Heliyon 9 (2023) e22634

Contents lists available at ScienceDirect

Heliyon

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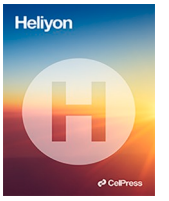

Efficacy and safety of ciprofol (HSK3486) for procedural sedation and anesthesia induction in surgical patients: A systematic review and meta-analysis

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ARTICLE INFO

Keywords:
Ciprofol
HSK3486
Anesthesia
Surgical patients
Safety
Efficacy
Meta-Analysis

ABSTRACT

Background: Ciprofol (HSK3486) is a novel gamma-aminobutyric acid type A (GABAA) receptor agonist that has attracted wide attention because of its lower injection pain and fewer adverse events. We summarized all available evidence and analyzed the efficacy and safety of ciprofol during procedural sedation and anesthesia induction.

Methods: An electronic search of PubMed, Embase, Cochrane Library, Web of Science, Google Scholar, Science Direct, the Chinese National Knowledge Infrastructure, Wan Fang Data, and the VIP Chinese Journal Service platform was conducted from inception of databases to March 1, 2023. Risk ratio (RR) and mean difference (MD) with 95 % confidence interval (CI) were used separately for binary categorical and continuous variables. We performed trial sequential analysis and the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology to judge the certainty of evidence.

Results: Fifteen randomized controlled trials with 2441 patients were included in this study. Ciprofol showed similar advantages to propofol in terms of induction success rate (RR = 1, 95 % CI = 0.99, 1.01, moderate certainty) and induction time (MD = 3.31, 95 % CI = −0.34, 6.95, low certainty), but did not increase the incidence of adverse events (RR = 0.88, 95 % CI = 0.78, 1.00, very low certainty), such as bradycardia (RR = 0.96, 95 % CI = 0.77, 1.21, high certainty), hypoxia (RR = 0.79, 95 % CI = 0.46, 1.37, p = 0.40, moderate certainty) and other adverse events. Although it may be associated with a longer time to be fully alert (MD = 1.22, 95 % CI = 0.32, 2.12, very low certainty), ciprofol significantly reduced injection pain (RR = 0.15, 95 % CI 0.09, 0.24, low certainty) and may have reduced the incidence of hypotension (RR = 0.77, 95 % CI = 0.63, 0.94, low certainty) and respiratory depression (RR = 0.29, 95 % CI = 0.15, 0.56, moderate certainty).

Conclusion: Ciprofol and propofol had similar effects on most outcomes. While the time to full alertness may be prolonged, injection pain was significantly reduced, and hypotension and respiratory depression may be reduced compared with propofol. We believe that ciprofol is an effective alternative to intravenous anesthetic agents.

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https://doi.org/10.1016/j.heliyon.2023.e22634
Received 28 September 2023; Received in revised form 15 November 2023; Accepted 15 November 2023
Available online 26 November 2023

1. Introduction

The gamma-aminobutyric acid type A (GABAA) receptor agonist, propofol, is one of the most widely used anesthetics in clinical practice. It is widely used for the induction and maintenance of surgical anesthesia as well as in auxiliary outpatient surgery owing to its rapid effect, short duration of anesthetic induction, and quick patient recovery[[1,2]]. However, propofol has some drawbacks, such as inhibition of the circulatory and respiratory systems and pain at the injection site [3].

