 (0, 5)	0.684
VFT (Motion)	7.5 (6, 9)	7 (5, 9)	0.110

Abbreviations: IQR, Interquartile Range; BMI, Body Mass Index; SD, Standard Deviation; HBP, Hypertensive Blood Pressure; DM, Diabetes Mellitus; CAD, Coronary Artery Disease; ASA, American Society of Anesthesiologists; MMSE, Mini-Mental State Examination; DST, Digit Span Test; VFT, Verbal Fluency Test.

Cognitive Outcomes and PND Incidence

The incidence of PND, including POD and POCD, was similar between the fospropofol disodium and propofol groups at all assessed time points. POD occurred in 14.77% of patients in the fospropofol group compared to 12.5% in the propofol group ($p > 0.05$, Table 2), while POCD rates at postoperative day 1 were 32.95% and 31.82% ($p > 0.05$), respectively. By the 1-month follow-up, POCD rates decreased to 7.95% in the fospropofol group and 5.68% in the propofol group ($p > 0.05$), with no statistically significant differences observed at any time point. The 95% confidence interval (CI) for the rate difference of PND is (−0.113, 0.1583), which meets the previously set non-inferiority criteria. From this criterion, we confirmed the non-inferiority of fospropofol disodium compared to propofol in preventing cognitive decline.

Hemodynamic Profiles and Intraoperative Stability

Hemodynamic disorder is one of the risk factors for postoperative cognitive dysfunction. Therefore, we evaluated the correlation between the two drugs in hemodynamic homeostasis. Fospropofol disodium demonstrated distinct hemodynamic effects compared to propofol during surgery. Patients receiving fospropofol maintained higher mean arterial pressure (MAP) during critical surgical phases, particularly at bone cement implantation. By comparing the vasoactive drugs between the two groups of patients, we found that the number of patients in the phosphopropofol disodium group used ephedrine (Group P: 35, Group F: 56, $p = 0.002$, Figure 2) more than that in the propofol group. And, Group P required more frequent ephedrine administration (median dose: 6 mg vs 0 mg), suggesting a need for adjusted vasopressor management (Figure 3). We also compared the mean arterial pressure and heart rate of the patients at

Table 2 Postoperative Changes in Cognitive Function in Two Groups of Patients

Items	Group P (n = 88)	Group F (n = 88)	*p*
POD (n, %)	11 (12.5%)	13 (14.77%)	0.660
POCD (n, %)			
1 day after surgery	28 (31.82%)	29 (32.95%)	0.872
3 days after surgery	28 (31.82%)	26 (19.55%)	0.744
7 days after surgery	17 (19.32%)	17 (19.32%)	1.000
1 month after surgery	5 (5.68%)	7 (7.95%)	0.550
PND (n, %)	39 (44.32%)	40 (45.45%)	0.880

Abbreviations: POD, postoperative delirium; POCD, postoperative cognitive dysfunction; PND, Perioperative Neurocognitive Disorders.

https://doi.org/10.2147/DDDT.S548597

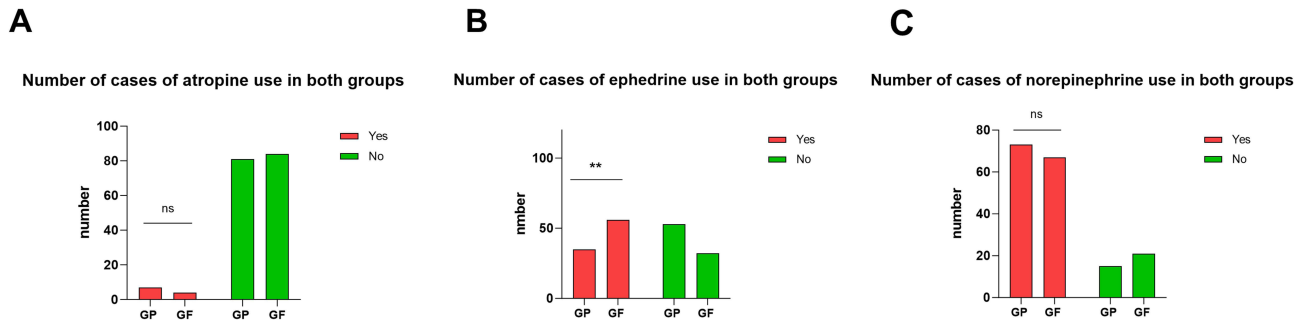

Figure 2 Comparison of the number of patients using vasoactive drugs during anesthesia in the two groups.
Notes: (**A**) Number of cases of atropine use in both groups; (**B**) Number of cases of ephedrine use in both groups; (**C**) Number of cases of norepinephrine use in both groups; Chi-square test (**A**–**C**). ns indicates no significance; ** indicates p < 0.01.
Abbreviations: GP, Propofol group; GF, Fospropofol Disodium group.

