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Efficacy and safety of HSK3486 for the induction and maintenance of general anesthesia in elective surgical patients: a multicenter, randomized, open-label, propofol-controlled phase 2 clinical trial

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Abstract. – OBJECTIVE: To evaluate the efficacy and safety of HSK3486 for the induction and maintenance of general anesthesia in elective surgical patients, but excluding emergency, cardiothoracic, cerebral and endoscopic sinus cases.

PATIENTS AND METHODS: A total of 40 eligible patients were randomly assigned to HSK3486 (n = 30) or propofol (n = 10) dosage groups in a ratio of 3:1. Drugs were administered as a bolus injection of 0.4 mg/kg (HSK3486) or 2.0 mg/kg (propofol) for induction, followed by maintenance infusion with the same anesthetic. An additional 6 non-randomized patients received propofol (2.0 mg/kg) for induction and were given HSK3486 for maintenance.

RESULTS: The primary efficacy endpoint – the success rate of anesthesia maintenance – was 100% in the 3 arms. The secondary efficacy endpoints included times from discontinuation of HSK3486 or propofol maintenance to full alertness, respiratory recovery, extubation and reaching the goal of the Aldrete score. Also, the proportion of patients who constantly maintained BIS40-60 or those with a period of BIS40-60 during maintenance anesthesia showed no significant difference in the HSK3486 and propofol groups (all $p > 0.05$).

Patients who received HSK3486 exhibited a higher satisfaction score from anesthesiologists during the induction period ($p = 0.024$). The occurrence and types of treatment-emergent adverse events were similar among the 3 arms, both with a severity of grade 1 or 2. Drug-related hypotension occurred in 14 (46.7%) and 7 (70.0%) patients treated with HSK3486 and propofol, respectively.

CONCLUSIONS: HSK3486 exhibited good efficacy for the induction and maintenance of general anesthesia and was well tolerated by patients who underwent elective surgery.

Key Words:
Propofol, General anesthesia, HSK3486, Maintenance anesthesia, Elective surgery.

Introduction

The drugs used for general anesthesia induce unconsciousness, analgesic effects, amnesia and reflex suppression, and a degree of muscular flaccidity ensuring that patients are able to complete the operation in an immobilized state[1]. Anesthetic drugs produce a balanced drug concentration and partial pressure (PaO_2) in plasma if the appropriate dosages are used to achieve maintenance anesthesia. Using inhalation anesthesia, it is easier to adjust the depth of anesthesia and maintain stable hemodynamics during an operation, but adult patients often prefer intravenous anesthesia due to its smooth and rapid induction, higher satisfaction, lower incidence of post-operative nausea and vomiting and less claustrophobia[2,3]. Propofol is a widely used intravenous anesthetic that exhibits a rapid onset and recovery, but has an obviously increased risk of producing hypotension, respiratory depression, or pain on injection, which can be improved by continuous infusion or combined anesthesia regimens[4-6].

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Combined anesthesia regimens with adjuvant opioid analgesics or neuromuscular blocking drugs are commonly used to reduce the induction duration and anesthetic usage to achieve complete analgesia or muscle relaxation during surgery[7,8]. Midazolam is widely used as a premedication before anesthesia induction, preventing post-operative nausea and vomiting (PONV) [9]. Sufentanil and remifentanil are highly selective μ-opioid receptor agonists, and in particular remifentanil has a rapid and predictable recovery from analgesia and sedation following the induction and maintenance of general anesthesia[10].

HSK3486, is a novel 2,6-disubstituted phenol derivative developed for the induction and maintenance of general anesthesia, which has a higher binding activity to the gamma-aminobutyric acid-A ($GABA_A$) receptor[11]. The major circulating metabolite of HSK3486 in plasma is M4 (79.3%), which has little residual effects and is finally excreted by the kidney in urine (87.3%)[12]. A former Chinese phase 1 trial conducted in healthy subjects indicated that HSK3486 was well tolerated up to a dose of 0.9 mg/kg and induced a rapid onset and recovery properties during the short-term general anesthesia[13]. HSK3486 had a 100% success rate for induction in the dose range 0.3-0.5 mg/kg in elective surgical patients in the completed phase 2a trial (NCT03698617). Having considered, however, the rare occurrence of an intubation reaction in the 0.4 mg/kg group, nevertheless 0.4 mg/kg was selected as the induction dose in the present trial.

This multicenter, randomized, open-label, propofol controlled phase 2 trial was carried out in patients undergoing elective surgery excluding emergency, cardiothoracic, cerebral or endoscopic sinus cases. The primary objectives were to evaluate the efficacy and safety of HSK3486 for the induction and maintenance of general anesthesia. The secondary objective was to investigate the pharmacokinetic characteristic of HSK3486 in patients undergoing elective surgery.