Ciprofol (HSK3486) is China's first independent innovation of a class 1 intravenous anesthetic, which is also a GABAA receptor agonist. Ciprofol is an innovative 2, 6-dissubstituted phenol derivative prepared by introducing a cyclopropyl group into the two or six side chains of propofol to change its lipophilicity, and by introducing a chiral center to change its symmetry. The chemical formula of ciprofol is 2-(1-Cyclopropylethyl)-6-isopropylphenol, which has a higher GABAA receptor-binding ability and a higher safety window, and its affinity for the GABAA receptor is approximately 4–5 times that of propofol [4]. Ciprofol has better liposolubility; therefore, fewer lipids reach the circulatory system than propofol does [5]. Ciprofol is absorbed intravenously and rapidly eliminated from plasma. The concentration-time curve of ciprofol was similar to that of propofol. After intravenous administration, the plasma concentration of ciprofol decreased in a polyphasic manner with a final elimination half-life of 1.58–2.47 h [6]. Ciprofol may be metabolized into harmless glucuronic acid conjugates through gluconalylation, oxidation, and sulfation and is primarily eliminated from the kidney [7]. The effect of ciprofol began 1–2 min after administration, followed by gradual recovery within 10–18 min, indicating that the effect of ciprofol was rapid and that the subject woke up smoothly and quickly [8]. Ciprofol has been approved for the induction and maintenance of anesthesia in adults, and for sedation and anesthesia during non-tracheal intubation procedures.

Clinical trials of ciprofol for the induction and maintenance of anesthesia are available, but studies are limited [9]. Therefore, we systematically reviewed previous studies to evaluate the efficacy and safety of ciprofol in the induction and maintenance of anesthesia and attempted to determine whether the results reached the size of the information required to draw conclusions in conjunction with the trial sequence analysis. This study provides a higher level of evidence for the clinical application of ciprofol.

2. Materials and methods

The PRISMA statement and guidelines in the Cochrane Handbook were followed to ensure the reliability and authenticity of the results[[10,11]]. The protocol for this meta-analysis was registered on PROSPERO (registration number CRD42023400589). The PRISMA checklist was used to report the findings (eTable1).

2.1. Systematic search

The two researchers searched the following databases: PubMed, Embase, Cochrane Library, Web of Science, Google Scholar, Science Direct, Chinese National Knowledge Infrastructure, Wan Fang Data, and VIP Chinese Journal Service Platform. We searched for related articles from inception to October 20, 2023, with no language restrictions. Among the MeSH terms and keywords were "ciprofol," "HSK3486," "safety," "adverse event," "efficacy," "sedation," and "anesthesia." To avoid omitting highly relevant literature, we screened additional studies from the list of references in the relevant articles.

2.2. Study selection

Trials meeting the following criteria were included: (1) Participants: Adult patients undergoing surgery with a clinical need for anesthesia and sedation. (2) Intervention: Intravenous injection of ciprofol at any dose; (3) Comparison: Intravenous injection of propofol or other sedatives at any dose; (4) Study design: RCTs and observational studies The exclusion criteria were as follows: (1) duplicate reports and secondary analyses, and (2) no outcome indicators available.

The outcome indicators included any of the following: (1) Primary outcomes included the time to successful anesthesia induction (from the start of drug administration to achieving a MOAA/S score of $\leq$1), time to being fully alert (from the end of drug administration to achieving a MOAA/S score of 5) and injection pain (evaluated immediately after the ciprofol was injected). (2) Secondary outcomes included procedure success (completion of the procedures, not requiring rescue sedatives), time to leave the operating room (the time from the end of drug administration to reach the fulfilment of discharge criteria), and measured adverse events (defined by the study authors), such as hypotension, bradycardia, hypoxia, body movement, respiratory depression, dizziness, rash, and prolonged QT interval.

2.3. Data extraction and quality assessment

Two reviewers (W and D) extracted and crosschecked the data independently and in duplicate using a designed data table. Disagreements were adjudicated by a third reviewer (Liu) through discussion. We collected data on title, author, year of publication, patient age, sex, number of cases, type of surgery, BMI, drug dose, and outcome indicators. We converted other types of continuous results, such as median and interquartile range, to mean and standard deviation[[12,13]]. If the trial established subgroups of different test scenarios or dosages, the results were reported for multiple groups. For comparison with the results of other trials, we followed the guidelines of the Cochrane Handbook to combine data from different subgroups for analysis.