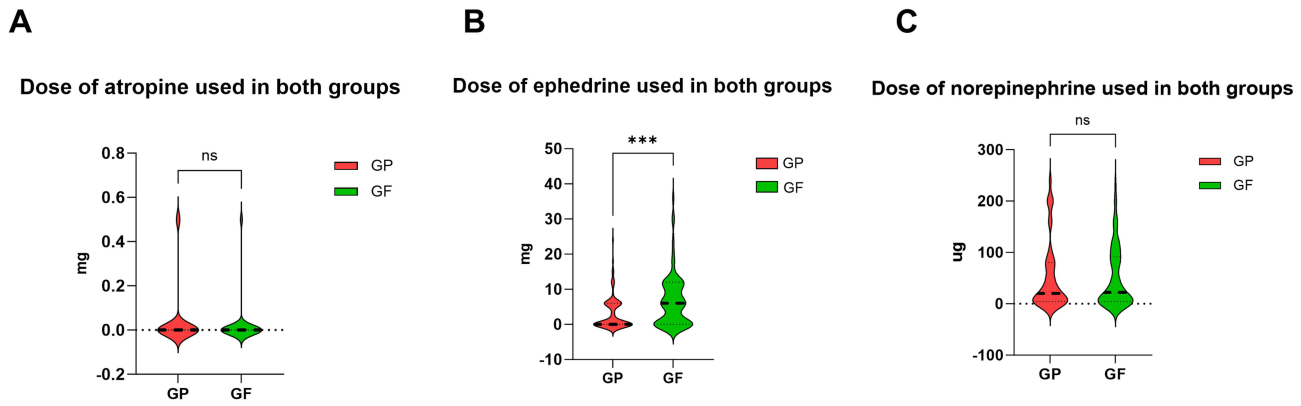

Figure 3 Comparison of vasoactive drug dosage during anesthesia in the two groups (IQR).
Notes: (**A**) Comparison of the dose of atropine used in the two groups; (**B**) Comparison of the dose of ephedrine used in the two groups; (**C**) Comparison of the dose of norepinephrine used in the two groups; *t*-test (**A**–**C**). *** indicates p < 0.001, ns indicates not significant.
Abbreviations: IQR, Interquartile Range; GP, Propofol group; GF, Fospropofol Disodium group.

different time points and found that at the beginning of the operation (T2), the MAP was higher in group F than in group P, with a statistically significant difference between the two groups (group P: 80.8 ± 8.8 mmHg, group F: 84.4 ± 11.7 mmHg, $p = 0.022$) (Figure 4A and B). At the time point of 10 minutes after bone cement implantation (T4), the heart rate of patients in the phosphopropofol disodium group was higher than that of the propofol group (Group P: 72 ± 2 bpm, Group F: 80 ± 3 bpm, $p < 0.0001$) (Figure 4C and D). At the time of discharge from the PACU, the heart rate of patients in the phosphopropofol disodium group was lower than that of the propofol group (Group P: 77 ± 13 bpm, Group F: 73 ± 10 bpm, $p = 0.037$) (Figure 4C and E). The two groups were statistically significant. There was no statistical difference in MAP and HR at the remaining time points ($p > 0.05$) (Figure 4). Although the heart rate is different during the operation at a certain time point, the overall difference during the whole operation is not obvious. These conclusions suggest that the inhibitory effect of phosphopropofol disodium on the autonomic nerve of the organism is light. Under the condition that ephedrine is used to maintain the hemodynamic steady state in phosphopropofol disodium group with little difference from propofol group during the whole operation, this may suggest that the effect of phosphopropofol disodium on hemodynamics is unlikely to indirectly affect postoperative cognitive function, consistent with the cognitive outcomes and PND incidence.

