

# Comparison of the Effects of Ciprofol and Propofol on Postoperative Nausea and Vomiting in Patients Undergoing Outpatient Hysteroscopy

Huaming Zhang\*, Min Zhang\*, Lina Hao, Qianqian Li, Qijian Li, Jia Yang, Yanhu Xie

Department of Anaesthesiology, The First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China, Hefei, Anhui, 230001, People's Republic of China

\*These authors contributed equally to this work

Correspondence: Yanhu Xie, Email xyh200701@sina.cn

**Purpose:** To evaluate and compare the effects of ciprofol and propofol on postoperative nausea and vomiting (PONV) in patients undergoing outpatient hysteroscopy.

**Design:** Double-blind randomized controlled trial.

**Methods:** This study included 1104 patients scheduled for elective outpatient hysteroscopy. Patients were randomly grouped to ciprofol Group (Group C,  $n = 539$ ) and propofol Group (Group P,  $n = 547$ ). Anesthesia was induced by sufentanil 0.1  $\mu\text{g}/\text{kg}$  combined with ciprofol 0.3 $\text{mg}/\text{kg}$  or propofol 2.5 $\text{mg}/\text{kg}$ . Anesthesia was maintained by ciprofol 1 to 1.5 $\text{mg}/\text{kg}/\text{h}$  or propofol 3 to 5 $\text{mg}/\text{kg}/\text{h}$ . The primary outcome of the study was PONV after surgery 1h and 24h. Secondary outcomes included heart rate (HR), mean arterial blood pressure (MAP), SpO<sub>2</sub> before anesthesia (T1), 3 min after anesthesia (T2) and at the end of surgery (T3); the time of consciousness loss, recovery, hysteroscopy and discharge; and the incidence of adverse drug reactions such as hypotension, respiratory depression, bradycardia and injection pain was recorded in the two groups.

**Results:** Compared with group P, MAP and SpO<sub>2</sub> at T2 were significantly increased in group C ( $P < 0.05$ ). Although there was no significant difference in the incidence of PONV at 1h and 24h after surgery between 2 groups ( $P > 0.05$ ), the incidence of hypotension, injection pain and respiratory depression in group C were significantly reduced, compared with group P. ( $P < 0.05$ ).

**Conclusion:** Compared with propofol, ciprofol has a similar incidence of PONV and lower adverse effects such as hypotension, injection pain and respiratory depression in outpatient hysteroscopy.

**Keywords:** postoperative nausea and vomiting, ciprofol, propofol, hysteroscopy

Hysteroscopy in outpatient clinics is considered the gold standard for evaluating intrauterine lesions, providing significant assistance in the early diagnosis and treatment of diseases.<sup>1</sup> The emergence of the concept of comfort care in medicine has led to the widespread adoption of painless hysteroscopy in outpatient settings. However, postoperative nausea and vomiting (PONV) is the most common adverse event after surgery. Studies have shown that the incidence of PONV is as high as 20–37%.<sup>2</sup> Despite the unclear PONV mechanism that drives the hindbrain central pattern generator (emesis) and forebrain pathways (nausea), several high-risk factors have been identified such as young age, female sex, lack of smoking, and a history of motion sickness.<sup>3</sup> Patients undergoing hysteroscopy in China are mostly young women with very low smoking rates, which is a high-risk group for PONV.

Previous studies have shown that propofol, a first-line anesthetic and sedative medication, can effectively reduce PONV in gynecological surgeries.<sup>4</sup> However, it also has drawbacks such as injection pain and significant impact on respiratory and circulatory systems.<sup>5</sup> Ciprofol, a new intravenous sedative anesthetic, is an (R)-isomer small-molecule compound and a short-acting GABA<sub>A</sub> receptor agonist. It exerts its sedative and anesthetic effects by enhancing GABA-mediated chloride ion influx, offering advantages such as rapid onset, minimal circulatory suppression, and less injection

pain, compared with propofol.<sup>6,7</sup> To the best of my knowledge, few studies reported on the effects of ciprofol on PONV after outpatient hysteroscopy. Therefore, our research aims to take PONV after surgery 1h and 24h as primary objectives and test the hypothesis that the incidence of PONV in ciprofol was lower than in propofol when patients undergoing outpatient hysteroscopy.

