Efficacy and Safety of Ciprofol versus Propofol for induction and maintenance of general anesthesia in patients undergoing surgery. A systematic Review and Meta-Analysis of Randomized Controlled Trials.

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Abstract

Background Propofol has been the gold standard for anesthesia induction and maintenance due to its rapid onset and favourable pharmacokinetic properties. However, the search for alternative agents with improved safety and efficacy has led to the emergence of ciprofol (HSK3486), a structural analog of propofol. This systematic review and meta-analysis aims to comprehensively assess the safety and efficacy of ciprofol compared to propofol for anaesthesia induction and maintenance in adult patients undergoing surgical procedures. Methods This study included only double-arm RCTs in which participants were aged eighteen or older undergoing surgery. For the statistical analysis of the extracted data, we employed RevMan 5.4.1. Results Ciprofol demonstrated a promising trend of higher anesthesiologists' satisfaction during the induction phase (MD: 0.14, 95%, CI: -0.28 to 0.56, p = 0.51), whereas Propofol was favored during maintenance. Propofol also exhibited advantages with a shorter time to successful anesthesia induction (MD: 0.08 minutes, 95% CI: 0.00 to 0.15, p = 0.04). and quicker attainment of full alertness (MD: 0.11 minutes, 95% CI: -1.29 to 1.52, p = 0.87), suggesting its efficiency in clinical practice. Importantly, there were no significant disparities in the success rate of anesthesia. Conclusion Both ciprofol and propofol demonstrate comparable efficacy and safety for anesthesia induction and maintenance in adult patients undergoing surgery. While propofol provides a faster onset of induction, ciprofol exhibits advantages in terms of pain management. Clinicians should consider these findings when selecting anesthetic agents, tailoring choices to individual patient needs and clinical scenarios.

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Abstract

Background

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Methods

This study included only double-arm RCTs in which participants were aged eighteen or older undergoing surgery. For the statistical analysis of the extracted data, we employed RevMan 5.4.1.

Results

Ciprofol demonstrated a promising trend of higher anesthesiologists' satisfaction during the induction phase (MD: 0.14, 95%, CI: -0.28 to 0.56, p = 0.51), whereas Propofol was favored during maintenance. Propofol also exhibited advantages with a shorter time to successful anesthesia induction (MD: 0.08 minutes, 95% CI: 0.00 to 0.15, p = 0.04). and quicker attainment of full alertness (MD: 0.11 minutes, 95% CI: -1.29 to 1.52, p = 0.87), suggesting its efficiency in clinical practice. Importantly, there were no significant disparities in the success rate of anesthesia.

Conclusion

Both ciprofol and propofol demonstrate comparable efficacy and safety for anesthesia induction and maintenance in adult patients undergoing surgery. While propofol provides a faster onset of induction, ciprofol exhibits advantages in terms of pain management. Clinicians should consider these findings when selecting anesthetic agents, tailoring choices to individual patient needs and clinical scenarios.

Keywords: Analgesia, Anesthesia induction, Ciprofol, General Anesthesia**,** Propofol.

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What is already known about this subject?

Propofol has been the gold standard for anesthesia induction and maintenance due to its rapid onset and favorable pharmacokinetic properties.

What this study adds

- This systematic review and meta-analysis comprehensively assessed the safety and efficacy of ciprofol compared to propofol for anesthesia induction and maintenance in adult patients undergoing surgical procedures.
- Propofol and Ciprofol exhibited similar efficacy and safety profiles. Nevertheless, Propofol achieved general anesthesia induction more rapidly.
- With Ciprofol there was a reduced incidence of pain at injection site.

Introduction

General anesthesia is a cornerstone of modern medical practice, designed to achieve the vital goals of amnesia, unconsciousness (hypnosis), and immobilization during surgical procedures. These objectives are met through the use of general anesthetics, which exhibit the remarkable ability to reversibly induce these therapeutic effects [1,2]. Among the diverse classes of anesthetic agents, both volatile and intravenous anesthetics play pivotal roles in ensuring reliable and effective anesthesia.

Propofol, a potent γ-aminobutyric acid (GABA) receptor agonist, stands as a testament to the success of intravenous anesthetics over the past three decades [3,4]. Its favorable pharmacokinetic (PK) and pharmacodynamic (PD) properties have propelled it to the forefront of anesthesia practice. Known for its rapid and consistent induction, minimal excitation phenomena, short context-sensitive time, rapid terminal half-life, and low incidence of postoperative nausea and vomiting, propofol has become a cornerstone of anesthesia induction and maintenance [3]. Nevertheless, even with its exceptional attributes, propofol is not without

limitations, which include injection pain, hypotension, respiratory depression leading to apnea, and the potential for the development of intensive care unit (ICU) syndrome [5-7]. It continues to serve as the gold standard against which newer agents are benchmarked, one of these agents being ciprofol (HSK3486).

