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Fospropofol disodium for preventing emergence agitation and relevant EEG features : a randomised controlled trial

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Abstract

Background

Emergence agitation is a clinically important complication during recovery from general anaesthesia. Preventive intervention before emergence may reduce its incidence and the need for rescue treatment. Fospropofol disodium is a water-soluble prodrug of propofol with a gradual sedative profile. We tested whether fospropofol disodium reduces emergence agitation after video-assisted thoracoscopic surgery and explored the potential electroencephalographic mechanisms.

Methods

In this prospective, single-centre, double-blind, randomised, placebo-controlled trial, adults aged 18–65 year undergoing elective video-assisted thoracoscopic surgery were allocated 1:1 to receive fospropofol disodium 7.5 mg kg^{-1} or an equal volume of saline at the end of surgery. The primary outcome was emergence agitation, defined as a Riker Sedation-Agitation Scale score ≥ 5 during emergence.

Results

All 138 randomised patients were analysed (69 per group). Emergence agitation occurred in 13 patients (18.8%) given fospropofol disodium and 31 patients (44.9%) given saline (risk ratio 0.42, 95% confidence interval 0.25–0.71; P = 0.001). Rescue propofol was given to 13 (18.8%) and 30 (43.5%) patients, respectively (risk ratio 0.43, 95% confidence interval 0.25–0.76; P = 0.002). Extubation time did not differ between groups, but post-anaesthesia care unit stay was longer with fospropofol disodium (median 55 [interquartile range 40–68.5] vs 45 [40–60] min; P = 0.021). No statistically significant between-group differences were detected in respiratory or haemodynamic adverse events.

Conclusions

A single dose of fospropofol disodium at the end of surgery reduced emergence agitation and rescue propofol use, but modestly prolonged post-anaesthesia care unit stay. Larger trials are required to evaluate safety and determine the optimal dose.

Clinical trial registration:

Chinese Clinical Trial Registry, ChiCTR2500106185 (registered 18 July 2025).

INTRODUCTION

Emergence agitation (EA) is a transient state of psychomotor excitement during recovery from general anaesthesia, characterised by restlessness, disorientation, and occasionally violent behaviour.[1] Although usually self-limited, EA is clinically relevant because it may lead to self-harm, accidental removal of catheters or drainage tubes, surgical-site bleeding and increased post-anaesthesia care utilisation. [2,3] The long-term consequences of EA remain uncertain, but it may overlap with or precede emergence delirium in some patients.[4]

Pharmacological strategies that provide a smoother transition from anaesthesia to wakefulness may reduce EA. Propofol-mediated sedation has been explored as a pharmacological approach to attenuate EA. Compared with volatile-based anaesthesia, propofol-based anaesthesia is generally associated with smoother recovery, and adult studies in high-risk nasal surgery have reported lower EA rates with propofol-based total intravenous anaesthesia than with sevoflurane-based anaesthesia.[5–7] In addition, paediatric studies suggest that a single intravenous bolus of propofol administered at the end of surgery can reduce the incidence and severity of EA after sevoflurane anaesthesia.[3,8–10] These findings support the concept that transient propofol-mediated sedation during early emergence may facilitate a more controlled transition from anaesthesia to wakefulness.

Fospropofol disodium (FP) is a water-soluble prodrug of propofol developed to overcome the limitations of conventional propofol.[11] Like propofol, FP produces sedative and anaesthetic effects by enhancing γ-aminobutyric acid type A (GABA_A) receptor-mediated chloride influx and inhibiting N-methyl-D-aspartate (NMDA) receptor-mediated calcium influx. Unlike propofol, FP does not require a lipid emulsion vehicle. Its gradual enzymatic conversion to active propofol results in a slower onset and more prolonged sedative effect,[11] potentially allowing administration at the end of surgery to provide sedation during extubation and the early post-extubation period—a vulnerable window for emergence agitation (EA). Clinical studies have demonstrated effective procedural and anaesthetic sedation with FP during endoscopy, induction of general anaesthesia, and mechanical ventilation in intensive care units.[11–14] Furthermore, phase II and III randomised trials showed that FP provided noninferior efficacy to propofol for general anaesthesia induction, with an acceptable safety profile.[12,14] Nevertheless, evidence supporting its use for EA prevention remains limited.

Therefore, we conducted a prospective, double-blind, randomised, placebo-controlled trial to test the hypothesis that a single intravenous bolus of fospropofol disodium administered at the end of surgery would reduce the incidence of EA in adults undergoing VATS. In a small subset of participants, we also conducted an exploratory EEG analysis to characterise perioperative EEG changes and explore their potential association with EA.

METHODS

Study design

This was a prospective, single-centre, double-blind, randomised, placebo-controlled clinical trial. The trial was approved by the Clinical Research Ethics Committee of the First Affiliated Hospital of Anhui Medical University (PJ2025-02-76) and was registered in the Chinese Clinical Trial Registry (ChiCTR2500106185; principal investigator: X. Liu; date of registration: July 18, 2025) before the first patient was enrolled. Patients were enrolled between 20 July 2025 and 15 January 2026. Written informed consent was obtained from all patients before participation, and the study was conducted in accordance with the Declaration of Helsinki. This report follows the Consolidated Standards of Reporting Trials (CONSORT) guidelines.[15]

Participants

Patients were eligible if they were aged 18–65 years, had an American Society of Anesthesiologists (ASA) physical status of I–III, had a body mass index of 18–30 kg m^{-2}, provided written informed consent, and were scheduled for elective VATS under general anaesthesia with an expected duration of more than 30 min.

Patients were excluded if they had severe hepatic or renal dysfunction, psychiatric disorders, long-term use of psychotropic medications, a history of alcohol abuse, known or suspected hypersensitivity to fospropofol disodium, opioids, or nonsteroidal anti-inflammatory drugs used in the perioperative analgesic regimen, cognitive impairment, exposure to general anaesthesia or sedation within 1 month before surgery, participation in another investigational drug study within the preceding 30 days, or language or communication barriers that prevented completion of cognitive and recovery-quality assessments.

Randomisation and masking

Eligible patients were randomised in a 1:1 ratio to receive either intravenous fospropofol disodium or intravenous 0.9% saline. The randomisation sequence was computer-generated using permuted blocks of four stratified by sex, because male sex has been reported as a significant risk factor for emergence agitation.[16] Separate randomisation sequences and sequentially numbered opaque envelopes were generated for male and female patients.

