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Efficacy and Safety of Fospropofol$_{FD}$ Compared to Propofol When Given During the Induction of General Anaesthesia: A Phase II, Multi-centre, Randomized, Parallel-Group, Active-Controlled, Double-Blind, Double-Dummy Study

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Abstract: The present phase II study aimed to compare the efficacy and safety of fospropofol disodium for injection (Fospropofol$_{FD}$) and propofol when given during the induction of general anaesthesia in patients scheduled for elective surgery. Fospropofol$_{FD}$ is a water-soluble prodrug of propofol. Approved by the Ethical Committee, 240 participants aged 18–65 years were equally randomly allocated to receive an intravenous bolus of Fospropofol$_{FD}$ 20 mg/kg or propofol 2 mg/kg without any anaesthetic pretreatment. The primary efficacy end-point was the sedation success rate within 5 min. after administering investigational drugs (the sedation success is defined as obtaining Modified Observer's Assessment of Alertness/Sedation scale score of 1). All the participants completed the induction and intubation within 25 min. after administration. The sedation success rates within 5 min. after administration of Fospropofol$_{FD}$ 20 mg/kg and propofol 2 mg/kg were 94.50% *versus* 100% in the intention-to-treat population and 95.10% *versus* 100% in the per-protocol population, respectively. The non-inferiority test obtained a *p*-value less than 0.025, and the lower limits of the one-sided 97.5% confidence interval were more than −0.09. This meant that Fospropofol$_{FD}$ 20 mg/kg was considered non-inferior to propofol 2 mg/kg for the primary efficacy end-point. Compared with propofol 2 mg/kg, Fospropofol$_{FD}$ 20 mg/kg had a slower sedation efficacy. No serious adverse events were observed in the two groups. The sedation success rate within 5 min. after administration of Fospropofol$_{FD}$ 20 mg/kg was non-inferior to propofol 2 mg/kg, and Fospropofol$_{FD}$ 20 mg/kg can be used for the induction of general anaesthesia safely.

Propofol is a widely used intravenous anaesthetic/sedative–hypnotic agent in the induction and maintenance of anaesthesia or sedation inside and outside operating rooms [1–3]. Propofol is highly lipophilic and has a very low solubility in water, so it is mainly formulated in a lipid emulsion. Although it is widely used in the present clinical practice, propofol emulsion still has some formulation-related adverse reactions, for example pain on injection, thrombophlebitis, hyperlipidaemia, potentially fatal microorganism infection, allergic risk and infusion symptom complex [1–5]. To avoid the emulsion formulation-related adverse reactions, some scientists have tried to search for a water-soluble pro-drug to replace propofol emulsion.

Fospropofol is a water-soluble pro-drug of propofol. Fospropofol is completely metabolized by alkaline phosphatases to propofol (active metabolite), formaldehyde and phosphate. Formaldehyde is further metabolized to formate, which is then primarily converted to carbon dioxide by oxidation [6]. Propofol liberated from fospropofol is further metabolized to propofol glucuronide and quinol derivatives [6]. Fospropofol does not require lipid emulsion as a drug carrier, so it can avoid disadvantages associated with the lipid emulsion formulation of propofol. For example, it can relieve the pain on injection, avoid hyperlipaemia after a long-time infusion and reduce the bacterial growth rate.

Fospropofol disodium for injection (hereafter referred to as Fospropofol$_{FD}$) is manufactured by Yichang Humanwell Pharmaceutical Co., Ltd., Hubei, P. R.China. Fospropofol$_{FD}$ is a sterile, non-pyrogenic, white or slightly yellow, lyophilized powder for intravenous administration. Each vial contains 500 mg of fospropofol disodium, which should be reconstituted with aqua pro-injection or normal saline to a clear and colourless solution before injection. This study was designed to compare the efficacy and safety of Fospropofol$_{FD}$ 20 mg/kg and propofol 2 mg/kg, both of which were used as sedatives to induce general anaesthesia in patients scheduled elective surgery.

Materials and Methods

Participants and study design. This study was performed in six study sites in China approved by both of the State Food and Drug Administration and the Ethics Committee, West China Hospital of Sichuan University. It was also registered at http://www.chictr.org/cn/ (registration number: ChiCTR-TRC-12002724) on 27 November 2012. It was conducted in accordance with the Declaration of Helsinki and guidelines on good clinical practice. All the participants gave their written informed consents before their participation in the study.

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A total of 240 participants were enrolled into this study, who had been scheduled for elective surgery under general anaesthesia. The participants were aged 18–65 years, with the body mass index (BMI) of 18–30 kg/m^2 and American Society of Anesthesiologists physical status of 1–2. The inclusion criteria for the study were as follows: systolic blood pressure (SBP) 90–140 mmHg and diastolic blood pressure ≤90 mmHg; normal or abnormal electrocardiogram (ECG) but with no clinical significance, such as heart rate 50–120 beats/min. (bpm), QTcB interval (a corrected QT interval by Bazett's formula) ≤450 msec. in the male participants and ≤470 msec. in the female participants; and normal or abnormal results of the routine laboratory tests [haematology, urinalysis, hepatic function (alanine transaminase, aspartate aminotransferase, total bilirubin, alkaline phosphatase and serum albumin), renal function (blood urea nitrogen, creatinine), blood glucose, blood lipid, serum myocardial enzyme (creatine kinase, creatine kinase MB) and electrolytes (Na^+, K^+, Ca^{2+})] but with no clinical significance.