We assessed the risk of bias independently using the Risk of Bias tool 2.0 [14]. We determined the overall risk of bias for each trial

based on the highest risk of bias in the seven domains. A bias risk assessment chart was derived using Revman5.4 software. Two open-label trials were assessed based on the risk of bias in non-randomized studies of interventions (ROBINS-I) as recommended by the Cochrane Group.

2.4. Date analysis

We used Revman5.4 for data analysis. Our meta-analysis used the DerSimonian and Laird random effects models [15]. We measured the relative risk (RR) of dichotomous outcomes. For continuous results, we determined the mean difference (MD) and calculated the corresponding 95 % confidence interval (CI). The I2 index was calculated to assess statistical heterogeneity, and I2<50 % indicated low heterogeneity [16]. Through STATA V.16.0 software, publication bias was determined by visual inspection of funnel plots and Egger's test [17].

Predesigned subgroup analyses were performed to examine whether baseline factors affected the statistical significance of outcomes and to explore the heterogeneity between trials. Subgroup analysis results were determined based on the experimental procedure and drug concentration. We conducted a meta-regression analysis in Stata 16.0, to examine the relationship between primary outcome measures and the mean age of patients. To assess whether the results were robust, we performed a sensitivity analysis by retaining only low-bias risk studies.

To determine whether we met the sample size required for statistical significance, we used TSA software v. 0.9.5.10 Beta test sequence analysis (TSA) [18]. The conclusion can be considered firmly accepted or rejected when the Required Information Size (RIS) is larger than the Accrued Information Size (AIS) or when the cumulative Z-curve crosses the sequential monitoring boundary. Further studies are required to verify these findings. Type-I error (Alpha-2) and power were set to 0.05 and 0.80, respectively.

Two reviewers assessed the quality of the evidence using GRADE of Recommendations Assessment, Development, and Evaluation (GRADE) [19]. The study results were evaluated using the GRADEpro software based on bias, inconsistency, indirection, imprecision, and publication bias. The quality levels were categorized as high, medium, low, or very low [20].

3. Results

3.1. Search results

A preliminary search identified 172 citations (PubMed, 33; Embase, 37; Cochrane Library, 30; Web of Science, 35; CNKI, 13; Wan Fang, 17; VIP database, 7) and 69 remained after the removal of duplicate records. The titles and abstracts were screened. Subsequently, 38 records were excluded. The full texts of 31 articles were carefully read for eligibility. The full texts of 16 articles were excluded for various reasons. Finally, 15 trials were included in the analysis. Fig. 1 shows the PRISMA flowchart of the search process.

3.2. Study characteristics

Overall, 15 eligible trials enrolled 2441 patients. Table 1 presents the baseline characteristics of the included studies. The trials were published between 2021 and 2023 and were conducted in China. All trials used propofol as the control group. The number of study participants ranged from 40 to 460. The mean age of the patients was 44.91 ± 14.89 years. Statistically, 59.2 % of participants were female. The average BMI of 1787 patients in 12 trials was 23.24 ± 3.31. In terms of intervention, most trials had an infusion rate of 0.4 mg/kg and a propofol infusion rate of 2.0 mg/kg. In terms of drug use procedures, nine trials enrolled patients undergoing endoscopic surgery and six trials enrolled patients undergoing routine surgery. All 15 trials, including two open-label trials, were published in full manuscript form.

3.3. Risk of bias

According to the Cochrane Bias Risk Tool, seven of the 13 RCTS were found to have a low risk of bias. These studies were included at a moderate quality level. Subsequently, these projects were evaluated. A total of 85 % (11/13) of the studies employed an appropriate random sequence generation method, and 62 % (8/13) reported a detailed description of assignment hiding. A total of 62 % (8/13 of the studies described blinding procedures for participants and people, and 54 % (7/13) mentioned blinding procedures for outcome evaluation. Each article lists the reasons and figures for withdrawal or abandonment. Seven studies were of high quality, and all had a low risk of bias. The other two open-label trials were evaluated using the risk of bias in nonrandomized studies of interventions (ROBINS-I). After the evaluation, we concluded that both trials had a moderate risk of bias. Details of the bias risk assessment are shown in eFigure1, 2 and eTable2.