The allocation envelopes were sealed and controlled by investigators who were not otherwise involved in patient recruitment, data acquisition, outcome assessment, or clinical care. Shortly before surgery, an independent assistant who was not otherwise involved in the trial opened the corresponding envelope and prepared the allocated study drug. Fospropofol disodium 7.5 mg kg^{-1} was diluted with normal saline to a total volume of 20 mL, and the placebo consisted of 20 mL of normal saline. Both study drugs were prepared in identical 20-mL syringes and administered at the same rate. The 7.5 mg kg^{-1} dose, corresponding to 37.5% of the labelled adult induction dose, was selected as a subinduction dose to provide transitional sedation during emergence while limiting excessive residual sedation.

Patients, clinicians, investigators responsible for recruitment and data collection, and assessors responsible for follow-up evaluations were blinded to treatment allocation. Clinicians were allowed to withhold or discontinue administration of the study drug if necessary for safety reasons. Emergency unblinding was permitted only when knowledge of the treatment allocation was considered essential for patient safety.

Interventions and perioperative management

Patients were screened on the day before surgery according to the predefined eligibility criteria. Written informed consent was obtained by a trained investigator. Baseline characteristics were recorded, and preoperative cognitive function and anxiety were assessed using the Montreal Cognitive Assessment (MoCA) and the Amsterdam Preoperative Anxiety and Information Scale (APAIS), respectively.

When patients transferred to the operating room, peripheral venous access and arterial catheterisation were established. Ultrasound-guided intercostal nerve block was performed using 20 mL of 0.33% ropivacaine. Standard monitoring included electrocardiography, invasive arterial pressure, pulse oximetry, and patient state index (PSI). Dexamethasone 10 mg was administered intravenously before induction. Anaesthesia was induced with midazolam 0.02 mg kg^{-1}, sufentanil 0.3 μg kg^{-1}, and ciprofol 0.3–0.4 mg kg^{-1}. When the PSI reached 25–50, cisatracurium 0.2 mg kg^{-1} was administered. After loss of the eyelash reflex and establishment of adequate neuromuscular blockade, tracheal intubation was performed 3–5 min later. Mechanical ventilation was then initiated and adjusted to maintain end-tidal carbon dioxide at 35–40 mmHg.

Anaesthesia was maintained using a standardised balanced anaesthesia protocol in both groups. Sevoflurane 1–3%, remifentanil 0.1–1 μg kg^{-1} min^{-1}, and ciprofol 0.8–1.5 mg kg^{-1} h^{-1} were used for maintenance of anaesthesia. Cisatracurium was administered as needed. The PSI was maintained between 25 and 50. The intraoperative anaesthesia and analgesia protocols were identical between the two groups, except for the administration of fospropofol disodium or placebo at the end of surgery.

Sevoflurane was discontinued after restoration of two-lung ventilation, and then azasetron 10 mg was administered intravenously. Residual neuromuscular blockade was antagonized with neostigmine 1 mg and atropine 1 mg according to institutional practice. Immediately after skin closure and discontinuation of remifentanil and ciprofol, patients received fospropofol disodium 7.5 mg kg^{-1} or an equal volume of saline. The dose of fospropofol disodium was calculated according to actual body weight. The study drug was administered intravenously over 30 s.

After recovery of spontaneous respiration, all patients were transferred to the post-anaesthesia care unit (PACU) with the tracheal tube in place. During transfer and in the PACU, standard monitoring was continued. In the PACU, patients received supplemental oxygen at 5 L min^{-1}. Extubation was performed by a blinded anaesthetist according to standardised criteria. Patients were extubated when they

responded to verbal commands and met all of the following criteria: respiratory rate > 8 breaths min^{-1}, end-tidal carbon dioxide < 45 mmHg, and PSI > 60.

Emergence agitation was assessed independently by two investigators and confirmed by consensus. If agitation occurred, pain intensity and other reversible causes of agitation, including hypoxaemia, airway obstruction, haemodynamic instability, and residual neuromuscular blockade, were assessed immediately. Patients with an NRS score ≥ 4 received sufentanil 5 μg and were reassessed. For the primary outcome, EA was defined by an RSAS score ≥ 5 during the prespecified emergence period (see Outcomes); pain and other reversible-cause assessments guided management but were not additional outcome criteria. Verbal reassurance was attempted first in patients with EA. If verbal reassurance was ineffective, propofol 0.5 mg kg^{-1} was administered intravenously. Patients were discharged from the PACU when the Aldrete score was ≥ 9.

All patients received standardised intravenous patient-controlled analgesia (PCA), which contained sufentanil 0.4 μg kg^{-1} and flurbiprofen axetil 150 mg diluted with normal saline to a total volume of 150 mL. The PCA pump was programmed with a background infusion of 2 mL h^{-1}, a bolus dose of 2 mL, and a lockout interval of 15 min. In the ward, patients were instructed to use PCA when the NRS score reached 3. Additional analgesics and antiemetics were administered at the discretion of the treating physician.

On postoperative day 1, a trained anaesthetist assessed recovery quality using the 15-item Quality of Recovery questionnaire (QoR-15), pain using the NRS, and postoperative nausea and vomiting using the PONV score.

Outcomes

The primary outcome was the incidence of emergence agitation. The emergence period was defined as the interval from discontinuation of anaesthetic agents to 2 min after extubation. Emergence agitation was assessed using the RSAS. RSAS scores were defined as follows: 1–3, unarousable to sedated; 4, calm and cooperative; 5, agitated, anxious, or mildly agitated, attempting to sit up but calmed by verbal instruction; 6, very agitated, not calmed despite repeated verbal reminders, requiring physical restraint, or biting the tracheal tube; and 7, dangerously agitated, including pulling at the tracheal tube, attempting to remove catheters, climbing over the bed rail, striking staff, or thrashing. Emergence agitation was defined as an RSAS score ≥ 5, and dangerous agitation was defined as an RSAS score of 7.