The exclusion criteria were as follows: allergic diseases or hypersensitivity to the investigational drugs or the drugs with a similar structure, contraindication to the investigational drugs, family history of malignant hyperthermia, pregnancy (a positive urine pregnancy test) or having a pregnancy plan within 1 month perioperatively, primary or secondary hypertension, central nervous system diseases, coagulation disorders, presence of or expected difficult airway, history of surgery under general anaesthesia within 3 months perioperatively, history of alcohol or drug abuse, participation in an investigational drug study within 3 months perioperatively and previous exposure to some QT prolongation drugs within 3 months before eligibility for study participation.

This study was a phase II, multi-centre, randomized, parallel-group, active-controlled, double-blind, double-dummy study, designed to compare the efficacy and safety of Fospropofol$_{FD}$ 20 mg/kg and propofol 2 mg/kg when given during the induction of general anaesthesia in patients scheduled for elective surgery. All the 240 participants were randomly allocated (stratified by the study site) into two groups to receive an intravenous injection of Fospropofol$_{FD}$ 20 mg/kg or propofol 2 mg/kg, respectively, in an allocation ratio of 1:1 based on a computer-generated random list.

The Fospropofol$_{FD}$ dose was determined according to previous phase I studies, in which doses of Fospropofol$_{FD}$ higher than 15 mg/kg resulted in 100% of the participants obtaining the Modified Observer's Assessment of Alertness/Sedation scale (MOAA/S) score of 2 within 5 min. after being administered with the 50% effective dose of 8 mg/kg [7,8]. The primary efficacy end-point in this phase II study was the sedation success (defined as obtaining a MOAA/S score of 1) rate within 5 min. after the investigational drug administration; therefore, 20 mg/kg was selected as the Fospropofol$_{FD}$ dose. As the related medical literature reported, propofol 2 mg/kg could result in 85–100% of the sedation success rates, and 2–2.5 mg/kg of propofol was recommended for inducing general anaesthesia by Diprivan. Therefore, 2 mg/kg was selected as the propofol dose [9–16].

Fospropofol$_{FD}$ was reconstituted with normal saline to prepare a clear, colourless, aqueous solution containing 5% (w/v, 50 mg/ml) fospropofol disodium before administration in this study. Diprivan (AstraZeneca SpA, Caponago, Italy) was a white, oil-in-water emulsion containing 1% (w/v) propofol, 10% soybean oil, 2.25% glycerol and 1.2% egg lecithin. This study was an active-controlled, double-blind, double-dummy study, but fospropofol disodium solution and propofol emulsion had different appearances. Therefore, normal saline was used as an analogue of fospropofol, and lipid emulsion was used as an analogue of propofol emulsion, which contained 10% (w/v) soybean oil and 1.2% egg lecithin. As per the requirement of the double-blind method, the participants in the Fospropofol$_{FD}$ group were given Fospropofol$_{FD}$ and lipid emulsion intravenously at the same time, while the participants in the propofol group were given propofol emulsion and normal saline intravenously.

All the medical investigators were blinded to the information about the investigational drugs, except the study nurses who prepared the investigational drugs. All the participants were also blinded to this information. Identical syringes and drug volumes were used in the groups so that the double-blind could be maintained.

Study procedures. Before administering the investigational drugs, the participants were fasted for at least 10 hr. In the operating room, 18-gauge venous indwelling needles were placed in the median cubital veins of the patient's two arms. The lactated Ringer's solution 500 mL was infused within 30 min. before administering the investigational drugs. Pulse oxygen saturation (SpO_2), respiratory rate (RR), SBP, mean arterial pressure (MAP), heart rate (HR), body temperature (T) and standard 12-lead electrocardiogram (ECG) were continuously monitored by the multi-parameter monitors during the whole operation and at 24 hr after start of the investigational drug administration. A bispectral index (BIS) sensor was applied to the forehead before inducing anaesthesia, and the BIS values were measured continuously during the operation. The baseline values of vital signs, ECG and BIS were obtained from all the participants.

Before administering the investigational drugs, no pre-operative medication was given. The investigational drugs (emulsion, 0.2 mL/kg; aqueous solution, 0.4 mL/kg) were, respectively, injected into the right or left median cubital vein at the same time for 1 min. by two investigators. After the initial bolus dose was intravenously administered, the patient obtained the MOAA/S score of 1 (table 1) [17] and soon was given midazolam 0.04 mg/kg, fentanyl 3 μg/kg and rocuronium bromide 0.9 mg/kg (hereafter referred to as the combined administration) intravenously to complete the induction of general anaesthesia. Then, the tracheal intubation was performed at 2 min. after the combined administration. If the patient failed to obtain the MOAA/S score of 1 within 5 min. after the initial doses of the investigational drugs, a supplemental dose (half of the initial dose) was injected immediately. If the MOAA/S score of 1 was obtained within 20 min. after the supplemental dose, the combined administration was continued; otherwise, the patient was considered to fail in the sedation and was withdrawn from the study.

In this study, sevoflurane and remifentanil were used for maintaining anaesthesia after the tracheal intubation. The recommended sevoflurane concentration for the maintenance was 1.5–2% with 2 L/min. of oxygen flow, and the recommended remifentanil infusion speed was 0.1–0.2 μg/(kg·min). The doses for the maintenance could be adjusted by the investigators according to the depth of anaesthesia. All the participants were extubated after operation and observed in the post-anaesthesia care unit for at least 30 min. until their full recovery.

End-points. The primary efficacy end-point was the sedation success rate within 5 min. after administration. The secondary efficacy end-points included the sedation success rate within 25 min., the supplemental rate of the investigational drugs (defined as the number of patients requiring a supplemental dose to obtain the MOAA/S score of 1), the time to the MOAA/S score of 1, the time to the loss of the eyelash reflex and the BIS values [18].