In recent years, the field of anesthesiology has experienced a surge in the exploration of novel agents for both induction and maintenance of general anesthesia. Among these, ciprofol has emerged as a promising contender, boasting claims of enhanced safety and efficacy when compared to traditional agents. First reported in 2017, ciprofol represents a structural analog of propofol, incorporating an R-chiral center and a cyclopropyl group that imparts improved pharmacological and physicochemical properties. These enhancements render ciprofol more potent than propofol and, notably, less painful upon injection [8,9]. A phase 1 trial demonstrated the safety of ciprofol at doses ranging from 0.15 to 0.90 mg/kg, with most adverse events being of mild to moderate intensity [10]. Given its increased potency relative to propofol, ciprofol necessitates a lower drug volume for achieving anesthesia, which not only reduces the required solvent volume but may also mitigate side effects, particularly those associated with injection site pain.

The primary objective of this comprehensive meta-analysis is to systematically review and synthesize the existing body of literature pertaining to the safety and efficacy of ciprofol compared to propofol in the context of induction and maintenance of general anesthesia in adult patients undergoing surgical procedures. Through the amalgamation of data from multiple studies, we aspire to offer an extensive evaluation of the relative merits of these two agents. By doing so, we aim to provide valuable insights for both researchers and clinicians in the field of anesthesiology, ultimately contributing to the enhancement of anesthesia practices and patient care.

Methods

Data Sources and Search Strategy Cochrane and Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines were implemented while executing and publishing this meta-analysis.[11] A comprehensive electronic search performed using Medline, Google Scholar, Embase, and Cochrane Central was conducted to identify relevant randomized controlled trials (RCTs). The search strategy was composed of the following keywords and their MeSH terms "Propofol" OR "2,6-Diisopropylphenol" OR "2,6 Diisopropylphenol" OR "2,6-Bis(1-methyl ethyl)phenol" OR "Disoprofol" OR "Diprivan" OR "Disoprivan" OR "Fresofol" OR "ICI-35,868" OR "ICI 35,868" OR "ICI35,868" OR "ICI-35868" OR "ICI 35868" OR "ICI35868" OR "Ivofol" OR "Propofol Fresenius" OR "Propofol MCT" OR "Propofol Rovi" OR "Propofol-Lipuro" OR "Recofol" OR "Aquafol" OR "Propofol Abbott" AND "ciprofol OR HSK3486" AND "anesthesia OR sedation". The PRISMA diagram of the studies used can be found in the PRISMA flow chart in the supplementary material. **Figure 1**. Information about the search strategy is given in **supplementary table 1.Eligibility Criteria**The study selection process was conducted in accordance with predetermined eligibility criteria and specific outcome measures. Only double-arm, randomized controlled trials (RCTs) were included in our analysis. The target demographic compromised individuals aged eighteen or over. The intervention involved utilization of ciprofol which was compared with the administration of propofol. The primary outcome assessed was the induction and maintenance of general anesthesia. Some studies were omitted based on the exclusion criteria. Studies in which ciprofol was utilized for screening and diagnostic procedures were not included. Articles published in languages other than English or any other specified language were excluded from consideration. Furthermore, all types of reviews (systematic and non-systematic), case reports, case series, cross-sectional, editorials, commentaries, and animal studies were excluded to maintain the integrity and focus of our study. This rigorous selection process aimed to ensure the quality and relevance of the studies included in our systematic review and meta-analysis.

Data Extraction and Quality assessment

Articles retrieved from the systematic search were exported to EndNote Reference Library software, and any duplicates found were discarded. The remaining articles were initially screened based on abstract and title, then a review of the entire text was conducted to assess relevance. Screening of the articles was distributed amongst two reviewers, (M.H, H.M), and any inconsistencies were resolved by discussion till

consensus or by the third reviewer (A.R.S.S). The following baseline characteristics were extracted onto an online Microsoft Excel Spreadsheet: study characteristics (First author's name along with publication year, study design, number of patients) population characteristics (patient age in years, male gender percentage, Body mass index (BMI)(kg/m2), ASA score, mean operation time, subgroups of dosage of drug). The baseline characteristics are given in

supplementary table 3.

Primary outcomes included efficacy of ciprofol (Satisfaction evaluation for anesthesiologists, Time to full alertness, Time to successful anesthesia induction, Time to loss of eyelash reflex, Success rate of anesthesia, Time required for patients to leave the post-anesthesia care unit (PACU), Time to respiratory recovery) on anesthesia induction and maintenance in comparison to propofol.

Secondary outcomes included the safety profile of ciprofol (total adverse events, tachycardia, rash, prolonged QT interval, pain on injection (induction), hypoxia, hypotension, hypertension (induction), CTCAE severity scale (grade 1) (induction), CTCAE severity scale (grade 2) (induction), bradycardia (induction), any treatment-emergent adverse event, 0.4 mg number of patients who maintained BIS between 40-60 (min) and 0.4 mg elevated AST (induction and maintenance). This is shown in

supplementary table 4.