3.4. Primary outcomes

3.4.1. Induction time

Ten studies involving 1518 patients were analyzed. There was no significant difference in induction time between ciprofol and propofol (MD = 3.31, 95 % CI = −0.34, 6.95, p = 0.08, low certainty, Table 2, eTable3, Fig. 2A). Sensitivity and subgroup analyses, excluding studies with a high bias risk, found no effect correction, which suggests the robustness of our results. The results were highly heterogeneous (I2 = 56 %, p = 0.02); therefore, a subgroup analysis was performed to explore the potential sources of heterogeneity.

Subgroup analysis was performed according to procedure (endoscopy vs surgery) and drug dose (≤0.4vs > 0.4). We found that the drug dose had no significant effect on the induction time. In addition, no credible subgroup effects were observed in the different procedure (Table 2, Fig. 3A, eFigure18-20). The meta-regression analysis revealed no relationship between the age of patients and induction time (p = 0.957, eFigure3A). We excluded the high-bias test from the sensitivity analysis and found no effect modification, suggesting the robustness of our findings. In the analysis of the test sequence, AIS was smaller than RIS. The cumulative Z-curve did not cross the invalid boundary; therefore, the conclusion was not conclusive, and further tests are required (Fig. 4A). Publication bias was not detected using Egger's test (P = 0.106, Fig. 5A).

3.4.2. Time to fully alert

Twelve studies (n = 1688) examined the difference between ciprofol and propofol in terms of time to complete awakening. When using ciprofol instead of propofol for anesthesia induction, patients had a longer time to be fully alert (MD = 1.22, 95%CI = 0.32, 2.12, p = 0.008, very low certainty, Table 2, eTable3, Fig. 2B). There was high heterogeneity across the studies (I2 = 87 %, p < 0.01), and subgroup analyses showed uncertainty in the outcomes of patients undergoing surgery and those receiving >0.4 mg/kg. The results of