The secondary outcomes included the incidence of agitation and dangerous agitation at 5, 10, and 15 min after extubation; systolic and diastolic blood pressure and heart rate measured before administration of the study drug, 3 min after administration, and 5, 10, and 15 min after extubation; extubation time; length of stay in the PACU; rescue analgesic and sedative requirements in the PACU; and adverse events in the PACU, including nausea and vomiting, pruritus, tachycardia, bradycardia, hypertension, hypotension, respiratory depression, and hypoxaemia.

Hypertension was defined as systolic blood pressure > 180 mmHg or an increase > 20% from baseline. Hypotension was defined as systolic blood pressure < 90 mmHg, mean arterial pressure < 65 mmHg, or a decrease > 20% from baseline. Tachycardia was defined as heart rate > 100 beats min^{-1} or an increase > 20% from baseline, and bradycardia was defined as heart rate < 50 beats min^{-1} or a decrease > 20% from baseline. Respiratory depression was defined as respiratory rate < 10 breaths min^{-1}, apnoea, or the need for airway support or assisted ventilation. Hypoxaemia was defined as SpO_2 <90% or an absolute decrease > 5% from baseline. Postoperative nausea and vomiting was defined as any nausea, retching, or vomiting occurring in the PACU or within 24 h after surgery.

Additional secondary outcomes included the QoR-15 score, pain score, PONV score, and postoperative length of hospital stay.

Exploratory EEG outcomes included spectral measures and EEG-derived emergence-state characteristics. Spectral measures included absolute and relative power in the δ, θ, α, and β bands, as well as power spectral density, assessed during the 2-min period from 7 to 9 min after study drug administration and from 90 s before to 30 s after extubation. The burst suppression ratio was calculated during the 2-min post-administration period. EEG-derived emergence-state characteristics were assessed over the 10 min before extubation. EEG epochs were classified into three exploratory states: delta-dominant slow-wave activity (ddSWA), alpha-associated slow-wave activity (adSWA), and non-slow-wave activity (nSWA).

Sample size calculation

The sample size calculation was based on the expected incidence of EA in a high-risk adult surgical population. Although the reported incidence of EA varies widely according to surgical type and diagnostic criteria, ranging from 0.25% to 90.5%, a previous randomised trial in adults undergoing nasal surgery under volatile-based general anaesthesia reported an EA incidence of 52% in the placebo control group.[3,19] Considering that patients undergoing thoracoscopic surgery are also exposed to several emergence-related stimuli, including double-lumen tube irritation, chest-drain stimulation, and postoperative pain[20–23], we assumed an EA incidence of 50% in the control group. We hypothesised that fospropofol disodium would produce a 50% relative reduction in EA incidence, from 50% to 25%. Based on a two-sided test for two independent proportions, 55 patients per group were required to achieve 80% power at an α level of 0.05. To allow for an anticipated dropout rate of 20%, 138 patients were planned for enrolment, with 69 patients allocated to each group. Sample size estimation was performed using PASS 2021 software (NCSS, LLC, Kaysville, UT, USA).

Statistical analysis

All efficacy analyses were conducted according to the intention-to-treat principle, with all randomised patients analysed in their originally assigned groups. Safety outcomes were analysed according to the treatment received. No imputation was performed because there were no missing data for the primary outcome. Continuous variables were assessed for normality using the Shapiro–Wilk test and are

reported as mean with standard deviation or median with interquartile range, as appropriate. Categorical variables are reported as numbers and percentages.

Continuous variables were compared between groups using the independent-samples t test or Mann–Whitney U test, as appropriate. Categorical variables were compared using the chi-square test or Fisher's exact test. The primary outcome, the incidence of emergence agitation, was analysed using the chi-square test or Fisher's exact test, as appropriate, and treatment effects are presented as risk ratios and risk differences with 95% confidence intervals.

Repeated haemodynamic measurements were analysed using linear mixed-effects models, with treatment group, time, and the group-by-time interaction included as fixed effects. Repeated binary outcomes, including agitation and dangerous agitation at 5, 10, and 15 minutes after extubation, were analysed using generalised estimating equations with a logit link and an exchangeable working correlation structure, with treatment group and time included as fixed effects. Results are presented as odds ratios with 95% confidence intervals. Repeated Riker Sedation-Agitation Scale scores were analysed as ordinal outcomes using a proportional odds generalised estimating equation model including treatment group, time, and the group-by-time interaction. An exploratory logistic regression analysis was performed to examine factors associated with emergence agitation. Variables considered clinically relevant or associated with emergence agitation in univariable analysis were entered into the multivariable model. These analyses were considered exploratory and were not used to define the primary treatment effect. Secondary outcomes were analysed without adjustment for multiplicity and should therefore be interpreted as exploratory.

EEG signals were sampled at 178.154 Hz, combined from Fp1 and Fp2 using pointwise median, filtered, and screened for artifacts. Multitaper analysis (NW = 2; three DPSS tapers; 4-s windows; 2-s steps) was used to calculate absolute and relative δ (0.5–4 Hz), θ (4–8 Hz), α (8–13 Hz), and β (13–30 Hz) power; relative power was referenced to total power from 0.5 to 30 Hz. PSDs were summarized using participant-level medians, and event-related power was aggregated in 10-s intervals. BSR was estimated using a peak-to-peak amplitude threshold of ≤ 5 μV in 0.5-s windows. For emergence-state analysis, standardized spectral features were classified by three-class K-means; state durations, proportions, and transitions were calculated per participant. Group comparisons used analysis of variance or the Kruskal–Wallis test, as appropriate, with false-discovery-rate correction for omnibus comparisons.

All tests were two-sided, and a P value < 0.05 was considered statistically significant. Analyses were performed using R software version 4.5.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient flow and baseline characteristics

Between July 2025 and January 2026, 180 patients were screened for eligibility. Forty-two patients were excluded, and 138 patients underwent randomisation. Sixty-nine patients were assigned to the saline

group and 69 to the fospropofol disodium group. All randomised patients received the assigned intervention and were included in the intention-to-treat analysis (Fig. 1). Baseline characteristics were generally balanced between the two groups (Table 1).

Table 1
Baseline characteristics of the study population.