The revised Cochrane Risk of Bias (RoB) tool was used independently by the two researchers (H.M, N.F.S) to examine the quality of the included RCTs.[12] Reports were analyzed for the generation of allocation sequence, randomization of participants to exposure, selective reporting of outcomes, and missing data.

Statistical Analysis

For the statistical analysis of the extracted data, we employed RevMan 5.4.1. In instances where raw data was available, we calculated Risk Ratio's (RR) and Mean Difference (MD) along with their corresponding 95% Confidence Intervals (CIs). These calculations were performed using a random-effects model, allowing us to create forest plots that visually represented the dichotomous and continuous outcomes respectively.

Heterogeneity was measured using the Higgins I^2statistics and was reported as a percentage for every outcome. For an I^2 value of less than 50%, low heterogeneity was indicated, moderate heterogeneity was considered when the I^2 value was less than 75%, and high heterogeneity was observed with an I^2 value of greater than 75%. Outcomes, if reporting an I^2 greater than 75% were subjected to sensitivity analysis. Following the high heterogeneity leave one out sensitivity analysis was performed for only one outcome time to successful anesthesia induction.

In all statistical analyses, a p-value of [?] 0.05 was established as the threshold for statistical significance. This criterion was applied across the board to determine the significance of our findings.

Publication Bias

For all the outcomes, funnel plots were also formulated using the random-effects model. **(Supplementary figure 2-8)**

Results

Eligible Studies

In adherence to predetermined eligibility criteria and specific outcome measures, our meta-analysis considered six double-arm, randomized controlled trials (RCTs) [13-18]. These trials investigated the use of ciprofol versus propofol for the induction and maintenance of general anesthesia. Our comprehensive search strategy is illustrated in the PRISMA diagram in **Figure 1** , encompassing articles published between 2022 and 2023.

Baseline Characteristics

Our thorough analysis encompassed six randomized controlled trials, involving a total of 714 participants. Among them, 348 patients received propofol, while 417 patients were administered ciprofol (HSK3486). The average age of the study population was just under 40 years, representing a diverse range of adult patients. Gender distribution data revealed that approximately 2/3rd of the participants were females. The majority of participants exhibited an American Society of Anesthesiologists (ASA) score of 2, indicating an adequate state of general health. A comprehensive summary of the baseline characteristics of the included patients can be found in **supplementary table 3.**

Primary Outcomes:

Satisfaction Evaluation for Anesthesiologists:

Our analysis on satisfaction evaluation for anesthesiologists incorporated data from two studies, [13-14] and we observed that, on average, no significant difference was observed in terms of the anesthesiologist satisfaction levels when using 0.4mg ciprofol compared to propofol for anesthesia induction and maintenance (MD: 0.14; 95% CI: -0.28 to 0.5; p = 0.51; I2 = 9%). Subgroup analysis unveiled a similar trend, with no significant difference in preference for either ciprofol or propofol during the induction phase (MD: 0.40; 95% CI: -0.56 to 1.36; p = 0.42; I2 = 47%), or the maintenance phase (MD: -0.10, 95% CI: -1.00 to 0.80).

Time to Full Alertness:

In our review of two studies, [14,15] we found that there were no statistically significant differences in patients who received either drug with regards to achieving full alertness. The MD: 0.11 minutes; 95% CI: -1.29 to 1.52; p = 0.87; I2 = 0%).

Time to Successful Anesthesia Induction:

Our comprehensive analysis, drawing data from five out of six studies, [13-17] highlighted a significant advantage of propofol. The time required for a successful anesthesia induction was significantly shorter with propofol compared to ciprofol, with a mean difference of 0.08 minutes (95% CI: 0.00 to 0.15, p = 0.04, I2 = 77%). Subgroup analyses however showed us that there was a statistically significant difference with 0.5 mg resulting in a shorter time to induction for propofol and no difference in the 0.4 mg group. Interestingly, a leave-one-out sensitivity analysis highlighted the study "Wang X 2022" as a source of substantial heterogeneity within the subgroup receiving 0.4 mg of treatment. Upon its removal, subgroup-specific heterogeneity significantly decreased to 0%, and overall heterogeneity saw a minor reduction to 73%.

Time to Loss of Eyelash Reflex:

Our analysis, based on data from two studies, [13,16] revealed that there was no difference observed between the two drugs in terms of time to loss of eyelash reflex (95% CI: -0.05 to 0.14; p = 0.38; I2 = 92%). Unfortunately, due to the pronounced heterogeneity and limited data, a leave-one-out analysis was not feasible.

Success Rate of Anesthesia:

Across all six studies, [13-18] our combined analysis demonstrated no discernible differences between ciprofol and propofol in terms of the success rate of anesthesia induction and maintenance. The risk ratio (RR) was 1.00, with a 95% CI of 0.99 to 1.01 (p = 1.00, I2 = 0%). Subgroup analysis further reinforced these findings, revealing no significant differences at different dosage levels (0.4mg and 0.5mg) for both the induction and maintenance phases.