Patients and Methods

Study Design and Patients

This was a multicenter, randomized, open-label, propofol controlled phase 2 trial involving 5 research centers in China that was conducted from December 9th 2019 to May 23rd 2020. The study protocol was approved by the Ethics Committee of Peking University First Hospital (Approval No. 2019-29) and all other participating centers. Informed consent was obtained from all individual participants included in the study. The trial was prospectively registered with ClinicalTrials.gov (identifier NCT04048811).

Patients aged 18 to 65 years old with an American Society of Anesthesiologists (ASA) rating of Class I-III, who required endotracheal intubation under general anesthesia, with expected operation duration of 1-6 h and a blood loss of ≤ 1,000 mL were included. Patients scheduled to receive emergency, cardiothoracic, cerebral, or endoscopic sinus surgery and those with contraindications to general anesthesia or with a history of previous anesthesia incidents were excluded. Detailed inclusion and exclusion criteria are presented in **Supplementary File 1**.

The sample size calculation was not statistically determined with 40 eligible patients scheduled to be competitively enrolled from the 5 centers randomly assigned to receive either HSK3486 (induction) + HSK3486 (maintenance) (30 cases) or propofol (induction) + propofol (maintenance) (10 cases) at a 3:1 ratio. In this trial, the random number and grouping information were generated with the interactive web response system (IWRS) for both the HSK3486 and propofol groups. In addition, another 6 eligible patients received propofol (induction) + HSK3486 (maintenance) on a non-randomized basis to explore whether HSK3486 maintenance could reach the anesthesia goal following induction with propofol.

This trial included a screening period day-14 – day-1, anesthesia induction (from the start of HSK3486 or propofol administration to the completion of intubation) plus maintenance (from the completion of intubation until HSK3486 or propofol was discontinued) period day 1. Post-operative observations plus the follow-up period occurred on day 1 and day 2.

Study Procedures

Monitoring: Enrolled patients were successively given the pre-anesthesia drugs midazolam (0.04 mg/kg, 15 s) and sufentanil (0.3 μg/kg, 30 s), followed by HSK3486 (0.4 mg/kg) or propofol (2.0 mg/kg) to induce anesthesia within 30 s. After successful induction, rocuronium bromide was administered and endotracheal intubation completed after the onset of its effect, followed by a remifentanil infusion and HSK3486 or propofol maintenance doses. The bispectral index (BIS) was used to adjust the HSK3486 or propofol dose during the maintenance of anesthesia (Figure 1).

Anesthesia induction: The Modified Observer's Assessment of Alert/Sedation (MOAA/S) (**Supplementary Table I**) was evaluated every 30 ± 10 s from the start of HSK3486 (0.4 mg/kg) or propofol (2.0 mg/kg) bolus injection (within 30 s) until MOAA/S was ≤ 1 or at 3 min (± 10 s) after the initial dose. Top-up drugs were administered using half of the initial dosage at intervals of 1 min (± 10 s) if a patient was still conscious (MOAA/S > 1) after the initial drug administration. If patients were still conscious after 2 top-up doses, rescue medication of propofol was used for the HSK3486 group and other anesthetic drugs for the propofol group, to reach a satisfactory induction depth. After successful rescue medication, patients continued to be anesthetized with the previous experimental drugs in the following maintenance period. Successful induction of anesthesia was confirmed when the patients reached a MOAA/S ≤ 1 after administering HSK3486 or propofol (up to 2 top-up doses allowed), without using any rescue anesthetic drugs.

Maintenance of anesthesia: Guided by the previous Australian phase 1c trial results (NCT04029766), the initial maintenance dose of the first 6 patients in the HSK3486 group was 1 mg/kg/h. After evaluation of the responses of patients, the range of the initial maintenance dose for the remaining enrolled patients was finally adjusted to 0.8 mg/kg/h. Propofol administration at a rate of 4 -12 mg/kg/h maintained a satisfactory anesthetic effect. Considering that the anesthetic effect of HSK3486 was comparable to 1/4-1/5 of the propofol dose administered in previous studies, propofol at 5 mg/kg was selected as the initial maintenance dose in the first 2 patients in the propofol group and finally adjusted to 6 mg/kg/h for the subsequently enrolled patients after careful evaluation. The adjustment dose range of HSK3486 and propofol was set to 20-40% based on clinical practice to accurately explore the appropriate infusion rate during the whole maintenance period. For patients in the propofol+HSK3486 group, the maintenance dose of HSK3486 was fixed at 1 mg/kg/h without any adjustment. Successful maintenance of anesthesia was confirmed when patients did not come around after the anesthetic infusion and did not receive rescue anesthetic drugs.