Characteristic	Saline group (n = 69)	Fospropofol disodium group (n = 69)
Age, years	57 (49–61)	56 (49–60)
Male sex	34 (49.3)	34 (49.3)
Body mass index, kg/m²	23.67 ± 2.73	23.10 ± 2.59
Smoking history	26 (37.7)	27 (39.1)
Drinking history	15 (21.7)	16 (23.2)
ASA physical status		
I	4 (5.8)	9 (13)
II	54 (78.3)	43 (62.3)
III	11 (15.9)	17 (24.6)
NYHA Classification		
I	52 (75.4)	46 (66.7)
II	17 (24.6)	23 (33.3)
ALP (U/L)	67 (58–84)	71 (59–91)
Comorbidities		
Hypertension	15 (21.7)	21 (30.4)
Diabetes mellitus	4 (5.8)	3 (4.3)
Previous surgical history	22 (31.9)	13 (18.8)
Preoperative cognitive score	28 (25.5–29)	28 (26–29)
APAIS score		
APAIS, anxiety	14 (8–16)	10 (8–16)
APAIS, need for information	4 (2-7.5)	4 (2–8)

Values are presented as mean ± standard deviation, median (interquartile range), or number (%). ALP, alkaline phosphatase; APAIS, Amsterdam Preoperative Anxiety and Information Scale; ASA, American Society of Anesthesiologists; BMI, body mass index; NYHA, New York Heart Association.

Primary outcome

Fospropofol disodium reduced the incidence of emergence agitation during the emergence period. Emergence agitation occurred in 13 of 69 patients (18.8%) in the fospropofol disodium group and in 31 of 69 patients (44.9%) in the saline group (relative risk, 0.42; 95% confidence interval, 0.25–0.71; P = 0.001; Fig. 2A). This corresponded to an absolute risk reduction of 26.1 percentage points. The distribution of Riker Sedation-Agitation Scale scores during the emergence period shifted towards lower agitation scores in the fospropofol disodium group (Fig. 2B and Table S1). Dangerous agitation, defined as a Riker Sedation-Agitation Scale score of 7, occurred in 2 patients (2.9%) in the saline group and in no patients in the fospropofol disodium group (Table S1).

Post-extubation agitation and recovery outcomes

The incidence of agitation after extubation decreased over time in both groups (Fig. 2C). In the proportional odds generalised estimating equation model for repeated Riker Sedation-Agitation Scale scores at 5, 10, and 15 minutes after extubation, the time effect was significant (P < 0.001), whereas the group-by-time interaction was not significant (P = 0.841). Fospropofol disodium was associated with lower odds of a higher Riker Sedation-Agitation Scale category, although this association did not reach statistical significance in the repeated ordinal analysis (common odds ratio, 0.38; 95% confidence interval, 0.13–1.07; P = 0.066; Table S2).

Secondary perioperative outcomes are shown in Table 2. Rescue propofol was administered to 13 of 69 patients (18.8%) receiving fospropofol disodium and 30 of 69 patients (43.5%) receiving saline (relative risk 0.43, 95% confidence interval 0.25–0.76; P = 0.002). Across all randomised patients, the cumulative rescue propofol dose was 0 (0–0) mg in the fospropofol disodium group and 0 (0–40) mg in the saline group (P = 0.001). No statistically significant between-group difference in rescue sufentanil use was detected in the post-anaesthesia care unit. Extubation time did not differ between the fospropofol disodium and saline groups (30 [21.5–42.5] minutes versus 30 [22–37] minutes; P = 0.731). Post-anaesthesia care unit stay was modestly longer in the fospropofol disodium group (55 [40–68.5] minutes versus 45 [40–60] minutes; P = 0.021).

Table 2
Secondary perioperative outcomes.

Outcome	Saline group (n = 69)	Fospropofol disodium group (n = 69)	P value
Surgery duration (min)	90 (55.5–122)	95 (63.5–140)	0.526
Anaesthesia duration (min)	116 (85–148)	125 (86.5–164)	0.434
Extubation time (min)	30 (22–37)	30 (21.5–42.5)	0.731
PACU length of stay (min)	45 (40–60)	55 (40-68.5)	0.021
Patients receiving rescue propofol, n (%)	30 (43.5)	13 (18.8)	0.002
Cumulative rescue propofol dose in all randomised patients (mg)	0 (0–40)	0 (0–0)	0.001
Rescue sufentanil dose in PACU (μg)	0 (0–0)	0 (0–0)	0.267
PACU resting NRS score	1 (0-1.5)	0 (0-1.5)	0.178
PACU movement NRS score	2 (2–3)	2 (1-2.5)	0.183
Sufentanil dose for analgesic pump (μg/kg)	3.77 (3.59–3.94)	3.75 (3.57–3.89)	0.350
Flurbiprofen axetil dose for analgesic pump (mg)	150 (150–150)	150 (150–150)	0.057
Postoperative day 1 QoR-15 total score	129.77 ± 7.74	132.41 ± 6.39	0.048
Postoperative day 1 resting NRS score	0 (0–0)	0 (0–0)	0.547
Postoperative day 1 movement NRS score	2 (1.5-2)	2 (1-2.5)	0.974
Postoperative day 1 PONV score	1 (1–1)	1 (1–1)	0.405
Length of hospital stay (days)	6 (5–7)	6 (5–7)	0.771

Values are presented as mean ± standard deviation, median (interquartile range), or number (%). Between-group comparisons were performed using the independent-samples t test, Mann–Whitney U test, chi-square test, or Fisher's exact test, as appropriate. NRS, numeric rating scale; PACU, post-anaesthesia care unit; PONV, postoperative nausea and vomiting; QoR-15, 15-item Quality of Recovery questionnaire.

No statistically significant between-group differences were detected in pain scores in the post-anaesthesia care unit or on postoperative day 1 (Table 2). The postoperative day 1 Quality of Recovery-15 total score was slightly higher in the fospropofol disodium group than in the saline group (132.41 ± 6.39 vs 129.77 ± 7.74; P = 0.048), although this secondary outcome should be interpreted as exploratory. Item-level Quality of Recovery-15 results are provided in Table S4. No statistically significant between-group differences were detected in postoperative nausea and vomiting scores or length of hospital stay

(Table 2). The cumulative doses of anaesthetic agents used for induction and maintenance and of perioperative rescue medications are summarised in Table S3.