Safety and Adverse Events

We compared the two groups of patients during their hospitalization. There was no statistical difference between the two groups in terms of anesthesia time, operation time, and PACU stay (P>0.05). Patients in the disodium fospropofol group

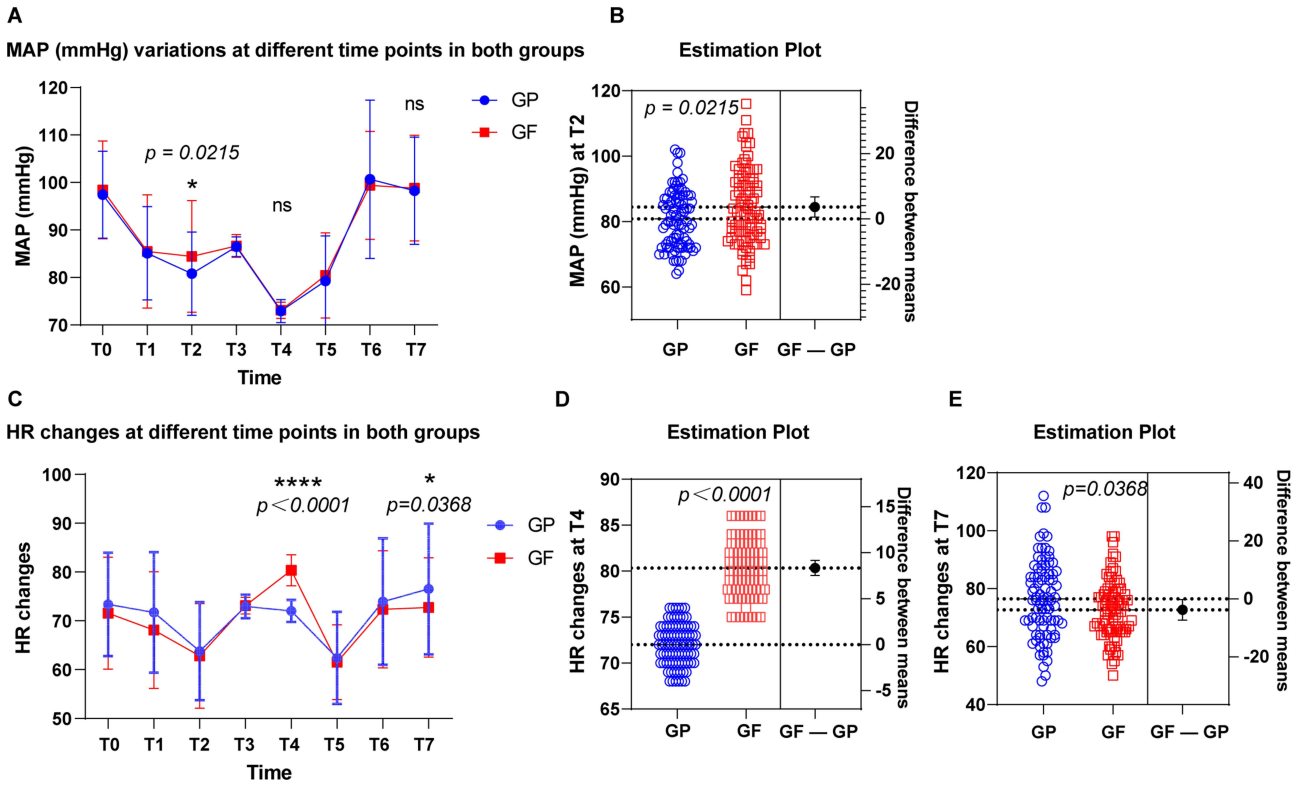

Figure 4 Changes in MAP and HR at different time points in both groups ($\bar{x}$ ±S).

Notes: (**A**) Line graph showing MAP (mmHg, mean ± SD) at sequential time points (T0~T7). Statistical significance between groups: * indicates p < 0.05 (specific comparison at T2: p = 0.0215), ns: not significant. (**B**) Estimation plot comparing MAP between GF and GP at T2 time point, with mean difference (center line), confidence intervals (error bars), and individual measurements (swarm plot). (**C**) Estimation plot of HR changes over time (T0~T7) for groups GF and GP, displaying mean differences and variability. **** indicates p < 0.0001 (specific comparison at T4); * indicates p < 0.05 (specific comparison at T7: p = 0.0368) (**D**) Estimation plot of the HR change at T4 time point, with mean difference (central dot), 95% confidence intervals (horizontal lines), and raw data distribution (swarm plot). (**E**) Estimation plot of the HR change at T7 time point, with mean difference (central dot), 95% confidence intervals (horizontal lines), and raw data distribution (swarm plot).