After discontinuation of HSK3486 or propofol postoperatively, MOAA/S was assessed at 0, 1 (± 10 s), 2, 3, 5, 7 and 9 min, and every 3 min from 12 min until the patients recovered full alertness (MOAA/S = 5 for 3 consecutive measurements). Patients were continuously monitored for BIS values every 2 min from the beginning of the HSK3486 or propofol induction until 10 min after completion of intubation, and every 5 min after completion of intubation to the end of the opera-

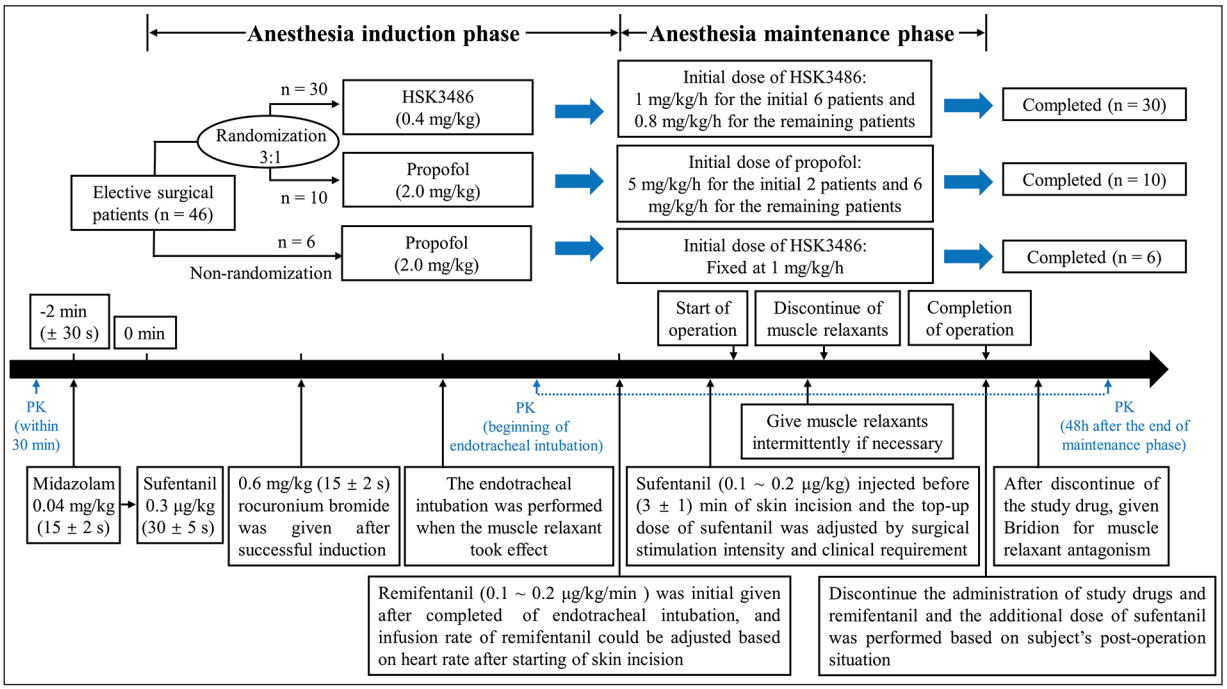

Figure 1. The procedure and patients' flowchart of the trial.