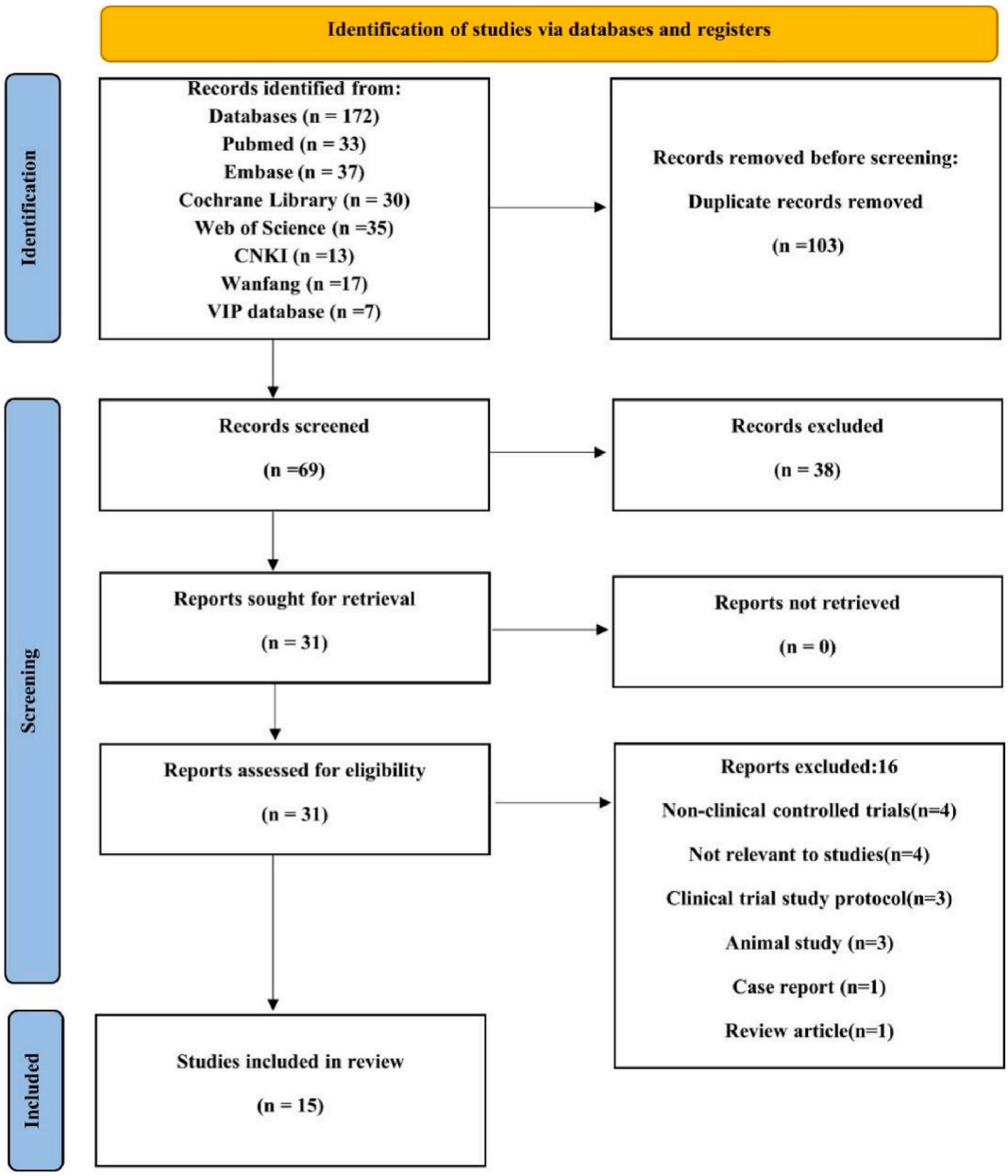


Fig. 1. Flow chart of the study selection process.

Table 1
Characteristics of included studies.