Abbreviations: MAP, Mean Arterial Pressure; HR: Heart Rate; GP, (Propofol group); GF, (Fospropofol Disodium group).

had longer extubation times than those in the propofol group, and there was a statistical difference between the two groups [Group P: 25min (15, 30), Group F: 29min (23.25, 38.5), $p < 0.001$]. The incidence of injection pain (Group P: 17.05%, Group F: 5.68%, $p = 0.018$) and nausea and vomiting (Group P: 31.82%, Group F: 18.18%, $p = 0.037$) was lower in patients in the fospropofol disodium group compared to the propofol group, with statistical differences between the two groups (Figure 5).

Risk Factors for Perioperative Neurocognitive Disorders

In this study, univariate regression analysis showed that age, ASA classification, preoperative MMSE score and preoperative VFT (movement) score were the associated risk factors for PND (p<0.05). Previous studies have shown that factors such as age and pain have an impact on the occurrence of developing PND (Table 3). Therefore, we included the factors with p<0.2 in the univariate regression analysis in the multivariate binary logistic regression analysis, and the results showed that age [*OR*, 1.149 (1.041, 1.268); p=0.006, Table 3] was a risk factor for PND, and the preoperative MMSE score was an independent protective factor affecting the occurrence of PND [*OR*, 0.693 (0.550, 0.872); p=0.002] (Figure 6). These associations remained significant after adjusting for potential confounders, and the model demonstrated good fit (Hosmer–Lemeshow test, $p = 0.714$). No significant associations were found between PND and other variables, including education level or intraoperative hemodynamic fluctuations.