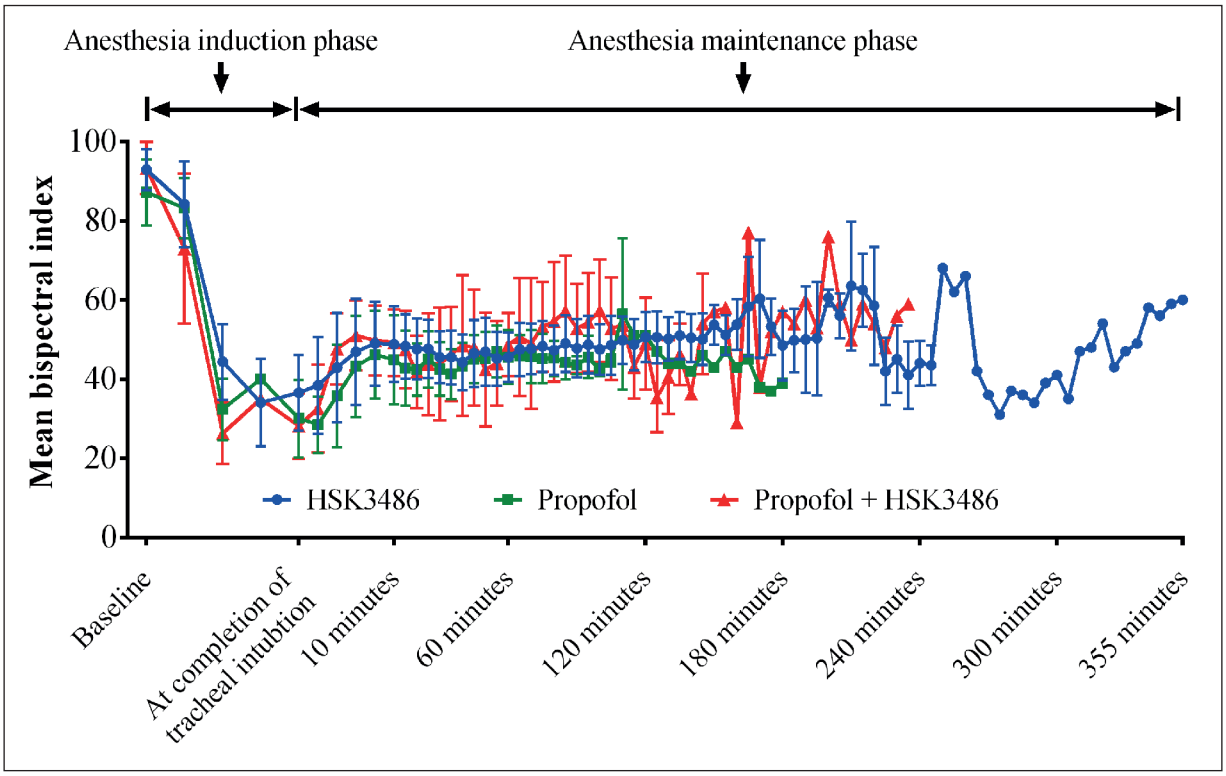

Figure 2. Changes in bispectral index (BIS) during the induction and maintenance period.

tion. After patients were fully relaxed and inhaled oxygen through a face mask for 5 min, the BIS value was monitored every 2 min, and the mean value of the undisturbed BIS (before midazolam administration) derived from 3 consecutive measurements was recorded as the baseline value.

Efficacy Outcomes

Primary efficacy outcome: The proportion of patients who achieved successful anesthesia maintenance.

Secondary efficacy outcome: This was: the proportion of patients with successful anesthesia induction; changes in BIS values during anesthesia; time from initial administration of HSK3486 or propofol to successful induction of anesthesia; time from the discontinuation of HSK3486 or propofol maintenance to full alertness; respiratory recovery (respiratory rate ≥ 8 breaths/min and tidal volume ≥ 5 mL/kg); extubation; leaving the operation room; leaving the post-anesthesia care unit (PACU); and reaching the goal of an Aldrete score ≥ 9 for 3 consecutive measurements. The administration of HSK3486, propofol or any rescue anesthetic drugs during the induction and maintenance periods was carefully documented. The usage of remifentanil during the maintenance periods, such as adjustment times, total dosage and dosage per unit, were also recorded. A scale ranging from 0-12 was used for the evaluation of satisfaction by anesthesiologists, with a higher score indicating better satisfaction (**Supplementary Table II**).

Safety Evaluation

Adverse events (AEs) were coded using the Medical Dictionary for Regulatory Activities (MedDRA 23.0) and classified according to the System Organ Class (SOC) and Preferred Term (PT), and the severity of AEs was classified based on the Common Terminology Criteria for Adverse Events (CTCAE 5.0). The AEs recorded in this trial were restricted to treatment emergent AEs (TEAEs). Sedation related AEs, including hypoxia, bradycardia and hypotension were evaluated from the time of initial administration of the study drug until patients left the operating room. Hypoxia was defined as SpO_2 < 90% that lasted for > 30 s; bradycardia as a heart rate < 50 beats/min and a duration of > 0.2 min; hypotension as systolic blood pressure (SBP) < 90 mmHg or a relative 30% decrease from baseline value

after oxygen inhalation that lasted for > 0.2 min. The occurrence of intraoperative awareness was assessed using the modified Brice questionnaire 1 day after an operation (**Supplementary Table III**). Vital signs, such as heart rate, respiratory rate, SpO_2, SBP, diastolic blood pressure (DBP), mean arterial pressure (MAP) and body temperature were all assessed. Laboratory measurements (routine blood and urine, blood biochemistry) and electrocardiogram (ECG) recordings (QT interval, QTcF interval, PR interval, QRS interval and RR interval) were also made.

Pharmacokinetic Evaluations

Blood samples (3 mL) were collected in K_2EDTA vacuum-anticoagulant tube pre-dose (within 30 min), at the start of intubation, at 1 min (± 10 s), 2 min (± 20 s), 5 (± 1) min, 10 (±1) min after the initial maintenance administration, and at each time point per dose adjustment (within 2 min after dose adjustment). Blood samples (3 mL) were also collected at 15 (± 2 min), 1 h (± 5 min), 6 h (± 10 min), 10 h (± 30 min), 24 h (± 1 h) and 48 h (± 1 h) after discontinuation of maintenance drug administration.

The plasma concentration of HSK3486 was determined by a validated high-throughput liquid chromatography-mass spectrometry (HPLC-MS/MS) method with Triple Quad 6500+ (Applied Biosystems/MDS SCIEX, Framingham, MA, USA) using electrospray ionization (ESI) in the negative ion mode with multiple reaction monitoring. The plasma concentration of propofol was determined by a validated HPLC-MS/MS method with Triple Quad 6500+ (Applied Biosystems/MDS SCIEX, Framingham, MA, USA) using atmospheric pressure chemical ionization (APCI) in the negative ion mode with multiple reaction monitoring. The linear ranges of plasma concentrations for HSK3486 and propofol were 5.0 ~ 5,000 ng/mL, both with a low limit qualification (LLOQ) of 5.0 ng/mL. The precision (coefficient of variation [%CV], maximum) and accuracy (%bias, range) range for the quality control samples in plasma were 4.9% and 0.0 ~ 4.0% for HSK3486; 5.2% and 0.0 ~ 8.0% for propofol. Non-compartmental pharmacokinetic parameters including the maximum plasma concentration (C_{max}), area under the concentration-time curve (AUC), time to C_{max} (t_{max}), half-life time ($t_{1/2}$), clearance (CL) and volume of distribution (V) were calculated.