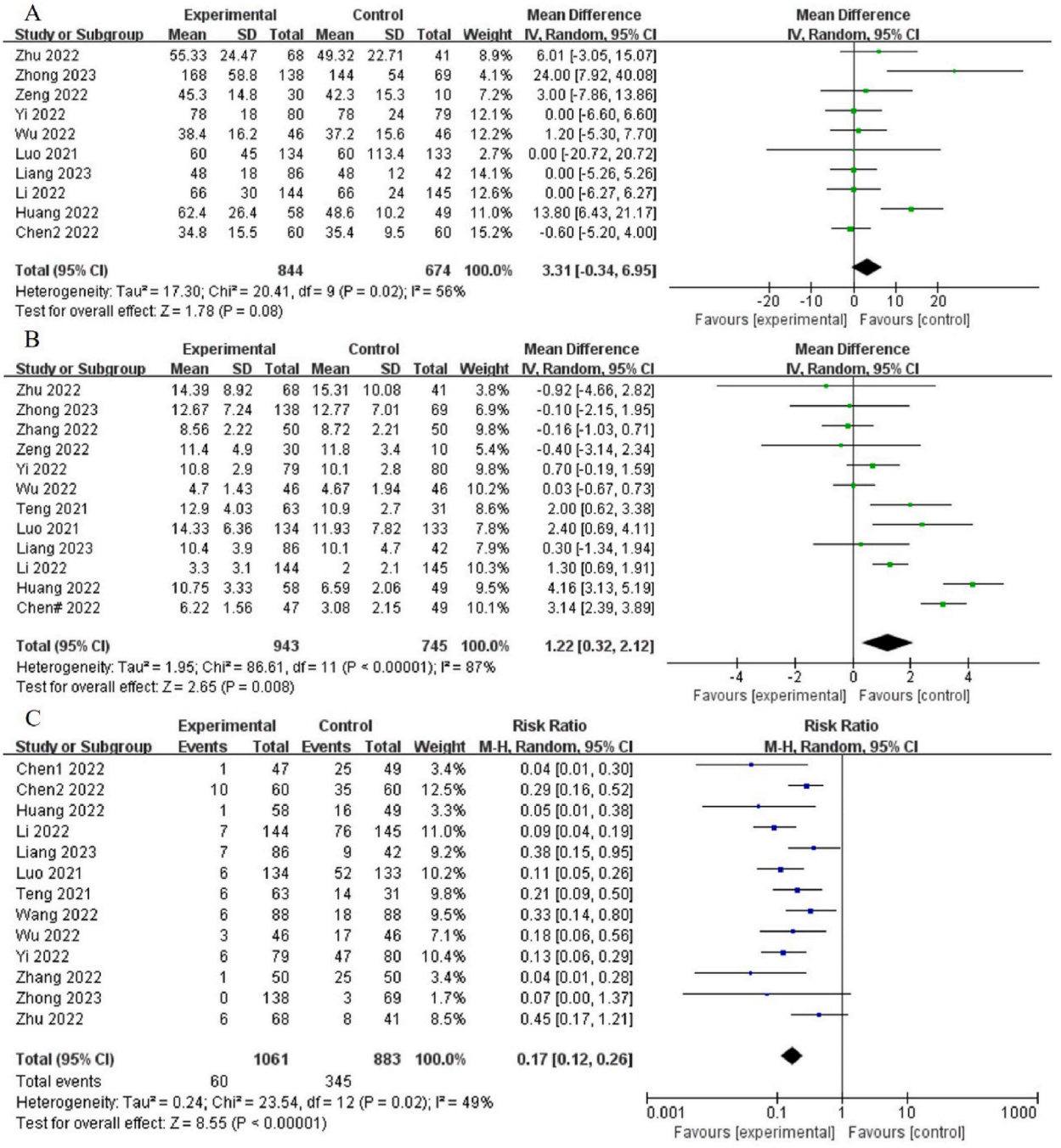
study	year	study type	Age (ciprofol/ propofol)	Gender (Male/ Female)	BMI (ciprofol/ propofol)	Number of Patients (ciprofol/ propofol)	Procedure type	ciprofol dose	propofol dose	Outcomes
Luo [21]	2021	RCT	46.60 ± 15.31/46.90 ± 13.98	135/132	23.20 ± 2.64/ 22.92 ± 2.60	134/133	Fiberoptic Bronchoscopy	0.4 mg/kg	2 mg/kg	1.2.3.4.5.6.7.8.9.11.12.13
Zeng [22]	2022	RCT, non-blinded	42.5 ± 10.3/ 46.4 ± 11.2	14/26	23.7 ± 3.0/ 23.6 ± 3.6	30/10	Elective Surgery	0.4 mg/kg	2.0 mg/kg	1.2.3.4.5.6.7.9.13.14
Liang [23]	2023	RCT	38.5 ± 10.1/ 40.5 ± 10.1	33/95	23.3 ± 2.8/ 23.3 ± 3.0	86/42	nonemergency, non-cardiothoracic and nonbrain elective surgery	0.4 mg/kg	2.0 mg/kg	1.2.3.4.5.6.7.8.9.13.14
Jia [24]	2022	RCT	31.0 ± 5.9/ 31.8 ± 6.0	0/460	N/A	230/230	Painless Artificial Abortion	0.4 mg/kg	2.0 mg/kg	4.10.11.12
Chen2 [25]	2022	RCT	33.9 ± 9.1/ 33.8 ± 9.6	0/120	22.2 ± 3.2/ 21.4 ± 2.8	60/60	Gynecological Surgery	0.4 mg/kg	2 mg/kg	1.4.5.6.7.8.11.
Li [26]	2022	RCT	43.8 ± 11.8/ 44.1 ± 11.3	118/171	23.2 ± 2.5/ 23.4 ± 2.6	144/145	Gastroscopy and Colonoscopy	0.4 mg/kg	1.5 mg/kg	1.2.3.4.5.6.7.8.9.10.12.14
Chen1 [27]	2022	RCT	43.20 ± 12.29/41.22 ± 11.63	39/57	23.46 ± 3.43/ 25.22 ± 10.12	47/49	Painless gastrointestinal endoscopy	0.4 mg/kg	1.5–2.0 mg/kg	2.3.4.5.8