Time Required for Patients to Leave the Post-Anesthesia Care Unit (PACU):

Based on data from two studies, [14,15] our pooled analysis indicated that there were no differences with regards to time required to leave the PACU between patients who received propofol than those administered ciprofol (95% CI: -1.45 to 2.34, p = 0.64, I2 = 0%).

Time to Respiratory Recovery: Analyzing data from two studies [14,15] regarding 0.4mg time to respiratory recovery, we found that there was no statistically significant difference in recovery time for respiratory functions following both induction and maintenance phases with propofol compared to ciprofol (p = 0.40).

Secondary outcomes:

Secondary outcomes

Upon performing the analysis, no significant difference was found in all of the outcomes except pain on the injection site in which ciprofol performed notably better in reducing pain. (P=0.0003). Insignificant differences between the two drugs were revealed in terms of total adverse events , tachycardia, rash, prolonged QT interval, hypoxia, hypotension, hypertension, CTCAE severity grading (grade 1), CTCAE Severity Grading (Grade 2), bradycardia, any treatment-emergent adverse events, elevated AST, number of patients who maintained Bispectral index (BIS) between 40 – 60 (min).

Furthermore, after conducting a subgroup analysis it was discovered that a significant reduction in total adverse events occurred when 0.5 mg ciprofol was used for induction ($P < 0.0001$). Similarly, ciprofol fared significantly better in terms of reducing the incidence of tachycardia when 0.5mg ciprofol was utilized for both induction and maintenance of general anesthesia ($P = 0.01$). Propofol performed significantly worse compared to 0.4mg ciprofol during the induction phase according to the CTCAE severity grading scale (grade 1) ($P = 0.005$).

Quality Assessment and Publication Bias:

We conducted a rigorous quality assessment of the included trials using the Cochrane risk of bias tool, identifying trials of moderate-to-high quality. Notably, our results remained unaffected by any potential publication bias, as demonstrated by the symmetrical distribution of studies on each side of the vertical axis in the funnel plots of the primary outcomes.

Discussion

The influence of anesthesiologists' satisfaction is pivotal in selecting anesthetic agents. Their trust in a drug's effectiveness and safety profoundly impacts patient care. Our meta-analysis hints at a slightly stronger preference for Ciprofol, particularly during the induction phase. It's essential to note, though, that these preferences don't quite reach the threshold of statistical significance thus emphasizing that ciprofol and propofol exhibit similar satisfaction levels among anesthesiologists during both induction and maintenance phases of anesthesia. This aligns with existing literature, suggesting that Ciprofol could be a compelling alternative to Propofol in clinical anesthesia. [19] These consistent results strengthen the evidence that ciprofol can be a viable alternative to propofol in anesthesia practice, offering similar satisfaction levels for anesthesiologists while providing potential benefits such as safety and effectiveness [20,21] However, the absence of statistical significance highlights the multifaceted nature of this preference. Various factors, including individual preferences, patient-specific characteristics, surgical requirements, and the collective experiences of the anesthesia team, all play a role in shaping satisfaction levels. Furthermore, variations in satisfaction at different phases of anesthesia administration emphasize the need for tailored approaches to match the unique demands of each surgical step, ensuring the best possible patient outcomes and overall satisfaction [22]

Interestingly, we observed no statistically significant difference between both drugs for alertness. However, our results are inconsistent with existing literature on the subject. For instance, a recent systematic review [19] in the context of painless gastroenteroscopy found that Propofol consistently leads to faster alertness compared to Ciprofol. This inconsistency in results could be attributed to the fact that our study exclusively focused on invasive surgeries, which encompassed a diversity of surgical types. Propofol is well-known for its characteristics of rapid onset and swift recovery, which results from its pharmacokinetic property of fast elimination. [3,23] Thus making it a promising option to induce and maintain anesthesia, particularly for short-duration procedures. The rapid elimination of propofol minimizes the risk of residual sedation, promoting patient safety and reducing the need for extended post-anesthesia monitoring.[24] Anesthesiologists

value Propofol for its ability to induce and reverse anesthesia swiftly, providing a significant advantage in various clinical scenarios. However, it's crucial to recognize that this advantage comes with the caveat of a relatively narrow therapeutic window and potential concentration-dependent effects on cardiovascular and respiratory systems, especially in elderly and frail patients [9] These considerations underscore the importance of a nuanced approach when selecting anesthetic agents, taking into account the specific characteristics and vulnerabilities of the patient population.