Statistical Analysis

All statistical analyses were performed using SAS 9.4 software (SAS Institute Inc., Cary, NC, USA). Continuous variables are given as the mean ± standard deviation (SD), and categorical variables as numbers and percentages. The comparison of all efficacy outcomes was only performed between the HSK3486 and propofol groups; otherwise, the results for the propofol+HSK3486 group are given only as an exploratory outcome without any statistical analysis. The exact probability method was used to provide 95% confidence intervals (CIs) and *p*-values to compare categorical variables between 2 groups. For continuous variables, such as the times of top-ups and adjustment of doses, dosage of drugs, and the satisfaction evaluation, a *t*-test was employed to provide 95% CIs and *p*-values of normally distributed data between the 2 groups. Comparisons of the times to successful induction, full alertness, respiratory recovery, extubation, leaving the operation room and leaving PACU, as well as reaching the goal of an Aldrete score ≥ 9 between the 2 groups, were analyzed using a Wilcoxon rank sum test.

All values below the LLOQ were recorded as below the quantification limit (BQL), and all BQL values were recorded as 0 for calculation of mean plasma concentration. Non-compartmental pharmacokinetic parameters were calculated using Phoenix WinNonlin software (Certara, Princeton, NJ, USA).

Results

Disposition, Baseline, and Demographics Characteristic of Patients

A total of 55 patients were recruited from 5 research centers, of which 9 patients were excluded due to a failure to meet the eligible criteria (n = 3), withdrawal of informed consent (n = 5) or other reasons (n = 1). Of 46 patients, 40 were randomly assigned to the HSK3486 (30) or propofol (10) groups, and 6 were directly assigned to the propofol + HSK3486 group without randomization. All 46 patients (100.0%) completed the trial and enrolled for subsequent efficacy, pharmacokinetic and safety analyses.

Table I summarizes the demographics and baseline characteristic of the enrolled patients. The mean age was 41.9 ± 11.0 (range 19 – 59) years and most of them (69.6%) were female. All patients had a baseline ASA class of I or II, of which 22 (47.8%) were class I and 24 (52.2%) were class II. The mean operation duration was 99.4 ± 56.7 min, with 35 (76.1%) lasting for < 2 h, 10 (21.7%) for 2 – 4 h, and the remaining 1 (2.2%) in the HSK3486 group for > 4 h. The demograph-

Table I. The baseline and demographics characteristic of patients in the 3 groups.

Baseline characteristics		HSK3486 (n = 30)	Propofol (n = 10)	Propofol + HSK3486 (n = 6)	Total (n = 46)
Age, years	Mean ± SD	42.5 ± 10.3	46.4 ± 11.2	31.5 ± 9.3	41.9 ± 11.0
Gender, n (%)	Male	11 (36.7)	3 (30.0)	0	14 (30.4)
	Female	19 (63.3)	7 (70.0)	6 (100)	32 (69.6)
Height, cm	Mean ± SD	163.3 ± 9.1	161.7 ± 7.7	159.6 ± 5.7	162.5 ± 8.4
Weight, kg	Mean ± SD	63.3 ± 11.5	62.2 ± 13.4	53.7 ± 6.1	61.8 ± 11.6
BMI, kg/m^2	Mean ± SD	23.7 ± 3.0	23.6 ± 3.6	21.1 ± 2.1	23.3 ± 3.1
ASA classification, n (%)	Class I	16 (53.3)	4 (40.0)	2 (33.3)	22 (47.8)
	Class II	14 (46.7)	6 (60.0)	4 (66.7)	24 (52.2)
Modified Mallampati score, n (%)	Class I	15 (50.0)	9 (90.0)	4 (66.7)	28 (60.9)
	Class II	15 (50.0)	1 (10.0)	2 (33.3)	18 (39.1)
Anesthesia history, n (%)	Yes	20 (66.7)	6 (60.0)	2 (33.3)	28 (60.9)
	No	10 (33.3)	4 (40.0)	4 (66.7)	18 (39.1)
Drinking history, n (%)	Yes	1 (3.3)	0	0	1 (2.2)
	No	29 (96.7)	10 (100)	6 (100)	45 (97.8)
Operation time, min	Mean ± SD	105.3 ± 62.6	76.7 ± 36.1	107.7 ± 50.7	99.4 ± 56.7
	< 2 h	21 (70.0)	9 (90.0)	5 (83.3)	35 (76.1)
	2-4 h	8 (26.7)	1 (10.0)	1 (16.7)	10 (21.7)
	> 4 h	1 (3.3)	0	0	1 (2.2)
Past medical history, n (%)	Yes	30 (100)	10 (100)	6 (100)	46 (100)

Note: Data is presented as the mean ± SD or as numbers with percentages; ASA, American Society of Anesthesiologists.

ic and baseline characteristics among the 3 group were well balanced.