Safety outcomes

Prespecified adverse events are summarised in Table 3. No statistically significant between-group differences were detected in postoperative nausea and vomiting, pruritus, hypertension, hypotension, tachycardia, bradycardia, respiratory depression, or hypoxaemia. Haemodynamic trajectories during early recovery were also similar between groups (Fig. 3), although the trial was not powered to establish equivalence or safety.

Table 3
Adverse events in the post-anaesthesia care unit.

Adverse event	Saline group (n = 69)	Fospropofol disodium group (n = 69)	P value
Postoperative nausea and vomiting	4 (5.8)	3 (4.3)	> 0.999
Pruritus	0 (0.0)	0 (0.0)	NC
Hypertension	6 (8.7)	8 (11.6)	0.779
Hypotension	8 (11.6)	7 (10.1)	> 0.999
Tachycardia	3 (4.3)	4 (5.8)	> 0.999
Bradycardia	2 (2.9)	2 (2.9)	> 0.999
Respiratory depression	2 (2.9)	1 (1.4)	> 0.999
Hypoxaemia	2 (2.9)	1 (1.4)	> 0.999

Values are presented as number (%). PACU, post-anaesthesia care unit; NC, not calculated. P values were calculated using Fisher's exact test.

Exploratory logistic regression

Exploratory logistic regression was performed to examine factors associated with emergence agitation (Table S5). In the multivariable model, assignment to fospropofol disodium remained associated with lower odds of emergence agitation (odds ratio, 0.26; 95% confidence interval, 0.11–0.58; P = 0.001). These analyses were exploratory and were not used to define the primary treatment effect.

Exploratory EEG findings

In both time windows, the spectrograms showed prominent low-frequency activity. During the post-dose window, the FP group showed a more pronounced spectral peak around 10 Hz than the saline group. In the peri-extubation window, the mean power spectrum appeared higher in the FP group across much of the frequency range, particularly at lower frequencies (Fig. 4). The median BSR was zero in both groups,

with no significant between-group difference (H = 0.226, p = 0.634; FDR-adjusted p = 0.845). The selected representative EEG trajectories illustrated within-subject variability. In the non-agitation participant, EEG-state classifications alternated among nSWA, adSWA, and ddSWA, alongside fluctuations in δ and α power. In the agitation participant, nSWA and adSWA were observed earlier, followed by sustained ddSWA classification from approximately 200 s before extubation until extubation (Figure S1).

DISCUSSION

In this prospective, double-blind, randomised, placebo-controlled trial, a single intravenous dose of fospropofol disodium administered at the end of surgery reduced the incidence of emergence agitation in adults undergoing video-assisted thoracoscopic surgery. This reduction was accompanied by lower rescue propofol use in the post-anaesthesia care unit. No statistically significant between-group differences were detected in extubation time, respiratory depression, hypoxaemia, or haemodynamic events, although post-anaesthesia care unit stay was modestly longer in the fospropofol disodium group. These findings suggest that fospropofol disodium may provide a recovery-phase pharmacological strategy for reducing emergence agitation during the early transition from anaesthesia to wakefulness.

The reduction in emergence agitation may be related to FP's pharmacological profile. After intravenous administration, FP is hydrolysed by alkaline phosphatase to release propofol, phosphate, and formaldehyde, which is rapidly metabolised to formate. Because FP requires conversion to propofol, it has a slower onset and more prolonged sedative profile than conventional propofol.[11,24] This gradual delivery may provide more stable propofol exposure and sustained sedation during emergence, when airway and surgical stimuli may trigger agitation.[25] Preclinical findings on controlled propofol release suggest potential neuroprotective effects,[26] although our study did not assess pharmacokinetic or mechanistic differences. FP has been studied for bronchoscopy, colonoscopy, anaesthesia induction, and ICU sedation, but not specifically for preventing emergence agitation.[11–14,27,28] Our trial extends this evidence by evaluating FP administered at the end of surgery to reduce agitation during early recovery.

The clinical relevance of this effect is linked to the timing and surgical context of emergence agitation. In adults, emergence agitation is often concentrated around extubation and may be short-lived rather than sustained throughout postoperative recovery.[3] In the present trial, fospropofol disodium reduced agitation during the immediate emergence period, whereas between-group differences were less apparent at 5, 10, and 15 minutes after extubation. This temporal pattern is consistent with previous adult studies showing that agitation is most prominent immediately after extubation and usually resolves within several minutes.[21,23,29] Although this short duration might suggest a transient phenomenon, the peri-extubation period is clinically important because agitation at this time can lead to self-injury, accidental device removal, bleeding, or harm to healthcare staff.[3,30] This is particularly relevant in video-assisted thoracoscopic surgery, where double-lumen tube irritation, chest-drain stimulation, postoperative pain, and perioperative distress may converge during early recovery.

Therefore, an intervention that mainly reduces agitation during this vulnerable window may still provide clinically meaningful benefit.

The approximately 10-minute longer post-anaesthesia care unit (PACU) stay in the FP group may represent a trade-off consistent with its gradual conversion to active propofol.[11,24] It was not accompanied by delayed extubation, respiratory depression, hypoxaemia, or haemodynamic instability; its impact on PACU workflow and resource use warrants evaluation in larger pragmatic studies. Although the postoperative day 1 Quality of Recovery-15 score was statistically higher with FP, the between-group difference of 2.6 points was below the commonly reported minimal clinically important difference of approximately 6–8 points.[31,32] This finding therefore indicates a small statistical difference, not necessarily a clinically meaningful improvement. Previous studies, particularly in procedural sedation, have reported transient paraesthesia and pruritus with FP.[11,27,28] No pruritus was observed in our trial, and no statistically significant between-group differences were detected in postoperative nausea and vomiting, haemodynamic events, respiratory depression, or hypoxaemia. However, because paraesthesia and pruritus are subjective and may be difficult to assess during early emergence, their apparent absence should be interpreted cautiously.

In this exploratory EEG subset, the FP group showed a more prominent approximately 10-Hz peak during the post-dose window and descriptively higher peri-extubation power across much of the frequency range. Propofol-induced changes in slow-frequency and frontal alpha activity have been associated with transitions in responsiveness, providing a possible context for these observations; however, the present descriptive spectra cannot establish a drug-related mechanism or a difference in anesthetic depth [33]. EEG patterns during emergence are heterogeneous, with multiple state trajectories and transient transitional brain states reported during recovery [34,35]. Although the selected agitation case showed sustained ddSWA before extubation, this pattern was not supported by significant group-level differences in state duration, proportion, or transition probability. EEG changes during emergence do not necessarily predict clinical recovery[36]. A recent trial also found that propofol altered alpha power and burst suppression without changing delirium incidence [37]. Thus, the spectral trends and individual trajectory observed here should be considered hypothesis-generating.