## Materials and Methods

The study included patients scheduled for outpatient hysteroscopy from September 2023, to May 2024. Eligible patients were aged between 18 and 75 years, had a BMI between 18 and 30 kg/m<sup>2</sup>, and were classified as ASA I or II. Exclusion criteria included a history of psychiatric or neurological disorders, recent upper respiratory tract infection, severe pulmonary, hepatic, or renal insufficiency, allergies to soy products or eggs, and a history of alcohol or drug abuse. Patients were randomly grouped to one of the two groups using a random number table: the ciprofol group (Group C) and the Propofol group (Group P). This study was approved by the ethical committee of The First Affiliated Hospital of the University of Science and Technology of China (No. 2023KY171) and registered with the Chinese Clinical Trial Registry (ChiCTR2300075149). Informed consent was obtained from all patients. This study was complied with the Declaration of Helsinki.

## Anesthesiological Protocol

Patients were instructed to fast for 8 hours and abstain from drinking for 4 hours prior to the procedure. Upon arrival in the operating room, peripheral venous access was established. Routine monitoring included heart rate (HR), blood pressure (BP), electrocardiogram (ECG), oxygen saturation (SpO<sub>2</sub>), and bispectral index (BIS). Oxygen was administered at 2 L/min by nasal cannula.

Anesthesia induction for Group C involved intravenous injection of sufentanil at 0.1 µg/kg and ciprofol at 0.3 mg/kg, with the injection duration being at least 30 seconds. Hysteroscopy was performed on 1 minute after administration, the BIS value decreased to 40–60 and the Modified Observer's Assessment of Alertness/Sedation (MOAA/S) score was ≤1. If the patient's MOAA/S score remains greater than 1 and hysteroscope insertion fails 2 minutes after the initial induction, an additional dose of ciprofol at 0.15 mg/kg can be administered, with the injection duration being greater than 10 seconds. For anesthesia maintenance in Group C, ciprofol is administered via intravenous infusion at a rate of 1.0–1.5 mg/kg/h. For Group P, anesthesia induction involves intravenous injection of sufentanil at 0.1 µg/kg and propofol at 2.5 mg/kg, with the injection duration being at least 30 seconds. Hysteroscopy is then performed 1 minute after administration, the BIS value decreases to 40–60 and the MOAA/S score is ≤1. If the patient's MOAA/S score remains greater than 1 and hysteroscope insertion fails 2 minutes after the initial induction, an additional dose of propofol at 0.5 mg/kg can be administered, with the injection duration being at least 10 seconds.

For anesthesia maintenance, propofol is administered via intravenous infusion at a rate of 3–5 mg/kg/h.

If the heart rate is below 50 beats per minute and persists for more than 10 seconds, 0.5 mg of atropine is administered, which is recorded as bradycardia. In the event of hypotension lasting more than 10 seconds (mean arterial pressure <30% of baseline or systolic blood pressure <90 mmHg), 6 mg of ephedrine or 4–10 µg of norepinephrine is administered, which is recorded as hypotension. If hypoxemia occurs (SpO<sub>2</sub> <90% and lasts for more than 15 seconds), which recorded as respiratory depression, the patient's chin is lifted, and the oxygen flow rate is increased. If necessary, mask ventilation or insertion of a laryngeal mask airway for assisted ventilation with an anesthesia machine is performed. After the protocol, patients are transferred to postanesthesia care unit (PACU) for observation. They are allowed to leave the hospital only after they are fully awake, achieving an MOAA/S score of 5 for three consecutive assessments, a modified Aldrete score >9, and reporting no discomfort. The severity of PONV is assessed using a Verbal Rating Scale (VRS): 0 indicates no nausea; 1 indicates mild nausea with one episode of vomiting; 2 indicates moderate nausea with less than three episodes of vomiting; and 3 indicates severe nausea with three or more episodes of vomiting.

## Assessment of Primary and Secondary Outcomes

The primary outcome of the present study was the incidence of PONV at 1 hour and 24 hours post-procedure, which was followed up by telephone by an anesthesiologist. Secondary outcomes included HR, MAP, and SpO<sub>2</sub> at the following

time points: before anesthesia (T1), 3 minutes after anesthesia induction (T2), and at the end of the surgery (T3); time to loss of consciousness (loss of eyelash reflex), time to awakening (ability to respond correctly), duration of the hysteroscopic examination, and time to discharge. Incidence of adverse reactions such as hypotension, respiratory depression, bradycardia, and injection pain.