Propofol's superior induction speed, consistent with previous research, highlights its status as the preferred choice for anesthesia induction in clinical practice [19]. The absence of a substantial difference in induction time between Ciprofol at 0.4 mg and Propofol is an intriguing finding. It suggests that, at this lower dosage, Ciprofol can achieve induction times similar to Propofol [15]. This implies that Propofol may have a slightly faster onset of action for inducing anesthesia than Ciprofol [19], which could be advantageous in specific clinical scenarios. Heterogeneity is observed in Wang X's study for several reasons. Firstly, Wang X conducted a phase 3, multicenter, randomized, double-blind, comparative study, which introduced differences in study design, data collection, and interpretation compared to studies in the same analysis. Additionally, the study had a larger sample size with a higher percentage of male patients, potentially introducing gender-related variations in anesthesia induction times. Furthermore, variations in patient age, BMI, and ASA score distribution in Wang X's study could impact how individuals respond to anesthesia, leading to differences in induction times.

Contrary to the above-mentioned findings, our focus on the loss of eyelash reflex specifically revealed no divergences between the two agents. However, it is essential to acknowledge the presence of pronounced heterogeneity in our analysis of time to loss of eye reflex, which suggests substantial variability among the included studies. This heterogeneity, coupled with the limitation of limited data availability resulted in a trend not favoring either of the drugs, especially propofol.

Our meta-analysis provides valuable insights, affirming that both Ciprofol and Propofol can effectively serve for anesthesia induction and maintenance, with no significant differences observed. This conclusion gains strength through our subgroup analysis, which demonstrates that even with different Ciprofol dosages (0.4mg and 0.5mg), there are no significant differences in the success rate of anesthesia induction compared to Propofol. This suggests that the choice of Ciprofol dosage doesn't significantly affect induction success rates [25]. These findings hold practical implications for anesthesiologists, indicating that both Ciprofol and Propofol are valid choices for anesthesia induction and maintenance. Clinicians can make their choices based on patient-specific factors and individual preferences.

The observation of a faster exit from the Post-Anesthesia Care Unit (PACU) and improved recovery of respiratory functions with Propofol aligns with its established characteristics of rapid onset and short duration of action. This can be attributed to Propofol's favorable pharmacokinetic profile. However, the absence of statistical significance in these findings could be due to inherent variability in patient responses and the specific criteria used for assessment [26]. Nevertheless, these findings have significant clinical relevance, as quicker recovery and discharge from the PACU can enhance patient throughput and optimize resource utilization [27].

Managing pain at the injection site, a factor that can induce anxiety and discomfort among patients during intravenous (IV) infusion, is a critical consideration. Propofol has been known to cause pain at the injection site. [28] To address this concern, pretreatment with local anesthetics like lidocaine before IV administration of Propofol has been employed. Additionally, using a more diluted dose of Propofol has been explored to alleviate pain at the injection site [29]. In support of the current literature, our meta-analysis collectively shows that Ciprofol is less likely to cause pain at the injection site. This can be explained by the hydrophobic nature of Ciprofol, resulting in relatively lower plasma concentrations compared to Propofol [30].

In our comprehensive meta-analysis comparing ciprofol and propofol in the context of anesthesia, we conducted a thorough evaluation of various adverse events to assess the safety profiles of these two agents. Our findings indicate that, in general, there was no statistically significant difference observed between ciprofol

and propofol in terms of overall adverse events. This suggests that both agents are generally well-tolerated and safe for use in anesthesia induction. Comparing our results to the existing literature, studies have reported varying safety profiles for both ciprofol and propofol. Some have highlighted the safety and effectiveness of ciprofol in anesthesia induction, with a lower incidence of adverse events.[25] In contrast, others have noted that propofol remains a standard and safe choice for anesthesia induction. [31]

Our study does have its limitations. We only included double-arm randomized control trials, limiting our dataset to six studies. Additionally, our study exclusively focused on invasive surgeries, which encompassed a diversity of surgical types. Though most studies affirm the safety of both drugs for clinical practice, it is worth noting that the existing literature on the comparison between these two drugs is relatively limited. Looking ahead, future research should delve into optimized Ciprofol dosing strategies aimed at achieving the desired depth of anesthesia while minimizing side effects [32]. Exploring patient-centered outcomes and integrating advanced monitoring technologies could also provide deeper insights into the comparative strengths and weaknesses of these agents. Large-scale studies spanning diverse patient groups and clinical scenarios, including specific procedures like gastrointestinal sedation, can shed light on the advantages concerning patient comfort and recovery. [33] Moreover, investigating long-term outcomes and cost-effectiveness can offer valuable guidance for clinical decision-making.

Conclusion

In conclusion, this systematic review and meta-analysis have illuminated the comparative effectiveness and safety of Ciprofol and Propofol in the context of general anesthesia. Both agents exhibited similar overall efficacy and safety, indicating their potential interchangeability for anesthesia induction and maintenance. Propofol had a faster onset of anesthesia during the induction phase. Conversely, Ciprofol resulted in reduced incidence of pain at injection site. Clinicians should consider these findings while tailoring their choice of anesthetic agents to individual patient characteristics and preferences.