Efficacy

The success rates of anesthesia induction and maintenance were both 100% in the HSK3486 and propofol groups, with a rate difference of 0% (95% CI: -11.35, 27.75%) (Table II). The 6 patients in the propofol + HSK3486 group also reached the induction and maintenance goal (100%) without requiring a top-up dose or any rescue medication. The time from the discontinuation of HSK3486 or propofol maintenance to full alertness, respiratory recovery, extubation, leaving the operation room or PACU and reaching the Aldrete score appeared to be similar between the HSK3486 and propofol groups without a statistically significant difference (all $p > 0.05$), and both groups exhibited a shorter pattern than the propofol + HSK3486 group.

The changes in BIS during the induction and maintenance phase among the 3 groups are shown in Figure 2. Patients in the HSK3486 and propofol groups maintained a stable state of anesthesia, without a significant difference in the proportion of patients whose BIS values were always maintained between 40 and 60 (13.3% *vs.* 10.0%, $p = 1.000$) and the proportion of durations with BIS values of 40 to 60 during the whole anesthesia maintenance period (69.9 ± 24.7% *vs.* 70.5 ± 18.2%, $p = 0.948$) (Table II). The satisfaction score of anesthesiologists for patients receiving HSK3486 was significantly higher during the induction period ($p = 0.024$) and received a similar evaluation ($p = 0.814$) during the maintenance period compared to propofol.

During the maintenance period, the mean weighted infusion rate of HSK3486 after adjusting for the operative time was 0.8 mg/kg/h and 1.1 mg/kg/h in the HSK3486 and propofol + HSK3486 groups, respectively; the propofol dose was 5.2 mg/kg/h (**Supplementary Table IV**). The mean weighted infusion rate of remifentanil was 0.1 μg/kg/min in the 3 groups, with 14 (46.7%), 6 (60.0%) and 3 (50.0%) patients not requiring adjustment of the dose.

Safety

A total of 171 TEAEs were reported in 45 (97.83%) patients, with 121 TEAEs in 30 (100%)

Table II. Efficacy parameters of HSK3486 and propofol during the induction and maintenance period.

	HSK3486 (n = 30)	Propofol (n = 10)	HSK3486 vs. propofol		Propofol + HSK3486 (n = 6)
			Rate difference (95% CI)	*p*-value	
Success rate of anesthesia induction, n (%)	30 (100)	10 (100)	0 (-11.35, 27.75)	-	6 (100)
Success rate of anesthesia maintenance, n (%)	30 (100)	10 (100)	0 (-11.35, 27.75)	-	6 (100)
Time to successful anesthesia induction, s	45.3 ± 14.8	42.3 ± 15.3	-	0.840	56.7 ± 13.7
Time to fully alertness, min	11.4 ± 4.9	11.8 ± 3.4	-	0.575	13.5 ± 4.6
Time to respiratory recovery, min	11.0 ± 4.9	11.1 ± 4.4	-	0.698	11.8 ± 3.8
Time to extubation, min	11.2 ± 5.1	11.2 ± 4.3	-	0.745	11.8 ± 4.0
Time to leaving operation room, min	27.6 ± 5.6	26.4 ± 4.1	-	0.556	32.4 ± 8.1
Time to leaving PACU, min	70.2 ± 10.6	67.2 ± 11.6	-	0.302	106.3 ± 32.9
Time to reaching the goal of Aldrete score, min	27.1 ± 6.1	28.7 ± 4.8	-	0.436	29.6 ± 5.7
The proportion of time that BIS was maintained at 40-60 during the anesthesia maintenance period, %					
From the completion of intubation	69.9 ± 24.7	70.5 ± 18.2	-0.56 (-17.78, 16.66)	0.948	36.6 ± 32.0
From the start of skin incision	72.7 ± 28.8	79.8 ± 18.6	-7.15 (-26.90, 12.61)	1.000	30.9 ± 31.8
Number of patients with BIS was always maintained at 40-60 during the anesthesia maintenance period, n (%)					
From the completion of intubation	4 (13.3)	1 (10.0)	3.33 (-18.89, 25.55)	1.000	0
From the start of skin incision	10 (33.3)	3 (30.0)	3.33 (-29.70, 36.37)	1.000	0
Satisfaction evaluation for anesthesiologists (range 0-12)					
During induction period	11.8 ± 0.8	10.6 ± 2.4	1.2 (0.2, 2.2)	0.024	11.2 ± 2.0
During maintenance period	11.3 ± 1.1	11.4 ± 1.3	-0.1 (-1.0, 0.8)	0.814	10.3 ± 2.0

Note. Date is presented as the mean ± SD or as numbers and percentages; BIS, bispectral index; PACU, post-anesthesia care unit.