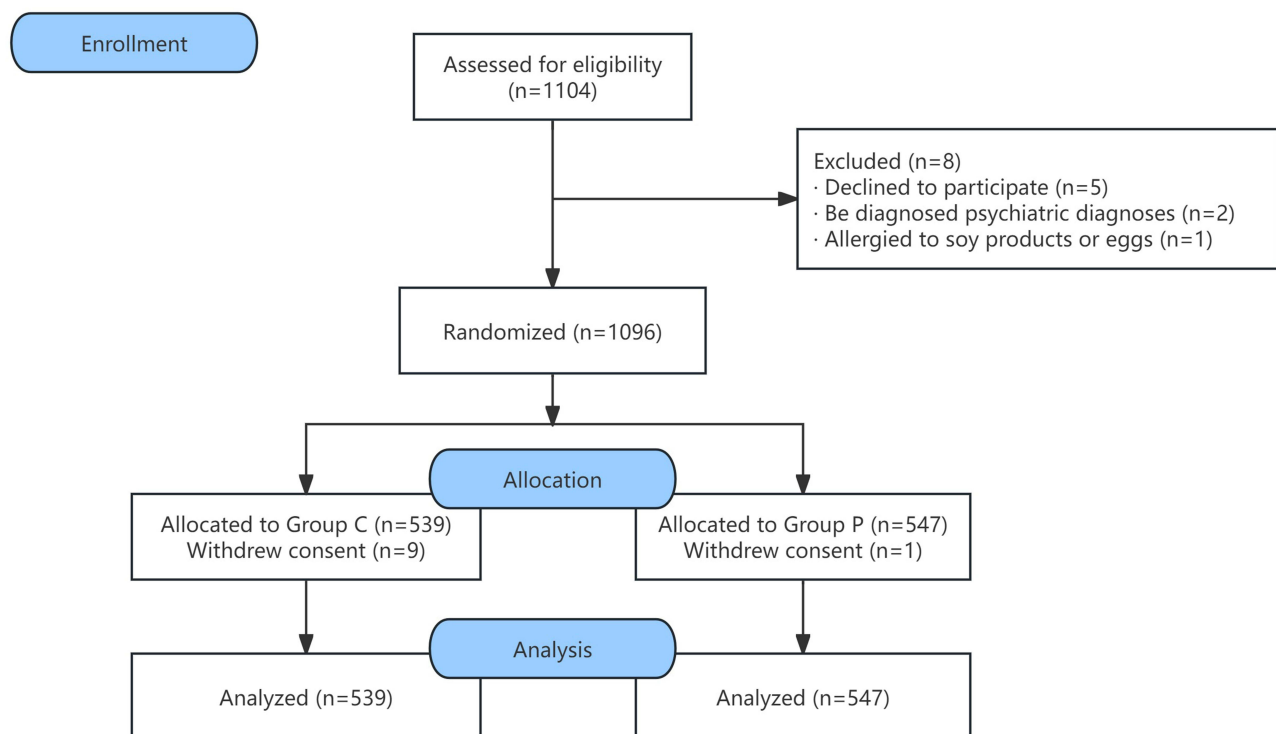
## Statistical Analysis

According to our pre-experimental results, PONV incidence rates of 14% for the Group P and 9% for the Group C. Using the PASS software with  $\alpha = 0.05$  and  $\beta = 0.20$ , each group requires 501 participants. Considering a 10% loss to follow-up and potential intraoperative exclusions, 552 participants will be enrolled in each group for this study. Data will be analyzed using the SPSS 25.0 software. The Kolmogorov–Smirnov test was performed to check the normality of continuous data. According to normality, continuous data were described as mean  $\pm$  standard deviation or median (interquartile range) and be analyzed by the students *t* test or Mann–Whitney *U*-test, respectively. Categorical data will be analyzed using chi-square test or Fisher’s exact test as appropriate. *P*-value  $<0.05$  will be considered statistically significant.

## Results

Of 1104 eligible patients, 1096 fulfilled the inclusion criteria, and 1086 agreed to participate and completed this study (Figure 1). These two groups had similar age, BMI and ASA classification, as showed in Table 1. Compared with the Group P, the Group C had a significantly higher MAP and SPO<sub>2</sub> at T<sub>2</sub> ( $P<0.05$ ). However, HR of patients at each time point had no significant difference between the two groups. These two groups had similarly time of hysteroscopy, consciousness loss, recovery and discharge, as shown in Table 2.

Considering perioperative complications (Table 3), a total of 99 patients experienced PONV after surgery, all of which were evaluated as 1 score, and no patients evaluated as 2 or 3 score. Compared with group P, the incidence of hypotension, injection pain and respiratory depression was significantly lower in Group C.