Wu [28]	2022	RCT	58.02 ± 5.47/ 57.48 ± 5.28	50/42	24.26 ± 1.75/ 24.49 ± 2.09	46/46	Fiberoptic Bronchoscopy	0.3 mg/kg	1.2 mg/kg	1.2.3.4.6.7.8.9.10.11
Wang [29]	2022	RCT	38.5 ± 12.1/ 41.1 ± 11.1	63/113	23.3 ± 2.9/ 23.3 ± 3.1	88/88	Elective Surgery	0.4 mg/kg	2.0 mg/kg	4.5.6.7.8.9
Huang [30]	2022	RCT	45.7 ± 12.7/ 43.8 ± 12.5	45/53	22.3 ± 2.6/ 23.4 ± 3.2	58/46	Painless Gastroscope	0.5–0.6 mg/kg	1.5 mg/kg	1.2.3.4.5.6.7.8.9.10.11.12.
Yi [31]	2022	RCT	69.6 ± 2.8/ 70.1 ± 2.9	83/76	23.2 ± 3.0/ 24.1 ± 3.1	79/80	Painless Gastroscope	0.2 mg/kg	1 mg/kg	1.2.3.4.6.7.8.10.11
Zhang [32]	2022	RCT	58.12 ± 4.26/ 58.44 ± 4.25	55/45	N/A	50/50	Painless gastrointestinal endoscopy	0.3–0.4 mg/kg	1–2 mg/ kg	2.4.6.7.8.10
Zhong [33]	2023	RCT	57.45 ± 13.1/ 56.9 ± 13.1	111/96	22.7 ± 2.8/ 22.2 ± 3.2	69/138	endoscopic submucosal dissection (ESD), endoscopic retrograde cholangiopancreatography (ERCP) and diagnostic and therapeutic flexible bronchoscopy (FB)	0.6–0.8 mg/kg/h	40 mg/ kg/h	1.2.3.4.5.6.7.8.9.11
Teng [34]	2021	RCT	46.86 ± 14.06/48.4 ± 13.7	42/52	N/A	63/31	Colonoscopy	0.4–0.5 mg/kg	2 mg/kg	2.3.4.5.6.7.8.10.12
Zhu [35]	2022	RCT, non-blinded	46.59 ± 12.28/43.68 ± 12.54	55/54	24.14 ± 2.76/ 24.50 ± 2.90	68/41	selective, non-cardiothoracic or non-neurosurgical surgery	0.3–0.5 mg/kg	2–2.5 mg/ kg	1.2.4.5.6.7.8.9.12.13.14