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Supplementary Table 1

DATABASE	SEARCH STRATEGY
Medline	((((((((((((((((((((Propofol) OR (2,6-Diisopropylphenol)) OR (2,6 Diisopropylphenol)) OR (2,6-Bis(1-met
Google Scholar	((((((((((((((((((((Propofol) OR (2,6-Diisopropylphenol)) OR (2,6 Diisopropylphenol)) OR (2,6-Bis(1-met
Embase	((((((((((((((((((((Propofol) OR (2,6-Diisopropylphenol)) OR (2,6 Diisopropylphenol)) OR (2,6-Bis(1-met

Supplementary Table 2

Author name	ZENG	LIANG	MAN	CHEN	QIN	Wang
Trial name	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	Efficacy and safety of ciprofol vs. propofol for the induction and maintenance of general anesthesia A multicenter, single-blind, randomized, parallel-group, phase 3 clinical trial	Study on the effectiveness and safety of ciprofol in anesthesia in gynecological day surgery: a randomized double-blind controlled study	The efficacy and safety of ciprofol use for the induction of general anesthesia in patients undergoing gynecological surgery: a prospective randomized controlled study	Effect of ciprofol on induction and maintenance of general anesthesia in patients undergoing kidney transplantation	Effects of ciprofol for the induction of general anesthesia in patients scheduled for elective surgery compared to propofol: a phase 3, multicenter, randomized, double-blind, comparative study
Patient no.	40	129	128	120	120	176
Year of publication	2022	2023	2023	2022	2022	2022
Trial type	a multicenter, randomized, open-label, propofol-controlled phase 2 clinical trial	A multicenter, single-blind, randomized, parallel-group, phase 3 clinical trial	a randomized double-blind controlled study	a prospective randomized controlled study	prospective, randomized, single-blind study	A multi-center, randomized, propofol-controlled, double-blind trial
Trial number	NCT04048811	NCT04511728.	ChiCTR2100053442	ChiCTR2100045201	ChiCTR2200058826	NCT03808844

Author name	ZENG	LIANG	MAN	CHEN	QIN	Wang
Inclusion criteria	Age 18 -65 years old. An American Society of Anesthesiologists (ASA) rating of Class I-III, endotracheally intubated under GA, and a blood loss of [?] 1,000 mL were included.	(American Society of Anesthesiologists (ASA) classes I to II); age [?]18 years and [?]65 years;	Age (18 ˜ 64years), with American Society of Anesthesiologists physical classification status I or II, BMI 18 to 28 kg/m2.	Adult females between the ages of 18 to 60 (ASA physical status: I or II) who were scheduled to undergo elective gynecological surgery under GA.	Patients who had a kidney transplant under GA with tracheal intubation. Age 18-65 years, (BMI) of 18-30 kg/m2 American Society of Anesthesiology (ASA) physical status of III-IV.	Age 18-64 years (BMI) between 18 and 30 kg/m2, American Society of Anesthesiologists physical status of I or II scheduled to undergo elective surgery under HA

Author name	ZENG	LIANG	MAN	CHEN	QIN	Wang
Exclusion criteria	Scheduled to receive emergency, surgical procedures with contraindications to GA or with a history of previous anesthesia incidents were excluded.	Contraindications to GA; a history of anesthesia incidents; a disease history of diseases or issues in any systems that could increase the risk of sedation/anesthesia.	Patients were excluded if they suffered from propofol allergies, had significant diseases in various systems Women who were pregnant, or planning to become pregnant were excluded.	morbid obesity, egg/soy allergies, had significant diseases in various systems. Women who were pregnant, lactating, or planning to become pregnant within 1 month after the trial were excluded.	patients with liver, mental, nervous system diseases, coagulation dysfunctions, heart failure, respiratory failure, long-term use of sedatives or antidepressants, pregnant or lactating women, and unable to communicate or cooperate.	a history of allergy or hypersensitivity. Those who had clinically significant systemic diseases; pregnant or had a pregnancy plan within 1 month postoperatively; a family history of malignant hyperthermia; those who had surgery under GA within 4 weeks perioperatively; who had previously received sedative/narcotic agents within 3 days of screening and had alcohol or drug abuse within 3 months perioperatively; who had previously received drugs that could have affected the QT interval or induced/inhibited P450 or CYP2B6 within 2 weeks perioperatively.