https://doi.org/10.2147/DDDT.S548597

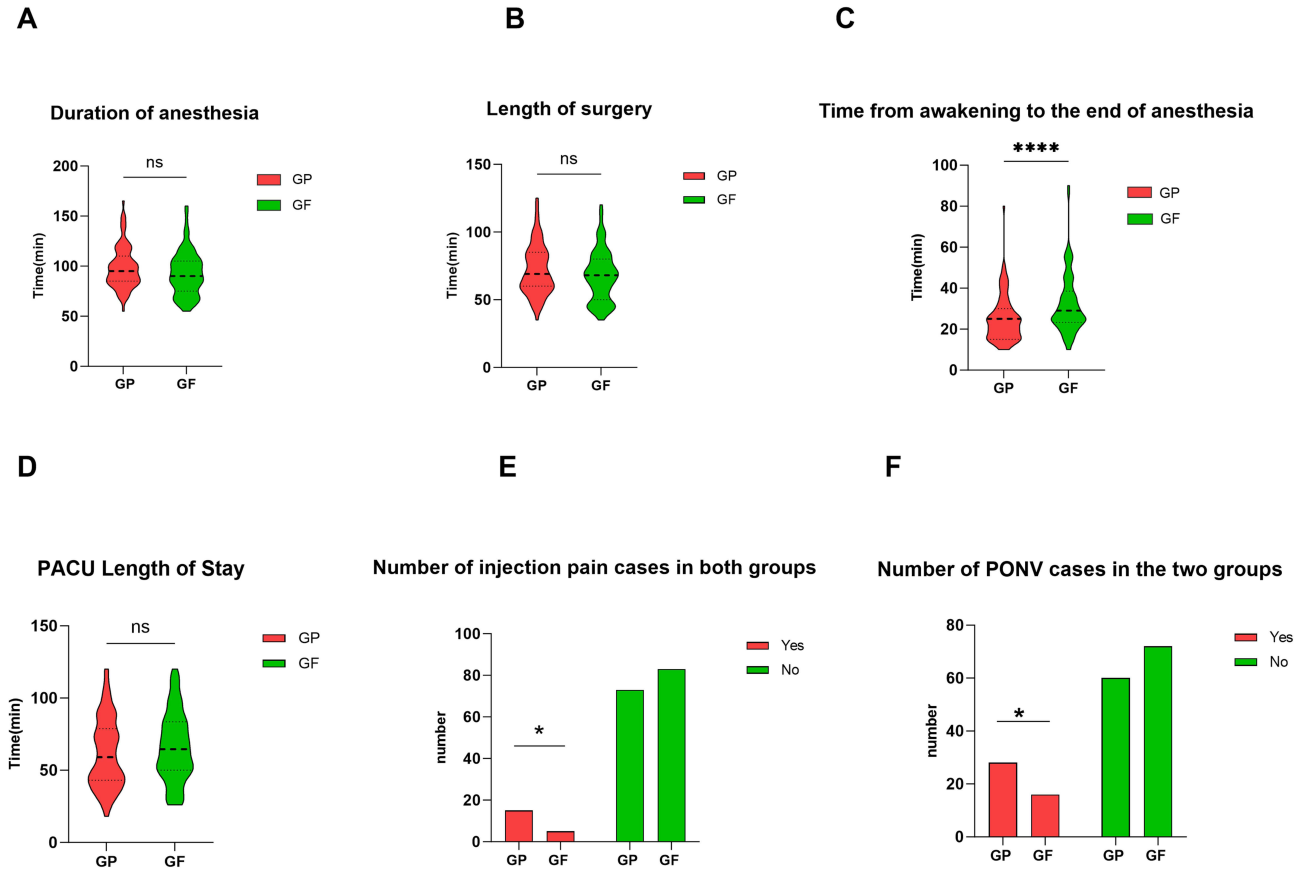

Figure 5 Comparison of hospitalization in the two groups (IQR).

Notes: (**A**) Comparison of anesthesia duration between the two groups; (**B**) Comparison of the duration of the two groups of surgeries; (**C**) Comparison of the duration of anesthesia to awakening between the two groups; (**D**) Comparison of PACU stay duration between the two groups; (**E**) Comparison of the number of injection pain cases between the two groups; (**F**) Comparison of PONV cases between the two groups; *t*-test (**A**–**D**); Chi-square test (**E** and **F**). * indicates $p < 0.05$, **** indicates $p < 0.0001$, ns: not significant.

Abbreviations: IQR, Interquartile Range; GP, (Propofol group); GF, (Fospropofol Disodium group); PACU, Post-Anesthesia Care Unit; PONV, Postoperative Nausea and Vomiting.

Discussion

The present randomized controlled trial provides compelling evidence that fospropofol disodium is non-inferior to conventional propofol in preventing PND in elderly patients undergoing total hip arthroplasty, while offering distinct

Table 3 One-Way Logistic Regression Analysis of Risk Factors Associated with PND ($\bar{x}$±SD or IQR)

Items	PND (n = 79)	NO-PND (n = 97)	Exp (B) (95% CI)	*p*
Age (years), median (IQR)	71 (68, 75)	69 (67.5, 71)	1.192 (1.092, 1.302)	<0.001
BMI (kg/m2), mean ± SD	23.85±3.39	24.02±3.05	0.984 (0.896, 1.080)	0.730
Female (n, %)	47 (59.49%)	61 (62.89%)	0.867 (0.471, 1.594)	0.646
HBP (n, %)	30 (37.97%)	46 (47.42%)	0.679 (0.371, 1.242)	0.209
DM (n, %)	10 (12.66)	22 (22.68%)	0.494 (0.219, 1.117)	0.090
Cerebral infarction (n, %)	6 (7.59)	6 (6.19%)	1.247 (0.386, 4.027)	0.713

(*Continued*)

Table 3 (Continued).

Items	PND (n = 79)	NO-PND (n = 97)	Exp (B) (95% CI)	*p*
ASA classification III (n, %)	45 (56.95%)	30 (30.93%)	2.956 (1.591, 5.492)	0.001
Illiterate (n, %)	28 (35.44%)	39 (40.21%)	Reference	-
Elementary school (n, %)	28 (35.44%)	23 (23.71%)	1.696 (0.813, 3.535)	0.159
Middle school (n, %)	13 (16.46%)	14 (14.43%)	1.293 (0.527, 3.173)	0.574
High school (n, %)	5 (6.33%)	13 (13.40%)	0.536 (0.171, 1.675)	0.283
University (n, %)	5 (6.33%)	8 (8.25%)	0.871 (0.257, 2.944)	0.823
Preoperative score				
MMSE	25 (24, 26)	25 (24, 28)	0.835 (0.705, 0.988)	0.036
DST (Orthopedic back)	7 (6, 8)	7 (6, 7)	1.164 (0.941, 1.440)	0.162
DST (Reverse back)	3 (2, 3)	2 (2, 3)	1.335 (0.939, 1.899)	0.107
VFT (Semantic)	13 (10, 15)	12 (8, 15)	11.074 (0.995, 1.158)	0.066
VFT (Phonological)	3 (1, 6)	1 (0, 4.5)	1.111 (0.998, 1.238)	0.055
VFT (Motion)	8 (6, 9)	7 (5, 9)	0.871 (0.768, 0.987)	0.031
Surgical time (min)	65 (55, 80)	70 (58.5, 85.0)	0.992 (0.976, 1.008)	0.327
Anesthesia time (min)	90 (80, 105)	95 (85, 106.5)	0.994 (0.980, 1.008)	0.392
Ephedrine (mg)	0 (0, 6)	3 (0, 6)	0.995 (0.549, 1.803)	0.988
Norepinephrine (ug)	20 (4, 80)	20 (4, 80)	1.000 (0.995, 1.004)	0.911
Atropine (mg)	0 (0, 0)	0 (0,0)	1.512 (0.444, 5.153)	0.508