Table 1.
Modified Observer's Assessment of Alertness/Sedation Scale (MOAA/S) score.

Responsiveness	Score
Responds readily to name spoken in normal tone	5
Lethargic response to name spoken in normal tone	4
Responds only after name is called loudly and/or repeatedly	3
Responds only after mild prodding or shaking	2
Responds only after painful trapezius squeeze	1
Does not respond to painful trapezius squeeze	0

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Safety was assessed at the baseline, during the operation, and at the 24-hr follow-up interview. The safety evaluation included assessments on the central nervous system (CNS), vital sign measurements (blood pressure, HR, RR, SpO_2, T), ECG, laboratory tests (serum chemistry, haematology, serum myocardial enzyme and urinalysis) and adverse reactions. The laboratory tests were performed before administration and at the 24-hr follow-up interview.

Statistical analysis. The primary objective of this study was to investigate whether Fospropofol$_{FD}$ 20 mg/kg was non-inferior to propofol 2 mg/kg in the sedation success rate within 5 min. after administration. Based on the results from the phase I studies of Fospropofol$_{FD}$, literature review and clinical research on propofol, the sedation success rate of 99% for propofol 2 mg/kg and the non-inferiority margin (Δ) of 9% was determined [6,8–16]. At the one-sided significant level of 0.025 and a power of 0.80, 100 of the participants in each group were required to have an investigation on whether Fospropofol$_{FD}$ 20 mg/kg was non-inferior to propofol 2 mg/kg. Considering the possible drop-outs (20%) during the study, 240 participants (120 participants in each group) were enrolled in this study.

The efficacy analyses were performed in the intention-to-treat (ITT) population and the per-protocol (PP) population with the ITT population as a priority. The ITT population included all the randomized participants who had received at least one dose of the investigational drugs. The PP population was defined as a subset of the ITT population, whose participants completed the study without any significant protocol violations. The safety analyses were performed in the safety population, which included all the randomized participants who had received at least one dose of the investigational drugs and at least one safety assessment.

The primary efficacy end-point data were analysed by the following two methods: (i) the non-inferiority test ($\alpha = 0.025$, $\Delta = 9\%$) and (ii) the lower limit of the one-sided 97.5% confidence interval (CI). Non-inferiority of Fospropofol$_{FD}$ 20 mg/kg to propofol 2 mg/kg was concluded if the non-inferiority test obtained a p-value less than 0.025, and the lower limit of the one-sided 97.5% CI for the difference in the sedation success rate was more than -9%. The efficacy and safety data were analysed using a proper statistical analysis method depending on their types and distributions as follows: quantitative variables were expressed as mean $\pm$ S.D. and analysed using Student's t-test or the Wilcoxon rank-sum test; categorical variables were analysed by the chi-square test or the Fisher exact test.

In this study, all the statistical tests except the primary efficacy end-point were two-tailed, and a p-value less than 0.05 was considered statistically significant unless otherwise specified. The statistical analyses were performed by statisticians in the Department of Biostatistics, Institute of Drug Clinical Trial • GCP Center, West China Hospital, using SAS 9.2 software (SAS Institute Inc., 100 SAS Campus Drive, Cary, NC, USA).

Results

Study population.

A total of 240 participants were randomized in six study sites in China, and the diagram of participant flow was investigated (fig. 1). A total of 262 participants were assessed for eligibility, and 240 participants were randomized. Of the 240 participants, 120 received propofol and 120 received Fospropofol$_{FD}$. One participant was excluded, as he was unblinded for post-operative haematuria during the study period, which resulted in 119 participants receiving Fospropofol$_{FD}$ and 120 participants receiving propofol to be analysed in the ITT population. Of the 119 participants receiving Fospropofol$_{FD}$, two were excluded, as they did not meet the inclusion criteria; then, 117 were analysed in the PP population. Of the 120 participants receiving propofol, five were excluded, as they did not meet the inclusion criteria; then, 115 were analysed in the PP population. All the demographic and intra-operative characteristics were comparable between the two groups except the weight and body mass index (BMI) (table 2). The Fospropofol$_{FD}$

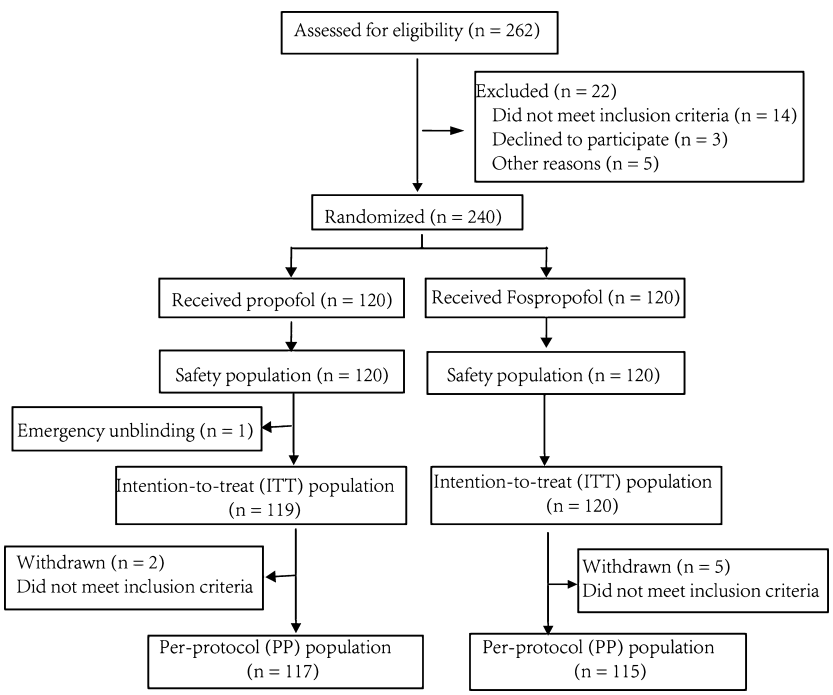

Fig. 1. Diagram of participant flow.