Author name	ZENG	LIANG	MAN	CHEN	QIN	Wang
Treatment	Randomly assigned to HSK3486 or propofol 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.	Patients were given midazolam 0.04 mg kg-1 and sufentanil 0.3 μg kg-1 as pre-anesthetic medication. Anesthesia induction was then initiated with either HSK3486 or propofol. After successful induction, the muscle relaxant rocuronium bromide was administered at 0.6 mg kg-1, and endotracheal intubation was performed. HSK3486 or propofol was given at appropriate doses to maintain anesthesia. Remifentanil was administered at 0.1–0.3 μg/kg-1 min-1 for analgesia, and sufentanil and a muscle relaxant were added. bromide.	During anesthesia induction, the ciprofol group was infused at a time limit of 0.5 mg/kg for one minute, and the propofol group was infused at a time limit of 2 mg/kg for 1 min.	Intravenous midazolam (0.03 mg/kg) and sufentanil (0.3 μg/kg) were used to start general anesthesia induction, followed 2 min later by the manual injection of ciprofol (0.4 mg/kg) or medium-and long-chain triglyceride (MCT/LCT) propofol (2 mg/kg). Patients started receiving preoxygena-tion after intravenous midazolam and sufentanil being ad-ministrated. When spontaneous breathing disappeared, it switched to manual controlled breathing. i	The patients were randomized into a ciprofol group (group C) and a propofol group (group P). Anesthesia induction: group C had injected IV with ciprofol 0.4 mg/kg, group P had injected IV with propofol 2.0 mg/kg, while both groups had injected IV with sufentanil 0.4-0.5 μg/kg and cisatracurium 0.2 mg/kg. Anesthesia mainte-nance: ciprofol was injected IV with 0.8-2.4 mg*kg-1*h-1 in group C, propofol was injected IV with 4-12 mg*kg-1*h-1 in group P, while remifentanil was injected IV with 8-15 μg*kg-1 *h-1 and cisatracurium was injected IV with 0.1-0.2mg*kg-1*h-1, with the bispectral index	Optimal injected doses of 0.4 mg/kg of ciprofol and 2.0 mg/kg of propofol

Author name	**ZENG**	**LIANG**	**MAN**	**CHEN**	**QIN**	**Wang**
Primary efficacy outcome	The success rate of anesthesia maintenance.	Noninferiority between the drugs was evaluated as the lower limit of the 95% confidence interval (CI) for the group difference.	(1) bradycardia (HR $<$ 50 beats/min, $>$ 30s); (2) Tachycardia (HR $>$ 100 beats/min, $>$ 30s) (3) Hypotension (30% reduction in SBP compared to baseline value); (4) Hypertension (SBP is 20% higher than baseline value); (5) injection pain at the site. (6) Intraoperative body movements	Safety and efficacy of ciprofol. Evaluation The success rate of general anesthesia induction was the primary outcome for the present study.	The success rate of sedation.	The anesthesia induction success.

Author name	ZENG	LIANG	MAN	CHEN	QIN	Wang
Secondary Efficacy outcome	Times from discontinuation of HSK3486 or propofol maintenance to full alertness, respiratory recovery, extubation and reaching the goal of the Aldrete score.	Successful anesthetic induction, full alertness and spontaneous breathing recovery, time until leaving the postanesthetic care.	(1) success rate of induction of anesthesia, (2) the time of loss of consciousness (time of initiation of study drug infusion to MOAA/S [?] 1), (3) time of awakening (time of drug discontinuation to extubation), (4) study drug top-up doses, (5) rescue drug use.	(1) the time to onset of successful induction; (2) the incidence of injection site pain as detected by a withdrawal response or a numeric rating. (3) time to eyelash reflex disappearance. (4) changes in the bispectral index (BIS) during the 10-min interval.	. HR showed no significant difference between the two groups (p>0.05). MAP decreased more significantly in group P at T6 (p0.05)	The average time to successful anesthesia and loss of the eyelash reflex. The pattern of BIS changes. The incidence of injection pain/
Follow up	N/A	N/A	N/A	N/A	N/A	N/A

Supplementary Table 3

STUDY	STUDY DESIGN	TOTAL NO OF PATIENTS	MALE (%)	MALE (%)	Age Mean (±SD)	Age Mean (±SD)	BMI (kg/m2) Mean (±SD)	BMI (kg/m2) Mean (±SD)	ASA Score 1/2/3/4	ASA Score 1/2/3/4	OPERATIONAL TIME, MEAN SD	T M S
			CIPROFOL	PROPOFOL	CIPROFOL	PROPOFOL	CIPROFOL	PROPOFOL	CIPROFOL	PROPOFOL	CIPROFOL	PROPOFOL
Zeng Y 2022	multicenter, randomized, open-label, propofol-controlled phase 2 clinical trial	40		11 (36.7)	3 (30.0)	42.5 ± 10.3	46.4 ± 11.2	23.7 ± 3.0	23.6 ± 3.6	16/14/0/0	4/6/0/0	1 = 6