Abbreviations: PND, Perioperative Neurocognitive Disorders; IQR, Interquartile Range; BMI, Body Mass Index; SD, Standard Deviation; HBP, Hypertensive Blood Pressure; DM, Diabetes Mellitus; CAD, Coronary Artery Disease; ASA, American Society of Anesthesiologists; MMSE, Mini-Mental State Examination; DST, Digit Span Test; VFT, Verbal Fluency Test.

advantages in terms of safety and tolerability. Our findings contribute to the growing body of literature on anesthetic neuroprotection in geriatric surgical populations, particularly in the context of orthopedic procedures where PND incidence remains alarmingly high.[1,16]

The comparable cognitive outcomes between fospropofol disodium and propofol groups across all assessment timepoints (POD: 14.77% vs 12.5%; POCD at 1 month: 7.95% vs 5.68%) are particularly noteworthy given their differing pharmacological profiles. While both agents ultimately deliver propofol as the active metabolite, the gradual enzymatic conversion of fospropofol disodium by alkaline phosphatase may provide more stable cerebral drug levels, potentially mitigating the abrupt neuronal effects associated with bolus propofol administration.[8] This finding aligns with recent preclinical evidence suggesting that controlled propofol release may enhance neuroprotective effects,[17] though our study was not designed to elucidate these mechanistic differences. The superior safety profile of fospropofol disodium, evidenced by significantly lower rates of injection pain (5.68% vs 17.05%, p=0.018) and PONV (18.18% vs 31.82%, p=0.037), represents a clinically meaningful advancement. These benefits likely stem from the elimination of lipid emulsion carriers, which are known to activate inflammatory pathways and TRP channels implicated in pain perception.[11] The reduced PONV incidence may reflect differential effects on 5-HT3 receptors or chemoreceptor trigger zone modulation,[18–20] though further pharmacodynamic studies are warranted to confirm these mechanisms. Our hemodynamic observations reveal a complex interplay between fospropofol disodium and cardiovascular stability.