This study has several limitations. First, it was a single-centre randomised trial including adults aged 18–65 years undergoing elective video-assisted thoracoscopic surgery, which may limit generalisability to older patients, obese patients, high-risk patients, and other surgical populations. Second, only one dose of fospropofol disodium, 7.5 mg kg^{-1}, was evaluated; therefore, the optimal dose for reducing emergence agitation while minimising delayed recovery remains unknown. Third, saline was used as the control, and no active comparator, such as propofol or remimazolam, was included. The findings therefore support the efficacy of fospropofol disodium compared with placebo but do not establish superiority or noninferiority relative to other sedative strategies. Fourth, despite standardised perioperative analgesia, antiemetic prophylaxis, and post-anaesthesia care management, emergence agitation may still have been influenced by multiple perioperative factors, including pain, double-lumen tube stimulation, and

chest tube-related irritation. Finally, the trial was powered for the primary outcome of emergence agitation rather than secondary recovery-quality or safety outcomes.

In conclusion, a single intravenous bolus of fospropofol disodium administered at the end of surgery reduced emergence agitation and rescue propofol use in adults undergoing video-assisted thoracoscopic surgery, but modestly prolonged post-anaesthesia care unit stay. Further dose-finding and active-comparator trials are warranted.

ABBREVIATIONS

adSWA
alpha-associated slow-wave activity
ALP
alkaline phosphatase
APAIS
Amsterdam Preoperative Anxiety and Information Scale
ASA
American Society of Anesthesiologists
BMI
body mass index
BSR
burst suppression ratio
CI
confidence interval
CONSORT
Consolidated Standards of Reporting Trials
ddSWA
delta-dominant slow-wave activity
EA
emergence agitation
EEG
electroencephalography
FDR
false discovery rate
FP
fospropofol disodium
$GABA_A$
gamma-aminobutyric acid type A
ICU
intensive care unit
MoCA

Montreal Cognitive Assessment
NC
not calculated
NMDA
N-methyl-D-aspartate
NRS
numeric rating scale
NYHA
New York Heart Association
PACU
post-anaesthesia care unit
PCA
patient-controlled analgesia
PONV
postoperative nausea and vomiting
PSD
power spectral density
PSI
Patient State Index
QoR-15
15-item Quality of Recovery questionnaire
RR
relative risk
RSAS
Riker Sedation-Agitation Scale
S
saline
SpO_2
peripheral oxygen saturation
VATS
video-assisted thoracoscopic surgery
nSWA
non-slow-wave activity.

DECLARATIONS

Ethics approval and consent to participate

The study was approved by the Clinical Research Ethics Committee of the First Affiliated Hospital of Anhui Medical University (PJ2025-02-76). Written informed consent was obtained from all patients before participation.

Consent for publication

Not applicable.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request, subject to institutional and ethical approval.

Competing interests

The authors declared no competing interests for this work.

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Authors' contributions

Q.-L.D.: Conceptualisation, formal analysis, writing original draft. J.-T.W.: Conceptualisation, formal analysis. Q.-Y.L.: Investigation. T.-T.P.: Investigation. L-L.T.: Investigation. P.-P.F.: Conceptualisation, investigation, methodology. X.-S.L.: Conceptualisation, methodology.