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group included the heavier participants compared with the propofol group (mean weight: 62.1 kg *versus* 59.4 kg, BMI: 22.7 *versus* 21.9) ($p < 0.05$).

Efficacy.

In this study, the primary efficacy end-point was the sedation success rate within 5 min. after administration. In the ITT and PP populations, no statistically significant differences were found in the sedation success rates within 5 min. after administration between the two groups ($p > 0.05$); logistic regression analysis was performed on the imbalanced weight at baseline in the two groups, resulting in a model parameter of *p*-value of 0.925 in the ITT population and 0.873 in the PP population. This result indicated that the weight imbalance at baseline did not affect the comparison between the two groups. In the ITT and PP populations, the non-inferiority test ($\alpha = 0.025$, $\Delta = 9\%$) obtained a *p*-value less than 0.025 and the lower limits of the one-sided 97.5% CI were more than $-\Delta$ (-0.09). These results indicated that the sedation success rate within 5 min. after administering $Fospropofol_{FD}$ was non-inferior to propofol (table 3).

In the two groups, the sedation success rates within 25 min. after administration were 100%. In the ITT population, the supplemental rates of the investigational drugs were 2.5% and 0.8% ($p = 0.317$) in the $Fospropofol_{FD}$ and propofol groups, respectively; in the PP population, they were 1.7% and 0.8% ($p = 0.620$), respectively. The time to the MOAA/S score of 1 and the time to the loss of the eyelash reflex were longer in the $Fospropofol_{FD}$ group than in the propofol group (fig. 2). The results showed that $Fospropofol_{FD}$ 20 mg/kg had a slower onset than propofol 2 mg/kg on the time to the MOAA/S score of 1 and the time to the loss of the eyelash reflex.

The BIS values were significantly higher in the $Fospropofol_{FD}$ group than in the propofol group at 1–4 min. after administration ($p < 0.05$), similar at 5 min. after administration, but significantly lower at 6–70 min. after administration ($p < 0.05$). These results indicated that the onset time was later in the $Fospropofol_{FD}$ group than in the propofol group on BIS values. The lowest BIS value (40.8 ± 13.0) in the propofol group was obtained at 5 min. after administration, while the lowest BIS value (25.5 ± 13.9) in the $Fospropofol_{FD}$ group was obtained at 12 min. after administration. Although the BIS values obtained after intubation could be affected by the variable concentrations of remifentanil and sevoflurane, it is suspected that the stronger and longer sedative effect in the $Fospropofol_{FD}$ group was induced by $Fospropofol_{FD}$ 20 mg/kg. It is also presumed that the greatest sedative effect for $Fospropofol_{FD}$ 20 mg/kg was later than that of propofol 2 mg/kg (fig. 3).

Table 2.

Demographic and intra-operative variables.

Characteristics	Propofol (n = 120)	$Fospropofol_{FD}$ (n = 120)	*p*-value
Age (mean ± S.D., year)	38.3 ± 11.7	38.5 ± 11.3	0.886
Sex			
Males, n (%)	59 (49.6)	60 (50.00)	0.948
Females, n (%)	60 (50.4)	60 (50.00)	
Height (mean ± S.D., cm)	164.3 ± 7.7	165.2 ± 7.5	0.361
Weight (mean ± S.D., kg)	59.4 ± 9.6	62.1 ± 10.2	0.034
BMI (mean ± S.D.)	21.9 ± 2.8	22.7 ± 2.8	0.032
ASA status, n (%)			
1	96 (80.7)	95 (79.2)	0.774
2	23 (19.3)	25 (20.8)	
BIS (mean ± S.D.)	94.6 ± 3.4	94.1 ± 3.3	0.104
Duration of operation (mean ± S.D., min)	90.7 ± 56.4	95.2 ± 64.7	0.968
Blood loss			
<200 mL	115 (96.6)	118 (98.3)	0.672
200–400 mL	4 (3.4)	2 (1.7)	
>400 mL	0 (0.0)	0 (0.0)	
Fluid infusion quantity (mean ± S.D., ml)	1169.3 ± 378.7	1209.9 ± 363.8	0.574
Surgical procedures			
General surgery	58 (52.3%)	53 (47.7%)	0.255
Ear–nose–throat surgery	37 (31.1%)	49 (40.8%)	
Urologic surgery	1 (0.8%)	1 (0.8%)	
Obstetric surgery	0 (0.0%)	2 (1.7%)	
Plastic surgery	17 (14.3%)	13 (10.8%)	
Stomatologic surgery	6 (5.0%)	2 (1.7%)	
Thoracic surgery	1 (0.8%)	0 (0.0%)	
SBP (mean ± S.D., mmHg)	119.9 ± 11.3	117.7 ± 11.1	0.164
MAP (mean ± S.D., mmHg)	89.8 ± 10.6	88.2 ± 9.7	0.156
HR (mean ± S.D., bpm)	76.3 ± 8.0	75.7 ± 7.6	0.581
RR (mean ± S.D., bpm)	18.0 ± 2.5	17.8 ± 2.9	0.707
SpO_2 (mean ± S.D., %)	99.9 ± 0.3	99.9 ± 0.5	0.755
T (mean ± S.D., °C)	36.4 ± 0.3	36.4 ± 0.3	0.821

S.D., standard deviation; BMI, body mass index; SBP, systolic blood pressure; MAP, mean arterial pressure; HR, heart rate; RR, respiratory rate; SpO_2, pulse oxygen saturation and T, temperature.