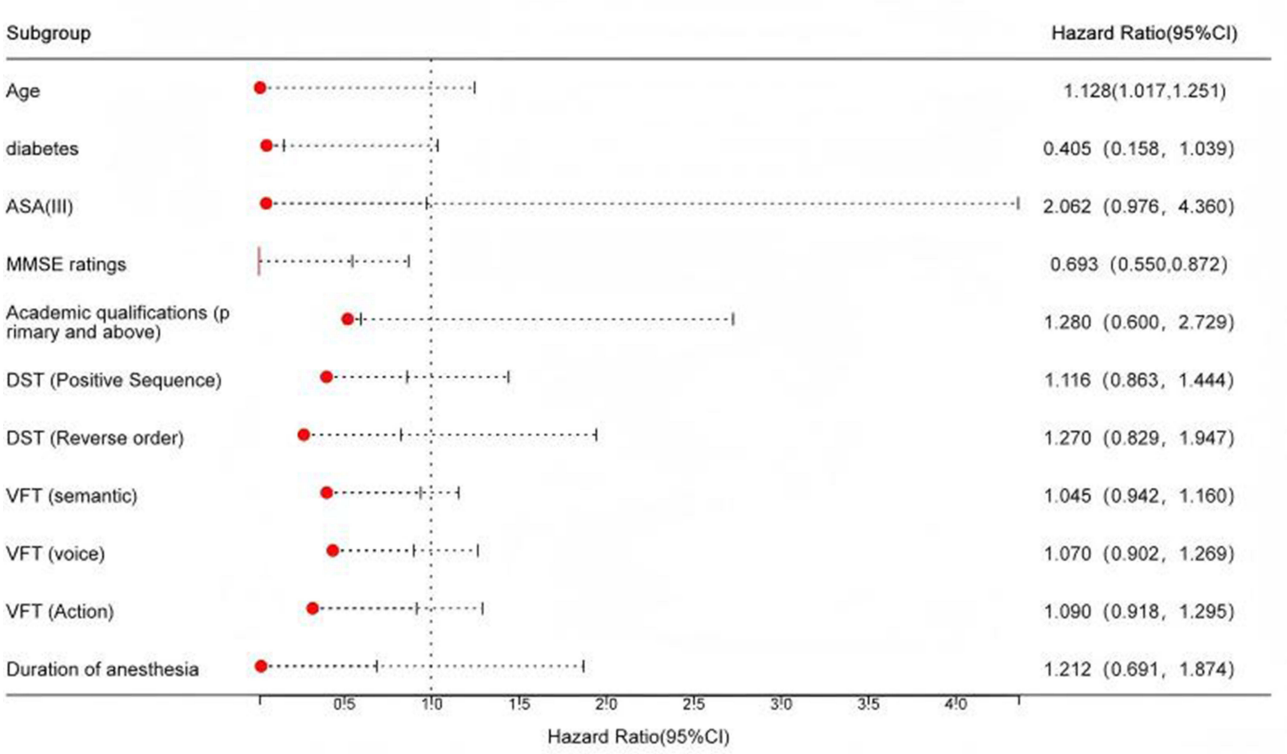

Figure 6 Binary Logistic Regression Analysis of Risk Factors Associated with PND.
Abbreviations: BMI, Body Mass Index; ASA, American Society of Anesthesiologists; MMSE, Mini-Mental State Examination; DST, Digit Span Test; VFT, Verbal Fluency Test.

While the higher MAP at the beginning of the operation (GF vs GP: 84.4±11.7 vs 80.8±8.8 mmHg, p=0.022) suggests better maintenance of perfusion pressure in fospropofol disodium – may be a critical factor in PND prevention - the increased ephedrine requirement (median 6 vs 0 mg, p<0.001) indicates nuanced cardiovascular effects or light inhibitory effect of phosphopropofol disodium. This paradox may reflect fospropofol's differential impact on sympathetic tone versus vascular resistance, highlighting the need for tailored hemodynamic management protocols when using this agent. From our results, fospropofol causes lower injection pain and PONV, but decreased cardiovascular stability with a tend towards a higher rate of postoperative cognitive dysfunction. Patients with phosphopropofol disodium group used ephedrine (Group P: 35, Group F: 56, p = 0.002) more than that in the propofol group. So, if ephedrine is not continuously compensated during operation, cardiovascular instability caused by fospropofol may increase the risk of PND. So, we should now emphasize that non-inferiority in cognitive outcomes does not imply equivalence in all clinical aspects. And anesthesiologists should attention cardiovascular instability caused by fospropofol and proactively adjust protocols by pre-loading intravascular volume, titrating the drug more gradually, and having vasopressors like ephedrine immediately available. The increased vasopressor requirement is likely due to fospropofol's unique pharmacokinetics, where hydrolysis within the vascular compartment may cause more pronounced initial vasodilation. While this is a manageable concern with vigilant monitoring, it warrants caution in patients with significant cardiovascular comorbidities, as the potential for hypotension could increase the risk of myocardial or cerebral ischemia. Ultimately, this necessitates careful patient selection and heightened hemodynamic management to ensure overall patient safety.

The identification of age (OR 1.149) and preoperative MMSE scores (OR 0.693) as independent predictors of PND risk reinforces established evidence[21,22] while emphasizing the importance of preoperative cognitive screening. Our finding that education level did not significantly influence PND risk contrasts with some previous reports,[23,24] possibly reflecting our sample's limited educational diversity or the protective effects of standardized anesthesia protocols.