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Figures

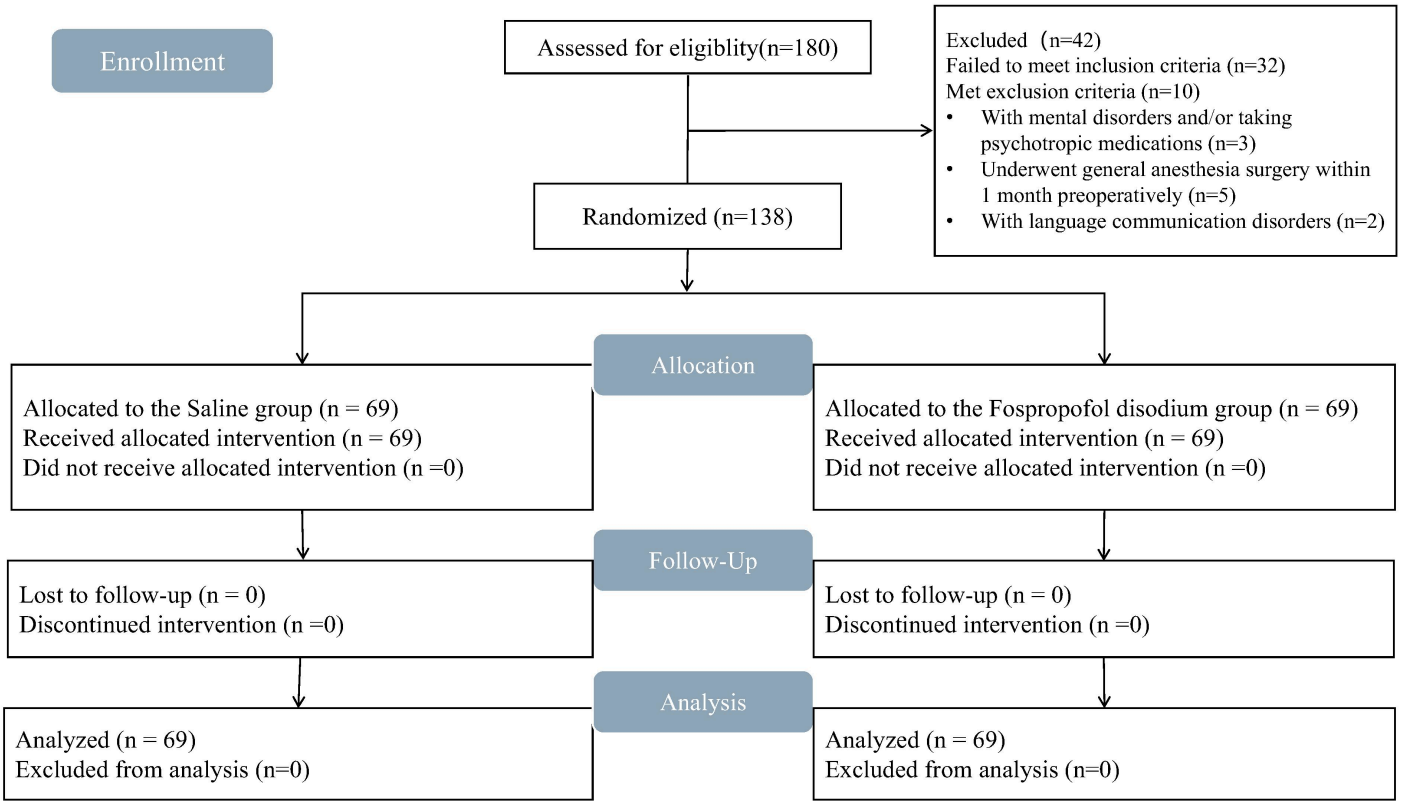


Figure 1

CONSORT flow diagram. CONSORT, Consolidated Standards of Reporting Trials.

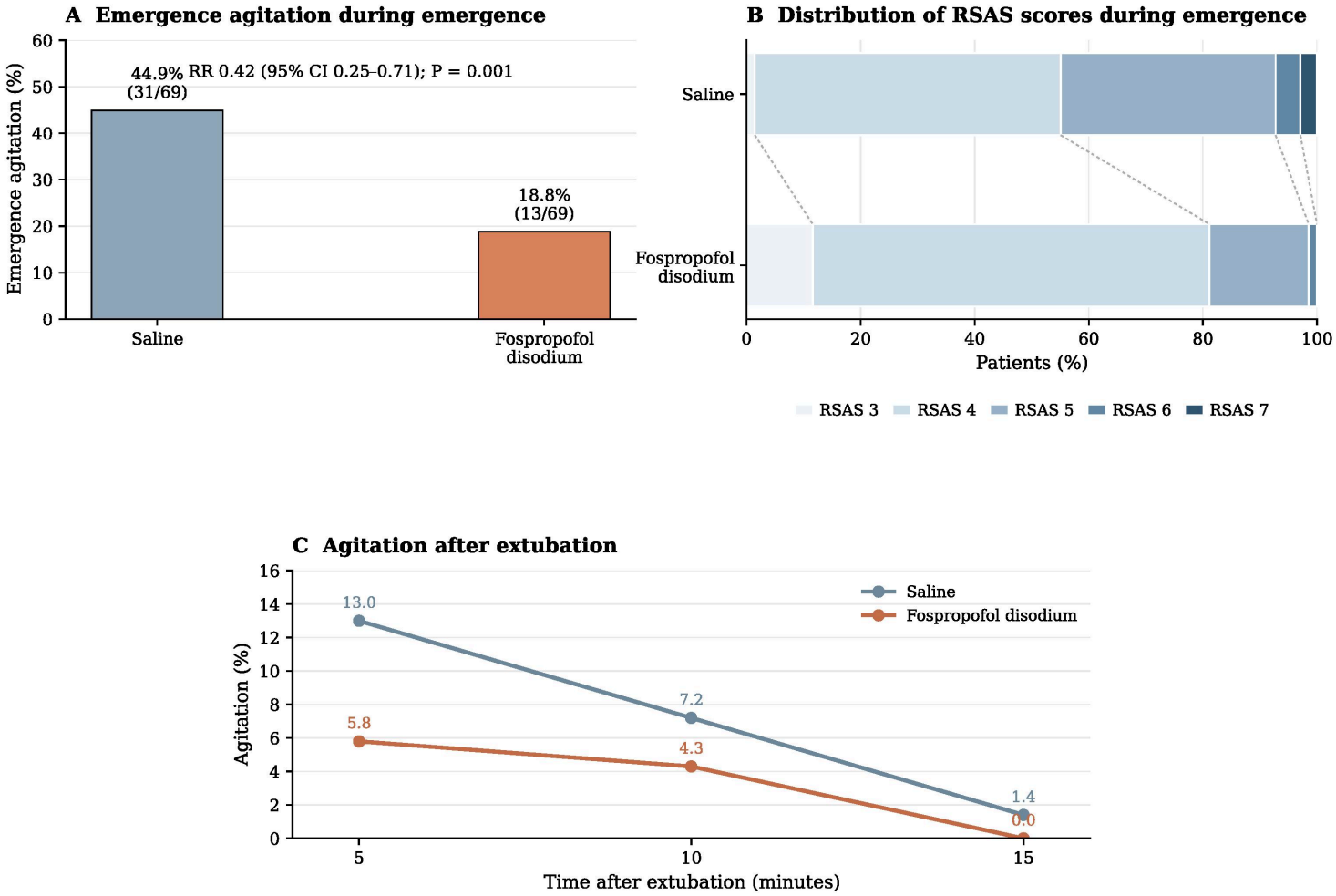


Figure 2

Primary outcome and Riker Sedation-Agitation Scale score distribution.
(A) Incidence of emergence agitation, defined as a Riker Sedation-Agitation Scale score of 5 or higher, during the emergence period. Bars show percentages, with numbers of patients shown as n/N. The treatment effect is presented as relative risk with 95% confidence interval. (B) Distribution of Riker Sedation-Agitation Scale scores during the emergence period. Dashed lines connect corresponding cumulative score boundaries between the saline and fospropofol disodium groups. (C) Incidence of agitation, defined as a Riker Sedation-Agitation Scale score of 5 or higher, at 5, 10, and 15 minutes after extubation.
CI, confidence interval; RR, relative risk; RSAS, Riker Sedation-Agitation Scale.