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Table 3.

The sedation success rates within 5 min. after administration.

Population	Group	Success (%)[1]	Not success (%)[1]	p (α = 0.025, Δ = 0.09, non-inferiority test)	The lowest limit of one-sided 97.5% CI
ITT	Propofol	119 (100.00)	0 (0.00)	<0.025	−0.05
	Fospropofol$_{FD}$	117 (97.50)	3 (2.50)		
PP	Propofol	117 (100.00)	0 (0.00)	<0.025	−0.04
	Fospropofol$_{FD}$	113 (98.26)	2 (1.74)		

[1]Data are expressed as numbers (%); CI, confidence interval; ITT, intention-to-treat population; PP, per-protocol population.

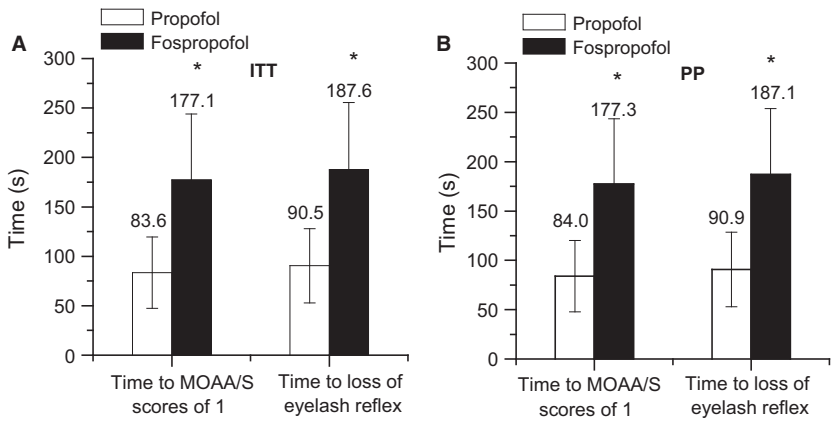

Fig. 2. Comparisons of the time to the MOAA/S score of 1 and the time to loss of the eyelash reflex between the two groups. The time to the MOAA/S score of 1 and the time to the loss of the eyelash reflex were longer in the Fospropofol$_{FD}$ group than in the propofol group. Data are expressed as mean ± S.D. *$p < 0.05$ between the two groups. ITT, intention-to-treat population; PP, per-protocol population.

Safety.

No intra-operative awareness, delayed recovery or cognitive disorder were found. These results indicated that the depressive effect of Fospropofol$_{FD}$ on the CNS did not significantly affect the brain function of the patients.

Fospropofol$_{FD}$ used in this study showed different pharmacological features related to sedative efficacy and actions on the circulatory system.

After administering the investigational drugs, significant changes occurred in the vital signs of the participants in the two groups. For example, HR had a biphasic profile in the two groups, showing a small initial increase followed by a decrease when compared with the baseline level. HR in the Fospropofol$_{FD}$ group was faster than that in the propofol group at 3 and 11–50 min. after administration ($p < 0.05$) (fig. 4A). The results indicated that the depressive effect on HR in the Fospropofol$_{FD}$ group was weaker than the effect in the propofol group. The blood pressures mainly showed a decrease immediately after administration in the propofol group, but a decrease from 3 min. after administration in the Fospropofol$_{FD}$ group (fig. 4B,C). SBP in the Fospropofol$_{FD}$ group was lower than that in the propofol group at 10, 11 and 45 min. after administration. MAP in the Fospropofol$_{FD}$ group was lower than that in the propofol group at 7 and 9–11 min. after administration. The results indicated more decrease in blood pressure in the Fospropofol$_{FD}$ group than in the propofol group. Although more decrease in blood pressure was found in the Fospropofol$_{FD}$ group, the incidence of hypotension was similar between the two groups (5.8% *versus* 3.3%, $p > 0.05$). Conventional treatment measures could relieve the hypotension.

When assistant ventilation and oxygen inhalation were used, the effects on SpO_2, RR and temperature were comparable between the two groups.

Anyway, 18 adverse reactions were found, and the incidences were 65.0% and 98.3% in the propofol group and the Fospropofol$_{FD}$ group, respectively ($p < 0.05$). In the two groups, adverse reactions such as pruritus/paraesthesia, QT interval prolongation, pain on injection, involuntary movement of limbs and hypotension were found at an incidence rate >1% (table 4). The most common adverse reaction in the Fospropofol$_{FD}$ group was pruritus/paraesthesia (95.0%), mainly moderate in severity (mild 25.9%, moderate 50.9% and severe 23.2%).