Table III. Summary of treatment emergent adverse events (TEAEs) in the 3 groups.

	HSK3486 (n = 30)		Propofol (n = 10)		Propofol + HSK3486 (n = 6)	
	Number of AEs	Patients (%)	Number of AEs	Patients (%)	Number of AEs	Patients (%)
Any TEAEs	121	30 (100)	29	9 (90.0)	21	6 (100)
Severity = 1	57	24 (80.0%)	17	8 (80.0%)	13	6 (100)
Severity = 2	64	26 (86.7%)	12	9 (90.0%)	8	5 (83.3%)
Severity ≥ 3	0	0	0	0	0	0
Drug-related TEAEs	40	23 (76.7)	17	8 (80.0)	9	4 (66.7)
Severity = 1	14	12 (40.0%)	9	7 (70.0%)	7	4 (66.7%)
Severity = 2	26	19 (63.3%)	8	7 (70.0%)	2	2 (33.3%)
Severity ≥ 3	0	0	0	0	0	0
Sedation-related TEAEs	34	20 (66.7)	13	6 (60.0)	9	4 (66.7)
Hypotension	22	14 (46.7)	11	5 (50.0)	5	4 (66.7)
Bradycardia	11	8 (26.7)	2	2 (20.0)	4	3 (50.0)
Hypoxia	1	1 (3.3)	0	0	0	0
Drug-related TEAEs termed by PT						
Hypotension	23	14 (46.7)	14	7 (70.0)	5	4 (66.7)
Bradycardia	12	9 (30.0)	3	2 (20.0)	4	3 (50.0)
Elevated AST	1	1 (3.3)	0	0		0
Prolonged QT interval	1	1 (3.3)	0	0		0
Elevated blood triglycerides	1	1 (3.3)	0	0		0
Hypoxia	1	1 (3.3)	0	0		0
Rash	1	1 (3.3)	0	0		0

Note: AEs, adverse events; AST, aspartate aminotransferase; PT, preferred term; TEAEs, treatment emergent adverse events.

patients (HSK3486 group), 29 TEAEs in 9 (90.0%) (propofol group) and 21 TEAE in 6 (100%) patients in the propofol + HSK3486 group (Table III). All the TEAEs occurred with a severity of grade 1 and 2; no TEAEs ≥ grade 3 or any SAEs occurred. No patients died or withdrew from the study due to TEAEs in the 3 groups during the whole treatment period and no patient experienced intraoperative awareness.

The incidence of drug-related TEAEs (76.7% *vs.* 80.0%) and sedation-related TEAEs (66.7% *vs.* 60.0%) was similar between patients treated with HSK3486 or propofol. Drug-related hypotension (46.7% *vs.* 70.0%) was found to be lower in the HSK3486 group compared to the propofol group, whereas the incidence of sedation-related hypotension (46.7% *vs.* 50.0%) was similar between the 2 groups. Among the sedation-related TEAEs, hypotension occurred most frequently followed by bradycardia, in 8 (26.7%) and 2 (20.0%) patients in the HSK3486 and propofol groups, respectively. Only 1 (3.33%) case of hypoxia (grade 2) occurred in the HSK3486 group, but the patient recovered quickly and the symptoms rapidly disappeared after the administration of oxygen.

The changes in vital sign including SBP, DBP, MAP, heart rate and oxygen saturation (SpO_2) after administration of HSK3486 and propofol during the whole treatment periods are shown in **Supplementary Figure 1**. The mean SBP and heart rate ranged from 102.5 – 122.0 mmHg and 62.4 – 82.1 beats/min within 150 min of completion of tracheal intubation in the HSK3486 group, with a change of -20.2 – -4.7% and -16.4% – 9.9% from baseline, respectively. In the propofol group, the mean SBP and heart rate fluctuated in the range 92.0 – 119.0 mmHg and 64.0 – 94.0 beats/min within 90 min of completion of tracheal intubation, with a change of -29.8% to -2.7% and -15.4% to 20.3%, respectively. During the anesthesia maintenance phase, 50.0% (23/46) of patients underwent additional intervention mea-

sures for decreased BP and heart rate, with 53.3% (16/30) in the HSK3486 group, 50.0% (5/10) in the propofol group and 33.3% (2/6) in the propofol + HSK3486 group. One patient in the HSK3486 group developed an abnormal cholesterol level and 2 patients in the propofol group developed abnormal triglyceride levels, both having clinical significance. Regarding drug-related TEAEs, only 1 (3.3%) patient in the HSK3486 group had elevated blood triglycerides. The mean blood oxygen saturation fluctuation remained stable around the baseline level values in the 3 groups.