In determining the changes in cognitive function, we used scales commonly used in clinical practice, including the Chinese version of the MMSE, the DST, the VFT, and the IQCODE questionnaire, which are widely used in clinical

practice to assess the cognitive function of surgical patients in the postoperative period, are simple to administer, and have good validity and reliability.[25–27] These scales can more comprehensively assess patients' perioperative cognitive function changes in terms of memory, awareness, reasoning, judgment, and language, and can track the change of patients' cognitive function situation after discharge, making our study more accurate. In determining cognitive decline, we used the Z-score method, which is more accurate compared to other scoring methods and removes the learning effect, which is considered an appropriate method for assessing PND by the new international guidelines.[28] We also used the 3D-CAM scale, which is widely used for delirium screening in the emergency department and in the elderly population, and is characterized by its simplicity and good accuracy.[29] After the patients were discharged from the hospital, we used the IQCODE questionnaire, which is independent of the patient's age, gender, and education level, as well as pre-morbid intelligence status, in a telephone follow-up mode. We recognized a score greater than or equal to 3.44 as cognitive decline based on previous studies, making our results more reliable.[30]

Another problem worth discussing is the influence of the different metabolic pathways of the two drugs on the outcome of neurocognitive function. Other major propofol prodrug that reached clinical practice, propofol hemifumarate (also known as Aquavan or GPI 15715). Its development was largely discontinued due to unpredictable drug release kinetics and adverse events. This provides a clear contrast to fospropofol disodium, which was designed to overcome the solvent-related side effects of propofol emulsion and offers a more predictable and controlled release profile due to its metabolism by endothelial alkaline phosphatases. This pharmacological distinction is key to our hypothesis that fospropofol may offer a different neurological side-effect profile. Nevertheless, this study does not completely address this issue, and it will be supplemented and enriched in future research.

Several limitations warrant consideration. First, the single-center design may limit generalizability, though standardized protocols enhance internal validity. Second, the 1-month follow-up precludes assessment of long-term cognitive outcomes. Third, the study was not powered to detect differences in rare adverse events. Future multicenter studies with extended follow-up could address these limitations while exploring potential subgroup effects. In conclusion, our results position fospropofol disodium as a viable alternative to propofol for elderly THA patients, offering comparable neurocognitive protection with improved tolerability. The distinct hemodynamic profile necessitates vigilant intraoperative monitoring, while the identified risk factors underscore the value of preoperative cognitive assessment. These findings should inform anesthetic selection for geriatric orthopedic patients and guide future research on optimized PND prevention strategies.

Conclusion

Fospropofol disodium demonstrated non-inferiority to propofol in preventing PND while offering advantages in procedural tolerability, including reduced injection pain and PONV. However, its distinct hemodynamic profile necessitated adjusted vasopressor management, and recovery times were slightly prolonged. Age and baseline cognitive function emerged as key predictors of PND risk, reinforcing the importance of preoperative assessment in elderly surgical patients. These findings support the safety and efficacy of fospropofol disodium may be a viable alternative in settings where injection pain and PONV are primary concerns, provided that hemodynamic stability is actively managed in elderly THA patients. While, we no longer broadly recommend it for all elderly patients without qualification.

Data Sharing Statement

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

Ethics Approval and Informed Consent

The study was approved by the Ethics Committee of the First Hospital Affiliated to the University of Science and Technology of China (Anhui Provincial Hospital) (Ethics Approval No. 2022KY Lun Audit No. 099) and has completed registration with the China Clinical Trial Registry (Registration No. ChiCTR2200061893). All study procedures were conducted in accordance with the Helsinki Declaration of 1964 (as revised in 2013). All subjects signed an informed consent form after being made fully aware of the research content and risks.

Acknowledgment

An unauthorized version of the Chinese MMSE was used by the study team without permission, however this has now been rectified with PAR.

The MMSE is a copyrighted instrument and may not be used or reproduced in whole or in part, in any form or language, or by any means without written permission of PAR (www.parinc.com).

Funding

This study was funded by National Natural Science Foundation of China, 82272225. National Natural Science Foundation of China, 81860249. USTC Research Funds of the Double First-Class Initiative YD9110002084. Health Research Program of Anhui Provincial Health Care Commission (AHWJ2023BAc20089), Anhui Province Health and Wellness "Backbone Talent" Program and Baeksuin Foundation, Keeping the Righteous and Innovative Baeksuin Anesthesia Depth Monitoring Research Support Project. This study was supported by Special Fund for Scientific Research from Hubei Chen Xiaoping Science and Technology Development Foundation (CXPJJH125001-2537).

Disclosure

The authors declare that they have no competing interests.

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