Pruritus/Paraesthesia (a sensation of burning, prickling, itching or tingling of the skin) was usually found in the perineal region and was self-limited and transient (10 sec. to 5 min.), requiring no intervention. The most common adverse reaction in the propofol group was pain on injection (46.5%), mostly mild to moderate in severity (mild 47.3%, moderate 43.6% and severe 9.1%). No patient was withdrawn from the study because of these adverse reactions. Most of these adverse reactions were mild to moderate in severity without any special treatment. No statistically significant difference was found

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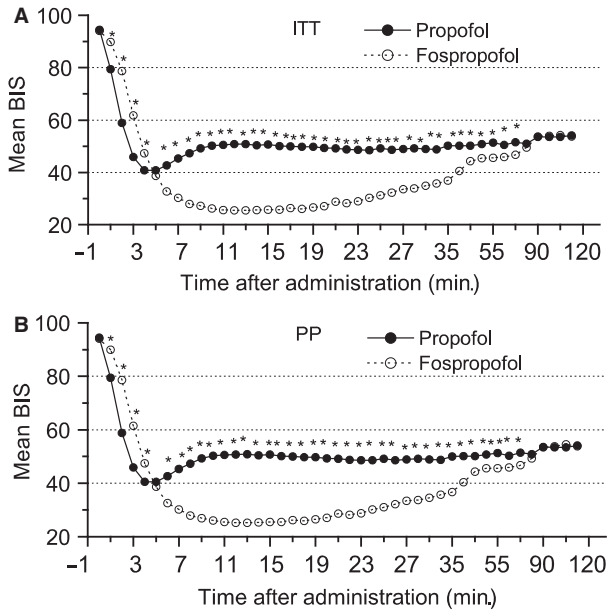

Fig. 3. Comparisons of bispectral index values between the two groups. The bispectral index values were significantly higher in the $Fospropofol_{FD}$ group than in the propofol group at 1–4 min. after administration ($p < 0.05$), similar at 5 min. after administration, but significantly lower at 10–70 min. after administration ($p < 0.05$). The bispectral index values obtained after intubation could be affected by the variable concentrations of remifentanil and sevoflurane. Data are expressed as mean. *$p < 0.05$ between the two groups. min., minute.

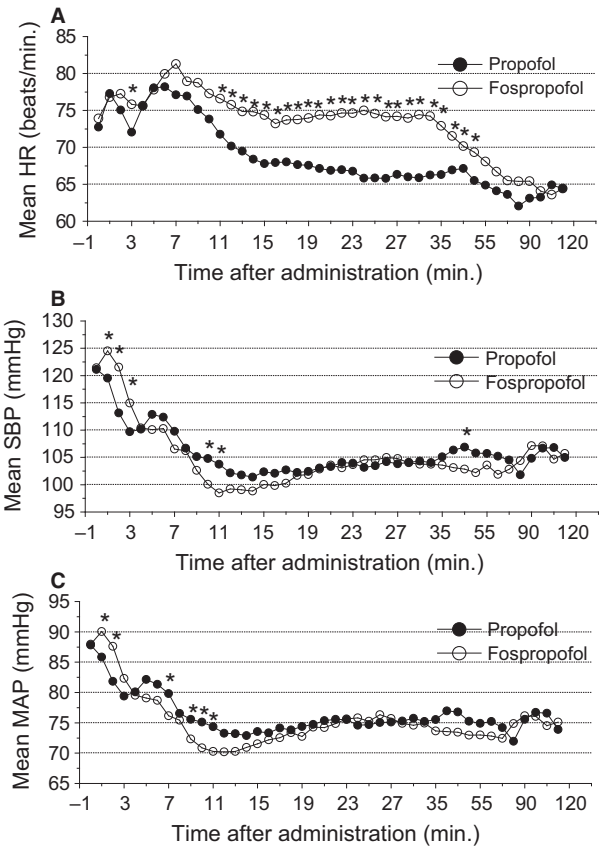

Fig. 4. Comparisons of heart rate, systolic blood pressure and mean arterial blood pressure between the two groups. The depressive effect on HR was less in the $Fospropofol_{FD}$ group than in the propofol group (A). The blood pressures mainly showed a decrease from 3 min. after administration in the $Fospropofol_{FD}$ group, and the decrease was more in the $Fospropofol_{FD}$ group than in the propofol group (B and C). The vital signs obtained after intubation could be affected by the variable concentrations of remifentanil and sevoflurane. Data are expressed as mean. *$p < 0.05$ between the two groups. min., minute; HR, hear rate; SBP, systolic blood pressure; MAP, mean arterial blood pressure.

in the severity extent of these adverse reactions between the two groups ($p > 0.05$).

The ECG-related adverse reactions included the QT interval prolongation, ST-T abnormality, short PR interval and bradycardia, but all of these changes had no statistically significant difference between the two groups ($p > 0.05$) (table 4). The ECG-related adverse reactions did not cause any significant clinical symptoms or signs and hence required no special treatment.

No drug-related abnormal laboratory test results were found in this study. All the laboratory test values at 24 hr after administration had no statistically significant difference between the two groups ($p > 0.05$). The plasma inorganic phosphate (propofol *versus* fospropofol: 1.16 ± 0.69 mmol/L *versus* 1.21 ± 0.60 mmol/L, $p > 0.05$) and the blood lipid (propofol *versus* fospropofol: 1.05 ± 0.23 mmol/L *versus* 1.07 ± 0.23 mmol/L, $p > 0.05$) were normal or lower than the baseline levels at 24 hr after administration.

In this study, no serious adverse reactions were observed.