Pharmacokinetics

As shown in **Supplementary Figure 2**, the plasma concentration of HSK3486 in the propofol + HSK3486 group of patients was basically the same as in the HSK3486 group during the anesthesia maintenance phase; the same pattern of propofol concentrations was evident in the propofol group during the anesthesia induction period. The drug exposure of propofol (C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, AUC_{t1-t2}, C_{EOI}, C_{avg}, C_{mean}) were about 4 ~ 5 times those of HSK3486, while the $AUC_{0-\infty}$ after adjusting for dosage ($AUC_{0-\infty, dose}$) was close to that of HSK3486 (**Supplementary Table V**). The half-life ($t_{1/2}$) and volume of distribution of HSK3486 (V_Z, V_{SS}, $V_{Z, weight}$, $V_{SS, weight}$) were slightly lower than for propofol, while the T_{max} and CL values were very similar to those of propofol.

Discussion

In the present phase 2 trial, HSK3486 exhibited comparable efficacy with propofol regarding anesthesia induction and maintenance, both drugs achieving a success rate of 100%, with an estimated 95% CI of -11.35% to 27.75%. Patients given propofol for induction and HSK3486 for maintenance also reached satisfactory anesthesia without the need for top-up doses or any rescue therapy. These findings suggested that HSK3486 is useful for maintaining anesthesia in restricted elective surgical patients and likely to have high efficacy even following induction with a different anesthetic drug.

During the induction phase, HSK3486 (0.4 mg/kg) had a comparable rapid onset of action to propofol (2.0 mg/kg), both producing successful induction within 1 min (45.3 *vs.* 42.3 s, p = 0.840). The initial maintenance dose of HSK3486 (1.0 mg/kg/h) was based on the completed Australian 1c trial (NCT04029766), that showed that HSK3486 administered as a combined 0.288 mg/kg bolus dose plus a 1 mg/kg/h infusion produced moderate to deep sedation with a maintenance BIS of 40 to 60. In the present trial, the mean weighted infusion rate of HSK3486 and propofol after adjusting for operative time was 0.8 mg/kg/h and 5.2 mg/kg/h, respectively. Anesthesiologists tended to be more satisfied with HSK3486 during the induction period, relative to the consistency of satisfaction between HSK3486 and propofol during the maintenance period. Therefore, these results confirmed that HSK3486 produced satisfactory general anesthesia at a lower dose, in agreement with previous studies [12-14].

BIS is an electroencephalogram-derived parameter used to monitor the depth of anesthesia. Patients who received HSK3486 had a comparable proportion of durations for BIS_{40-60} during the maintenance phase in the present trial, and similar to the preferred BIS range of 40 to 60 for propofol [15,16]. Regarding recovery profiles, the time from the discontinuation of HSK3486 or propofol maintenance to full alertness was virtually the same for HSK3486 and propofol (11.4 ± 4.9 *vs.* 11.8 ± 3.4 min, p = 0.575). Similar results were also found in other recovery-related durations (all $p > 0.05$), suggested that HSK3486 administered for induction and maintenance had a preferred ability of recovery.

HSK3486 exhibited good tolerance in elective surgery patients, with 121 TEAEs in 30 (100%) patients, all with a severity of grade 1 or 2. Between 76.7% and 80.0% of patients exhibited drug-related TEAEs, with the most frequent being hypotension in 46.7% of patients in the HSK3486 group and 70.0% in the propofol group, respectively. A higher incidence of hypotension elicited by propofol was also observed in the present trial, which had been previously reported[17]. Another commonly reported TEAEs, pain on injection, did not occur in the present trial[5], likely due to premedication with sufentanil and the analgesic effect of remifentanil during the maintenance period. Previous studies revealed that HSK3486 produced a lower incidence of pain on injection. This was likely associated with the less aqueous phase concentration of the drug in the lipid emulsion vehicle [11,12,18].

It is normal for anesthesiologists to adjust dosages according to the patient's individual condition. Premedication with sufentanil and midazolam, and intraoperative remifentanil and rocuronium are commonly used to produce general anesthesia. The present trial was designed to

be open-label, which inevitably led to theoretical bias, but the medication regimens were close to those employed in clinical practice in China. Pre-sedation with sufentanil and midazolam decreased the painful response of multiple nerve stimulation, needle phobia and relieved the anxiety of patients[19]. For the non-randomization enrolled patients who received propofol for induction and HSK3486 for maintenance, the results were more than satisfactory considering that they were given HSK3486 at a fixed dosage during the maintenance period. However, a weakness of our study was the small sample size. A further large cohort trial should be conducted to evaluate further the optimal maintenance dose range of HSK3486 following propofol induction.

Conclusions

HSK3486 produced a comparable effect to propofol for the induction and maintenance of general anesthesia in elective surgical patients. HSK3486 was well tolerated, with a slightly lower incidence of drug-related hypotension compared to propofol, which supports the view that a further clinical trial should be conducted at a recommended initial maintenance dose of 0.8 mg/kg/h.

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Conflicts of Interest
The authors declare no conflicts of interest.

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