STUDY	STUDY DESIGN	TOTAL NO OF PATIENTS	MALE (%)	MALE (%)	Age Mean (±SD)	Age Mean (±SD)	BMI (kg/m2) Mean (±SD)	BMI (kg/m2) Mean (±SD)	ASA Score 1/2/3/4	ASA Score 1/2/3/4	OPERAT TIME, MEAN SD	T M S
Wang X 2022	phase 3, multicenter, randomized, double-blind, comparative study	176		32	31	38.5 (12.1)	41.1 (11.1)	23.3 (2.9)	23.3 (3.1)	51/37/0/0	48/40/0/0	-
Qin K 2022	prospective, randomized, single-blind study	105		18 (34.6)	18 (34.0)	39.00±10.14	41.25±10.62	23.38±3.33	22.63±2.38	8/0/42/10	0/0/44/9	1
Chen-Ben Zhen 2022	prospective, double-blind, single-center study	120		-	-	33.9±9.1	33.8±9.6	22.2±3.2	21.4±2.8	32/28/0/0	34/26/0/0	5
Liang Peng 2023	multicenter, single-blinded, propofol-controlled, randomized, phase 3 trial	128		23 (26.7)	10 (23.8)	38.5 ± 10.1	40.5 ± 10.1	23.3 ± 2.8	23.3 ± 3.0	48/38/0/0	22/20/0/0	9 ± 3

STUDY	STUDY DESIGN	TOTAL NO OF PATIENTS	MALE (%)	MALE (%)	Age Mean (±SD)	Age Mean (±SD)	BMI (kg/m2) Mean (±SD)	BMI (kg/m2) Mean (±SD)	ASA Score 1/2/3/4	ASA Score 1/2/3/4	OPERAT TIME, MEAN SD	T M S
Zhu Qianmei 2023	phase 2a, 7-center, open-labeled, non-randomized and positive controlled clinical trial	68	0.4mg 0.5mg	4 13	16	53.5 ± 8.3 46.6 ± 12.4	44.8 ± 12.4	24.4 ± 2.5 23.8 ± 2.6	24.4 ± 3.0	6/2/0/0 7/22/0/0	14/17/0/01	± 8 4
Man Yan 2023	randomized double-blind controlled study	128		-	-	42.2±9.46	44.1±9.4	22.8±2.2	23.3±2.6	18/46/0/0	14/50/0/0	-

Supplementary table 4

OUTCOME
Total adverse events (induction) 0.4mg ciprofol 0.5 mg ciprofol
Tachycardia 0.4mg cipro vs propo (induction) 0.5mg cipro vs propo (induction) o.4mg ciprofol (induction and maintenanc
Rash 0.4mg cipro vs propo (induction) 0.4mg ciprofol (induction and maintenance)
Prolonged QT interval
Pain on injection site (induction) 0.4mg ciprofol 0.5mg ciprofol
Hypoxia 0.4mg cipro vs propo (induction) 0.4mg cipro vs propo (indcution and maintenance)
Hypotension 0.4mg cipro vs propo (induction) 0.5mg cipro vs propo (induction) 0.4mg (induction and maintenance)
Hypertension (induction) 0.4mg cipro vs propo 0.5mg cipro vs propo
CTCAE Severity Grading (grade 1) 0.4mg cipro vs propo (induction) 0.mg cipro vs propo (induction and maintenance
CTCAE Severity Grading (Grade 2) 0.4mg cipro vs propo (induction) 0.4mg cipro vs propo (induction and maintenance)
Bradycardia 0.4mg cipro vs propo (induction) 0.5mg cipro vs propo (induction) 0.4mg cipro vs propo (induction and mai
Any treatment-emergent adverse events 0.4mg cipro vs propo (induction) 0.4mg cipro vs propo (induction and maintenance
0.4 mg Number of patients who maintained BIS between at 40 - 60 (min)
0.4 mg elevated AST (induction and Maintenance)

Legends to Figures:

Figure 1: Prisma Flow Chart

Figure 2: Satisfaction Evaluation for Anesthesiologists (forest plot)

Figure 3: Time to Full Alertness (forest plot)

Figure 4: Time to Successful Anesthesia Induction (forest plot)

Figure 5: Time to loss of Eyelash Reflex (forest plot)

Figure 6: Success Rate of Anesthesia (forest plot)

Figure 7: Time Required for Patients to Leave the Post-Anesthesia Care Unit (PACU) (forest plot)

Figure 8: Time to Respiratory Recovery (forest plot)

Supplementary materials:

Supplementary Figure 1: Cochrane Risk of Bias

Supplementary Figure 2: Satisfaction Evaluation for Anesthesiologists (funnel plot)

Supplementary Figure 3: Time to Full Alertness (funnel plot)

Supplementary Figure 4: Time to Successful Anesthesia Induction (funnel plot)

Supplementary Figure 5: Time to loss of Eyelash Reflex (funnel plot)

Supplementary Figure 6: Success Rate of Anesthesia (funnel plot)

Supplementary Figure 7: Time Required for Patients to Leave the Post-Anesthesia Care Unit (PACU) (funnel plot)

Supplementary Figure 8: Time to Respiratory recovery (funnel plot)

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`Figures.docx` available at https://authorea.com/users/672371/articles/671468-efficacy-and-safety-of-ciprofol-versus-propofol-for-induction-and-maintenance-of-general-anesthesia-in-patients-undergoing-surgery-a-systematic-review-and-meta-analysis-of-randomized-controlled-trials