Discussion

Compared with 2 mg/kg propofol, 20 mg/kg $Fospropofol_{FD}$ had a slower onset time, and a probable stronger, longer sedative effect. The reasons for these results were as follows: firstly, the metabolism of a pro-drug without any self-active action leads to differences from propofol in the onset, peak effects and duration of action [19]. Secondly, the higher dose of $Fospropofol_{FD}$ (ten times of propofol) was also an important reason for the results. Thirdly, sevoflurane used for maintaining anaesthesia could increase the sedative efficacy of $Fospropofol_{FD}$. In this study, the concentration of sevoflurane for maintaining anaesthesia was not adjusted by the BIS values. If the depth of anaesthesia was adjusted by BIS values, the dose of sevoflurane would be decreased. Fechner *et al.* [20] reported that the total dose of $Fospropofol_{FD}$ when used for total intravenous administration for coronary artery bypass graft surgery was only about three times of that of propofol. Although a longer onset time of $Fospropofol_{FD}$ is a substantial disadvantage, the mean time to receive a MOAA/S score of 1 was about 177 sec. which can be accepted in a practical induction of general anaesthesia.

Propofol caused a decrease in the blood pressure immediately after administration, while $Fospropofol_{FD}$ caused a small initial increase in the blood pressure, followed by a decrease from 3 min. after administration. This result was probably due to the slower onset of $Fospropofol_{FD}$ and the nervousness of

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Table 4.
Comparison of the adverse reactions between the Fospropofol$_{FD}$ and propofol groups.

Sequence	Adverse reactions	Fospropofol$_{FD}$ (n = 120) n (%)	Propofol (n = 120) n (%)	*p*-value
1	Pruritus/paraesthesia	114 (95.0)	3 (2.5)	0.000
2	QT interval prolongation	21 (17.5)	26 (21.7)	0.416
3	Pain on injection	15 (12.5)	56 (46.7)	0.000
4	Involuntary movement of limbs	9 (7.5)	6 (5.0)	0.424
5	Hypotension	7 (5.8)	4 (3.3)	0.354
6	Dizziness/headache	4 (3.3)	0 (0.0)	0.121
7	ST-T abnormality	3 (2.5)	1 (0.8)	0.622
8	Involuntary muscle contraction	3 (2.5)	0 (0.0)	0.247
9	Rash	3 (2.5)	1 (0.8)	0.622
10	Oral cavity abnormality	2 (1.7)	0 (0.0)	0.498
11	Short PR interval	1 (0.8)	4 (3.3)	0.370
12	Sinus bradycardia	1 (0.8)	2 (1.7)	1.000
13	Nausea and vomiting	1 (0.8)	1 (0.8)	1.000
14	Fatigue	1 (0.8)	1 (0.8)	1.000
15	Excitation	1 (0.8)	0 (0.0)	1.000
16	Local site pain	1 (0.8)	0 (0.0)	1.000
17	Oedema	1 (0.8)	0 (0.0)	1.000
18	Flushing on the face	1 (0.8)	0 (0.0)	1.000

the participants. Therefore, the increased heart rates and the initial less decrease in blood pressure following a rapid bolus of Fospropofol$_{FD}$ are not considered to be direct physiological effects of the agent [21].

The less depressive effect on HR and the more decrease in blood pressure in the Fospropofol$_{FD}$ group might be caused by the large dose of Fospropofol$_{FD}$ or the variable concentrations of sevoflurane and remifentanil. Therefore, if the depth of anaesthesia is guided by the BIS values, the doses of Fospropofol$_{FD}$, sevoflurane and remifentanil can be decreased, and their depressive effects on the circulatory system can also be reduced significantly. In this study, no serious adverse reactions related to the circulatory system were observed, and the hypotension could be well treated by the investigators. Therefore, Fospropofol$_{FD,}$ as well as propofol, was safe for the participants from the aspect of the circulatory system.

Struys *et al.* [22] reported that fospropofol in a dose ≥15 mg/kg could cause apnoea. Chin lifting, tactile stimulation, oxygen inhalation or airway assistance could resolve this respiratory depression problem quickly. In this study, the participants were given assistant ventilation and other anaesthetics immediately after obtaining the MOAA/S score of 1, and then they were given mechanical ventilation during the whole operation. So, the drug effect on the respiratory system was not observed. SpO_2 was kept at a normal level in the two groups and the safety of the participants could be achieved.

In the Fospropofol$_{FD}$ group, the pain on injection was significantly reduced but pruritus/paraesthesia became a main adverse reaction. Almost all the previous studies on fospropofol reported that pruritus/paraesthesia was the most frequently encountered adverse reaction [23–25]. Although the incidence of pruritus/paraesthesia is aggravating, some treatments are available to relieve it. A previous study reported that pre-treatment using fentanyl or meperidine could reduce the incidence of this adverse reaction [26]. Several propofol pro-drugs have been developed that may generate less pruritus/paraesthesia than fospropofol [27].

All of the ECG-related adverse reactions in this study did not have any clinical significance and therefore required no treatment.

The present study had several limitations. In terms of statistics, the conventional probability of 20% was chosen as type II error without any concern. The calculation of sample size was based on some estimated data from literature review, such as the non-inferiority margin of 9% and type II error. Because only one dose of Fospropofol$_{FD}$ was used in the study, it was not adequate to compare the differences between the two investigational drugs. While maintaining general anaesthesia, the concentrations of sevoflurane and remifentanil administered were according to the individual patient's needs, which resulted in a low comparability between two groups.

In conclusion, Fospropofol$_{FD}$ 20 mg/kg was non-inferior to propofol 2 mg/kg when used for inducing general anaesthesia within 5 min. after administration. Although some adverse reactions, for example depressive effects on the respiratory and circulatory systems, still occur after administering Fospropofol$_{FD}$, they can be easily treated by the anaesthesiologists.

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Conflict of Interest

The authors have no conflict of interests.