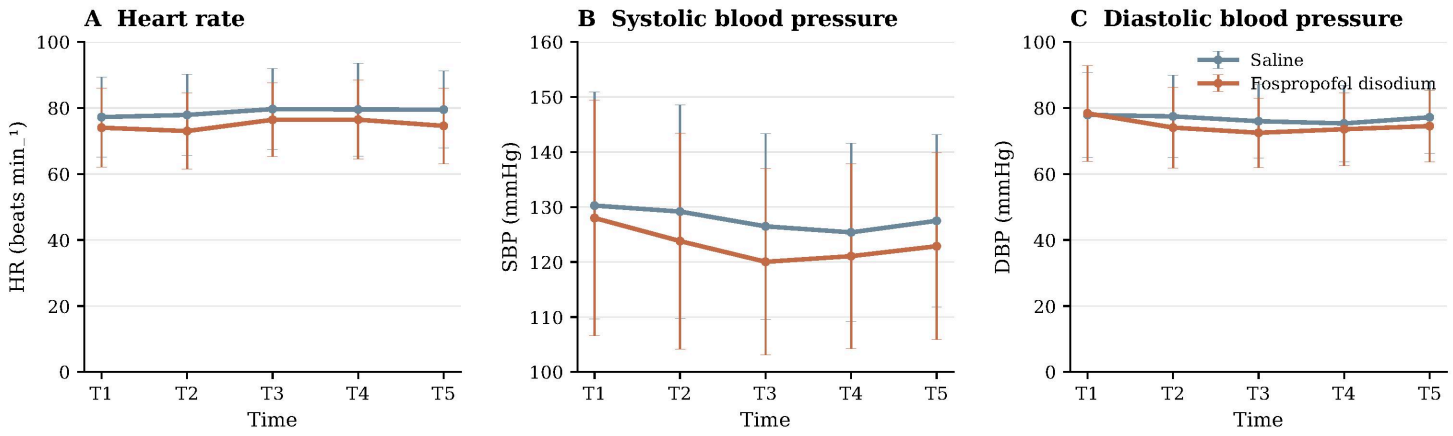


Figure 3

Haemodynamic changes during early recovery.

(A) Heart rate. (B) Systolic blood pressure. (C) Diastolic blood pressure. Data are presented as mean ± standard deviation. T1, before study drug administration; T2, 3 min after study drug administration; T3, 5 min after extubation; T4, 10 min after extubation; T5, 15 min after extubation.

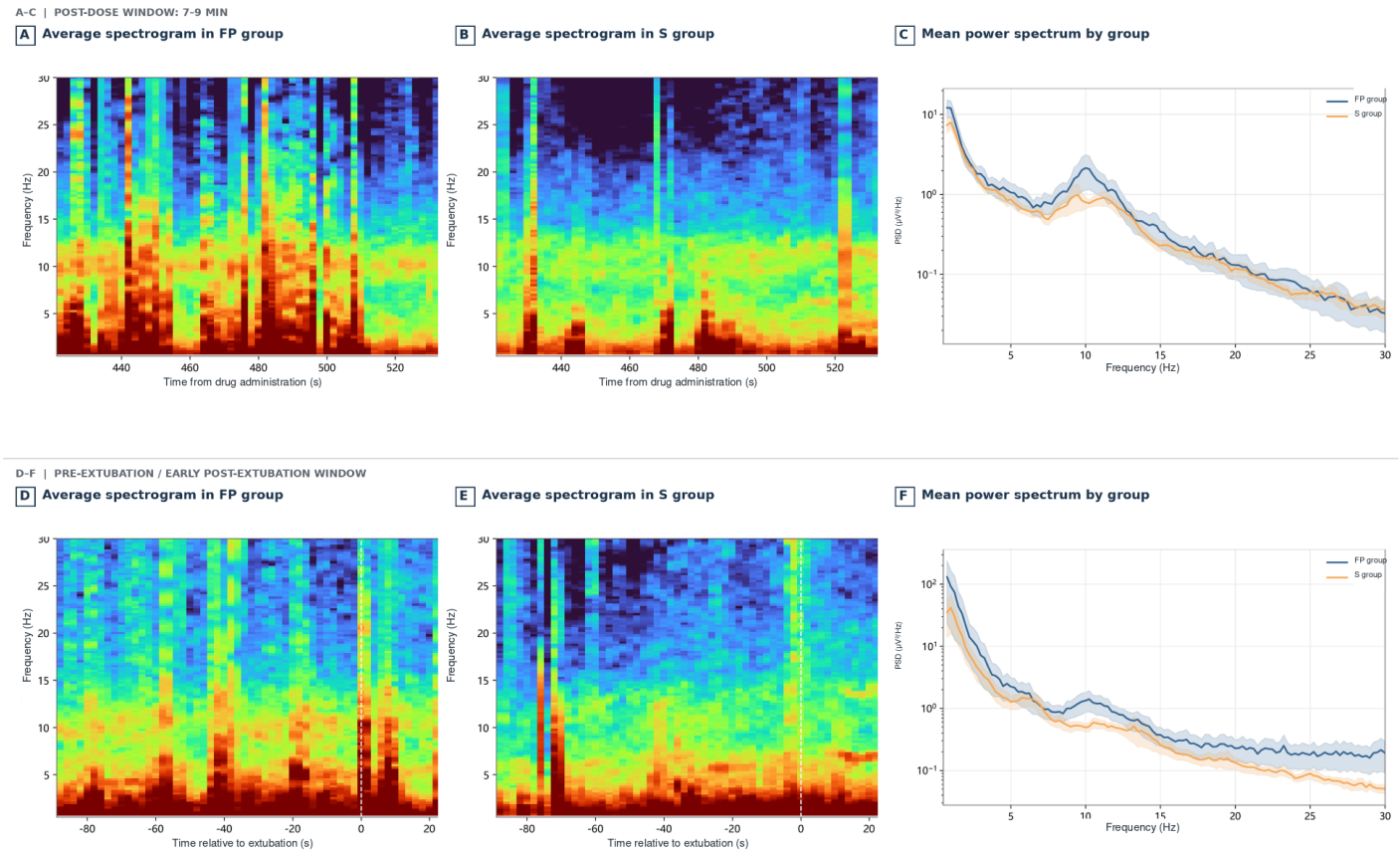


Figure 4

Exploratory EEG spectral characteristics in the fospropofol disodium (FP) and saline (S) groups.

(A, B) Mean spectrograms 7–9 min after study drug administration; (C) corresponding mean power spectra. (D, E) Mean spectrograms during the peri-extubation period; the dashed vertical line indicates extubation (0 s). (F) Corresponding mean power spectra in the pre-extubation window. Power spectral density (PSD) is plotted on a logarithmic scale. FP, fospropofol disodium; S, saline.

Supplementary Files

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