**Figure 1** Enrollment flow diagram of the study design.

**Table 1** Comparison of Baseline Between Two Groups

	<b>Group C (n=539)</b>	<b>Group P (n=547)</b>	<b>P value</b>
Age (years)	33.3±4.4	33.6±5.0	0.294
BMI (kg/m <sup>2</sup> )	22.31±2.81	22.35±2.75	0.813
ASA classification			0.279
I	125 (23.2)	112 (20.5)	
II	414 (76.8)	435 (79.5)	

**Abbreviations:** BMI, body mass index; ASA classification, American society of anesthesiologist classification.

**Table 2** Comparison of MAP, HR, SPO<sub>2</sub> and Perioperative Times Between Two Groups

	<b>Group C (n=539)</b>	<b>Group P (n=547)</b>	<b>P value</b>
MAP (mmHg)			
T1	81.1±10.5	80.4±11.1	0.286
T2	79.5±8.9	74.3±6.8	<0.001
T3	80.6±10.1	79.5±10.6	0.080
HR (bpm)			
T1	77.5±6.5	78.2±5.9	0.063
T2	73.9±10.5	74.9±10.3	0.113
T3	75.8±6.9	75.9±7.1	0.814
SPO <sub>2</sub> (%)			
T1	98.2±3.4	98.5±3.3	0.140
T2	93.2±3.7	91.5±2.3	<0.001
T3	98.3±2.7	98.5±2.4	0.197
Consciousness loss time (s)	50.3±31.3	51.1±29.4	0.664
Hysteroscopy time (min)	11.13±4.21	11.48±4.26	0.174
Recovery time (min)	6.9±3.2	7.2±2.9	0.106
Discharge time (min)	16.7±4.6	17.1±4.2	0.135

**Note:** Data represented as mean ± standard deviation.

**Abbreviations:** MAP, mean arterial pressure; HR, heart rates; SPO<sub>2</sub>, percutaneous arterial oxygen saturation; s, second.

**Table 3** Comparison of Perioperative Complications Between Two Groups

	<b>Group C (n=539)</b>	<b>Group P (n=547)</b>	<b>P value</b>
PONV at 1h			0.567
0 score	495 (91.84)	497 (90.86)	
I score	44 (8.16)	50 (9.14)	
PONV at 24h			0.163
0 score	519 (96.29)	517 (94.52)	
I score	20 (3.71)	30 (5.48)	
Adverse drug reactions (%)			
Hypotension	126 (23.4)	226 (41.3)	<0.001
Respiratory depression	34 (6.3)	110 (20.1)	<0.001
Bradycardia	81 (15.0)	85 (15.5)	0.815
Injection pain	36 (6.7)	211 (38.6)	<0.001

**Note:** Data represented as numbers (percentage).

**Abbreviations:** PONV, postoperative nausea and vomiting; h, hours.

## Discussion

This study found that ciprofol, compared with propofol, has similar incidence of PONV and lower adverse effects such as hypotension, injection pain and respiratory depression in outpatient hysteroscopy. A recent article suggests that ciprofol can prevent PONV when used for anaesthesia in patients undergoing painless gastroscopy, but it is weaker than propofol.<sup>8</sup> Whether this difference was due to different risk profiles was an interesting question. Studies have shown that the incidence of PONV is related to factors such as the patient's gender, age, smoking history, and history of motion sickness.<sup>9,10</sup> Female patients have a significantly higher incidence of PONV compared to males, particularly younger women under the age of fifty. Outpatient hysteroscopy patients are predominantly young women, making it especially important to monitor the incidence of PONV in this group.

Previous research has reported that sub-hypnotic doses of propofol (1 mg/kg/h) could effectively reduce the incidence of intraoperative nausea and vomiting in cesarean section patients.<sup>11</sup> This suggested that propofol had properties for both the prevention and treatment of nausea and vomiting. The mechanism might involve the inhibition of the central nervous system acting on the chemoreceptor trigger zone located on the ventral surface of the fourth ventricle. This effect could be due to the direct enhancement of GABA action and its indirect sedative effects.<sup>12</sup> Ciprofol is a new type of intravenous anesthetic sedative that is structurally similar to propofol and acts on  $\gamma$ -aminobutyric acid A receptors. It has completed several clinical trials and has shown good sedative effects and safety.<sup>13</sup> Ciprofol is derived from the chemical structure of propofol, with the introduction of a ciprofol group, forming a chiral structure that increases steric effects and enhances affinity for the GABAA receptor. This suggests that ciprofol also possesses properties for the prevention and treatment of nausea and vomiting.