References

1 Sebel PS, Lowdon JD. Propofol: a new intravenous anesthetic. Anesthesiology 1989;**71**:260–77.

2 Marik PE. Propofol: therapeutic indications and side-effects. Curr Pharm Des 2004;**10**:3639–49.

3 Lamperti M. Adult procedural sedation: an update. Curr Opin Anaesthesiol 2015;**28**:662–7.

4 Mahajan B, Kaushal S, Mahajan R. Fospropofol. J Pharmacol Pharmacother 2012;**3**:293–6.

5 Khan MS, Zetterlund EL, Gréen H, Oscarsson A, Zackrisson AL, Svanborg E *et al.* Pharmacogenetics, plasma concentrations, clinical signs and EEG during propofol treatment. Basic Clin Pharmacol Toxicol 2014;**115**:565–70.

6 http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022244s006lbl.pdf

7 Chernik DA, Gillings D, Laine H, Hendler J, Silver JM, Davidson AB *et al.* Validity and reliability of the Observer's Assessment of Alertness/Sedation Scale: study with intravenous midazolam. J Clin Psychopharmacol 1990;**10**:244–51.

8 Yi XQ, Li R, Zhang WS, Liu J, Xu J, Liao TZ. Effect of single doses of HX0507 on QTc intervals in healthy people: a phase I safety and tolerability study. Sichuan Da Xue Xue Bao Yi Xue Ban 2012;**43**:868–72.

9 Cummings GC, Dixon J, Kay NH, Windsor JP, Major E, Morgan M *et al.* Dose requirements of ICI 35,868 (propofol, 'Diprivan') in a new formulation for induction of anaesthesia. Anaesthesia 1984;**39**:1168–71.

10 Fahy LT, van Mourik GA, Utting JE. A comparison of the induction characteristics of thiopentone and propofol (2,6-di-isopropyl phenol). Anaesthesia 1985;**40**:939–44.

11 McCollum JS, Dundee JW, Halliday NJ, Clarke RS. Dose response studies with propofol ('Diprivan') in unpremedicated patients. Postgrad Med J 1985;**61**:85–7.

12 McCollum JS, Dundee JW. Comparison of induction characteristics of four intravenous anaesthetic agents. Anaesthesia 1986;**41**:995–1000.

13 Rolly G, Versichelen L, Huyghe L, Mungroop H. Effect of speed of injection on induction of anaesthesia using propofol. Br J Anaesth 1985;**57**:743–6.

14 Briggs LP, Clarke RS, Dundee JW, Moore J, Bahar M, Wright PJ. Use of di-isopropyl phenol as main agent for short procedures. Br J Anaesth 1981;**53**:1197–202.

15 Fragen RJ, de Grood PM, Robertson EN, Booij LH, Crul JF. Effects of premedication on diprivan induction. Br J Anaesth 1982;**54**:913–6.

16 Leslie K, Crankshaw DP. Potency of propofol for loss of consciousness after a single dose. Br J Anaesth 1990;**64**:734–6.

17 Cohen LB. Clinical trial: a dose-response study of fospropofol disodium for moderate sedation during colonoscopy. Aliment Pharmacol Ther 2008;**27**:597–608.

18 American Society of Anesthesiologists Task Force on Intraoperative Awareness. Practice advisory for intraoperative awareness and brain function monitoring: a report by the american society of anesthesiologists task force on intraoperative awareness. Anesthesiology 2006;**104**:847–64.

19 Wozniak KM, Vornov JJ, Mistry BM, Wu Y, Rais R, Slusher BS. Gastrointestinal delivery of propofol from fospropofol: its bioavailability and activity in rodents and human volunteers. J Transl Med 2015;**13**:170.

20 Fechner J, Ihmsen H, Schüttler J, Jeleazcov C. A randomized open-label phase I pilot study of the safety and efficacy of total intravenous anesthesia with fospropofol for coronary artery bypass graft surgery. J Cardiothorac Vasc Anesth 2013;**27**:908–15.

21 McIntosh MP, Iwasawa K, Rajewski RA, Fujisawa T, Goto H. Hemodynamic profile in rabbits of fospropofol disodium injection relative to propofol emulsion following rapid bolus injection. J Pharm Sci 2012;**101**:3518–25.

22 Struys MM, Vanluchene AL, Gibiansky E, Gibiansky L, Vornov J, Mortier EP *et al.* AQUAVAN injection, a water-soluble prodrug of propofol, as a bolus injection: a phase I dose-escalation comparison with DIPRIVAN (part 2): pharmacodynamics and safety. Anesthesiology 2005;**103**:730–43.

23 Cohen LB, Cattau E, Goetsch A, Shah A, Weber JR, Rex DK *et al.* A randomized, double-blind, phase 3 study of fospropofol disodium for sedation during colonoscopy. J Clin Gastroenterol 2010;**44**:345–53.

24 Gan TJ, Berry BD, Ekman EF, Muckerman RC 2nd, Shore N, Hardi R. Safety evaluation of fospropofol for sedation during minor surgical procedures. J Clin Anesth 2010;**22**:260–7.

25 Silvestri GA, Vincent BD, Wahidi MM, Robinette E, Hansbrough JR, Downie GH. A phase 3, randomized, double-blind study to assess the efficacy and safety of fospropofol disodium injection for moderate sedation in volunteers undergoing flexible bronchoscopy. Chest 2009;**135**:41–7.

26 http://www.accessdata.fda.gov/drugsatfda_docs/nda/2008/022244s000_ClinPharmR_P2.pdf

27 Lang BC, Yang J, Wang Y, Luo Y, Kang Y, Liu J *et al.* An improved design of water-soluble propofol prodrugs characterized by rapid onset of action. Anesth Analg 2014;**118**:745–54.

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