Our study found no significant difference in the incidence of PONV between two groups at 1 hour and 24 hours postoperatively. Additionally, the nausea and vomiting scores in both groups did not higher than 1 score, indicating that both drugs effectively provide painless sedation while also offering some degree of prevention and treatment of nausea and vomiting. Moreover, the low incidence of PONV may be attributed to the short duration of outpatient procedures and the small amounts of medication used.

Our study results indicate that, compared to propofol, the ciprofol had a lower incidence of respiratory depression and hypoxemia 3 minutes after anesthesia induction, which may be related to ciprofol having a mild suppression of the respiratory center and a lower probability of tracheal collapse.<sup>14</sup> It may also be due to the fact that ciprofol has a lesser impact on reducing tidal volume and inhibiting respiratory function compared to propofol; however, the specific mechanisms underlying these differences may require further research. Previous studies have shown that propofol may cause hypotension by inhibiting myocardial contractility or vascular tone, which is a common adverse effect during outpatient painless procedures. Our study demonstrated that the MAP in the propofol group was lower than in the ciprofol group 3 minutes after anesthesia induction, indicating that ciprofol has a milder effect on circulatory suppression. This finding is consistent with results from Phase III clinical trials.

For patients, the comfort of the procedure is of utmost importance, including the occurrence of PONV or injection pain. The results of this study indicate that the incidence of arm injection pain in the ciprofol group was significantly lower than in the propofol group. This could be due to the lower concentration of free drug in the aqueous solution for the same dosage of ciprofol compared to propofol, leading to less injection pain with ciprofol. Additionally, ciprofol has higher lipid solubility than propofol, resulting in a lower concentration of free molecules in the emulsion, which may also contribute to reduced injection pain. Furthermore, there was no statistically significant difference in the incidence of bradycardia between the two groups, consistent with previous research reports.<sup>15</sup> The underlying mechanism may involve the inhibitory effects on the myocardium in both groups, but the specific mechanisms require further exploration.

Hysteroscopy can cause pain during cervical dilation and certain simple treatments. Therefore, administering sedatives alone during the procedure can easily result in patient movement, which not only affects the surgeon's performance but also increases the risk of uterine perforation, causing greater harm to the patient. Sufentanil, with its small volume of distribution, short terminal elimination time, minimal accumulation, and good controllability, is effective at providing pain relief. Sufentanil at a dose of 0.1  $\mu$ g/kg has been shown to provide excellent analgesia for patients undergoing gastrointestinal endoscopy. Therefore, in this study, all patients received an intravenous injection of sufentanil at 0.1  $\mu$ g/kg before

administering the sedative. However, it is crucial to control the injection speed, as injecting too quickly can cause dizziness, leading to a poor patient experience.

Furthermore, the results of this study indicate that there are no significant differences between the two groups in terms of time to loss of consciousness, awakening time, and discharge time. This suggests that ciprofol not only meets the requirements for painless treatment but also does not affect the quality of patient recovery, achieving excellent therapeutic outcomes. This finding is similar to the results reported by Luo et al<sup>16</sup> which may be due to the similar molecular structure and pharmacokinetics of ciprofol and propofol.

This research had several limitations: first, it was a single-center study, which might introduce biases in the results, and the findings needed to be validated with larger sample sizes and multi-center trials. Second, this study only discusses the effects of ciprofol in patients undergoing outpatient hysteroscopy, and the bias of high-risk factors of PONV was not addressed. As a result, its effect on more complex or longer surgeries, as well as in populations with different risk profiles, awaits further research. Third, this study only recorded the incidence of respiratory depression, and failed to compare the severity of respiratory depression between the two groups. Fourth, this study only compared a single dose, and whether the effect of ciprofol in patients undergoing outpatient hysteroscopy is dose-dependent remains to be discussed. Additionally, the follow-up period for PONV was relatively short. Future research will extend the follow-up period to better investigate PONV.

In summary, the incidence of PONV in outpatient hysteroscopy is similar between ciprofol and propofol. However, ciprofol significantly reduces the incidence of adverse events such as injection pain, respiratory depression, and hypoxemia. These findings suggest that ciprofol is as safe and effective as propofol for anesthesia in outpatient hysteroscopy.

## Author Contributions

Huaming Zhang and Min Zhang are co-first authors. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors report no conflicts of interest in this work.

## References

1. Salazar CA, Isaacson KB. Office operative hysteroscopy: an update. *J Minim Invasive Gynecol*. 2018;25:199–208. doi:10.1016/j.jmig.2017.08.009
2. Stoops S, Kovac A. New insights into the pathophysiology and risk factors for PONV. *Best Pract Res Clin Anaesthesiol*. 2020;34:667–679. doi:10.1016/j.bpa.2020.06.001
3. Horn CC, Wallisch WJ, Homanics GE, et al. Pathophysiological and neurochemical mechanisms of postoperative nausea and vomiting. *Eur J Pharmacol*. 2014;722:55–66. doi:10.1016/j.ejphar.2013.10.037
4. Kim EG, Park HJ, Kang H, et al. Antiemetic effect of propofol administered at the end of surgery in laparoscopic assisted vaginal hysterectomy. *Korean J Anesthesiol*. 2014;66:210–215. doi:10.4097/kjae.2014.66.3.210
5. Zhao MJ, Hu HF, Li XL, et al. The safety and efficacy between remimazolam and propofol in intravenous anesthesia of endoscopy operation: a systematic review and meta-analysis. *Int J Surg*. 2023;109:3566–3577. doi:10.1097/JS9.0000000000000638
6. Qin L, Ren L, Wan S, et al. Design, synthesis, and evaluation of novel 2,6-disubstituted phenol derivatives as general anesthetics. *J Med Chem*. 2017;60:3606–3617. doi:10.1021/acs.jmedchem.7b00254
7. Chen BZ, Yin XY, Jiang LH, et al. The efficacy and safety of ciprofol use for the induction of general anesthesia in patients undergoing gynecological surgery: a prospective randomized controlled study. *BMC Anesthesiol*. 2022;22:245. doi:10.1186/s12871-022-01782-7
8. Zhao T. Comparison of the incidence of postoperative nausea and vomiting between ciprofol and propofol in patients undergoing painless gastroscopy. *Asp Biomed Clin Case Rep*. 2024;7:151–157. doi:10.36502/2024/ASJBCCR.6353
9. Matthews C. A review of nausea and vomiting in the anaesthetic and post anaesthetic environment. *J Perioper Pract*. 2017;27:224–227. doi:10.1177/175045891702701004

10. Kranke P, Meybohm P, Diemunsch P, Eberhart L.H.J. Risk-adapted strategy or universal multimodal approach for PONV prophylaxis? *Best Pract Res Clin Anaesthesiol.* 2020;34:721–734. doi:10.1016/j.bpa.2020.05.003
11. Bi Y, Zhong R, Huang J, Huang H. Effect of continuous infusion of a subhypnotic dose of propofol on nausea and vomiting after carboprost administration at cesarean delivery: a randomized, double-blind, placebo-controlled trial. *Int J Gynaecol Obstet.* 2022;157:283–288. doi:10.1002/ijgo.13742
12. Cechetto DF, Diab T, Gibson CJ, Gelb AW. The effects of propofol in the area postrema of rats. *Anesth Analg.* 2001;92:934–942. doi:10.1097/0000539-200104000-00027
13. Li J, Wang X, Liu J, et al. Comparison of ciprofol (HSK3486) versus propofol for the induction of deep sedation during gastroscopy and colonoscopy procedures: a multi-centre, non-inferiority, randomized, controlled Phase 3 clinical trial. *Basic Clin Pharmacol Toxicol.* 2022;131:138–148. doi:10.1111/bcpt.13761
14. Au AK, Steinberg D, Thom C, et al. Ultrasound measurement of inferior vena cava collapse predicts propofol-induced hypotension. *Am J Emerg Med.* 2016;34:1125–1128. doi:10.1016/j.ajem.2016.03.058
15. Liu Y, Yu X, Zhu D, et al. Safety and efficacy of ciprofol vs. propofol for sedation in intensive care unit patients with mechanical ventilation: a multi-center, open label, randomized, Phase 2 trial. *Chin Med J.* 2022;135:1043–1051. doi:10.1097/CM9.0000000000001912
16. Luo Z, Tu H, Zhang X, et al. Efficacy and safety of HSK3486 for anesthesia/sedation in patients undergoing fiberoptic bronchoscopy: a multicenter, double-blind, propofol-controlled, randomized, phase 3 study. *CNS Drugs.* 2022;36:301–313. doi:10.1007/s40263-021-00890-1

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