Explanations: 1. Time to successful anesthesia induction. 2. Time to fully alertness 3. Time to leaving operation room 4. Procedure Success 5. Total number of patients with adverse events 6. Hypotension 7. Bradycardia 8. Pain on injection 9. Hypoxia 10. Respiratory depression 11. Body moving 12. Dizziness 13 Rash 14. Prolonged QT interval.

Table 2
Binary outcomes and sensitivity analyses.

Category	Groups	No. of trials	No. with events/Total no. of patients		Estimate of effect and 95 % CI	I2	P-interaction	Certainty of evidence
			ciprofol	propofol				
Procedure Success								
	–	15	1314/1321	1113/1123	1.00 [0.99, 1.01]	0 %	N/A	Moderate
Time to successful anesthesia induction								
All trials	–	10	844	674	3.31 [-0.34, 6.95]	56 %	N/A	Low
Type	endoscopy	6	600	521	5.38 [-1.04,11.80]	70 %	0.2	
	surgery	4	244	153	0.67 [-2.42, 3.77]	0 %		
Dose	≤0.4	7	580	515	0.15 [-2.30, 2.61]	0 %	<0.01	
	>0.4	2	196	118	16.29 [7.70, 24.88]	22 %		
Risk of bias	high	5	522	453	2.19 [-3.09, 7.47]	53 %	0.58	
	low	5	322	221	4.32 [-1.13, 9.77]	62 %		
Time to fully alertness								
All trials	–	12	943	745	1.22 [0.32, 2.12]	87 %	N/A	Very low
Type	endoscopy	9	759	652	1.51 [0.50, 2.52]	90 %	0.07	
	surgery	3	184	93	−0.01 [-1.33, 1.31]	0 %		
Dose	≤0.4	8	616	555	0.98 [0.05, 1.92]	86 %	0.6	
	>0.4	2	196	118	2.13 [-2.04, 6.30]	92 %		
Risk of bias	high	5	525	424	1.08 [0.17, 1.99]	71 %	0.89	
	low	7	418	321	1.21 [-0.29, 2.71]	91 %		
Time to leaving operation room								
All trials	–	8	704	574	1.22 [0.32, 2.11]	70 %	N/A	Low
Type	endoscopy	6	588	522	1.33 [0.29, 2.37]	78 %	0.43	
	surgery	2	116	52	0.54 [-1.13, 2.21]	0 %		
Dose	≤0.4	7	566	505	1.44 [0.58, 2.30]	68 %	0.03	
	>0.4	1	138	69	−1.62 [-4.23, 0.99]	N/A		
Risk of bias	high	4	462	393	0.82 [-0.41, 2.06]	71 %	0.43	
	low	4	242	181	1.61 [0.12, 3.11]]	71 %		
Total number of adverse events								
All trials	–	11	621/916	539/717	0.88 [0.78, 1.00]	84 %	N/A	Very low
Type	endoscopy	6	384/584	350/476	0.85 [0.71, 1.01]	77 %	0.53	
	surgery	5	237/332	189/241	0.92 [0.76, 1.12]	88 %		
Dose	≤0.4	6	296/501	297/439	0.85 [0.67, 1.08]	82 %	0.66	
	>0.4	2	131/196	92/118	0.75 [0.44, 1.27]	86 %		
Risk of bias	high	6	426/627	398/526	0.87 [0.75, 1.01]	80 %	0.93	
	low	5	195/289	141/191	0.89 [0.65, 1.21]	89 %		
Hypotension								
All trials	–	13	305/1044	276/844	0.77 [0.63, 0.94]	51 %	N/A	Low
Type	endoscopy	9	198/742	181/613	0.73 [0.56, 0.96]	50 %	0.68	
	surgery	4	107/302	95/231	0.81 [0.55, 1.19]	61 %		
Dose	≤0.4	9	173/717	191/654	0.73 [0.53, 1.00]	64 %	0.33	
	>0.4	2	100/196	61/118	0.88 [0.72, 1.09]	3 %		
Risk of bias	high	7	7/97	9/91	0.87 [0.68, 1.13]	51 %	0.3	
	low	6	165/794	122/620	0.65 [0.51, 0.83]	8 %		
Bradycardia								
All trials	–	13	145/1044	104/844	0.96 [0.77, 1.21]	0 %	N/A	High
Pain on injection								
All trials	–	13	60/1061	345/883	0.17 [0.12, 0.26]	49 %	N/A	Moderate
Type	endoscopy	9	31/759	275/652	0.12 [0.08, 0.17]	0 %	<0.01	
	surgery	4	29/302	70/231	0.34 [0.23, 0.50]	0 %		
Dose	≤0.4	9	47/734	304/693	0.16 [0.10, 0.26]	55 %	0.24	
	>0.4	2	1/196	19/118	0.06 [0.01, 0.30]	0 %		
Risk of bias	high	6	22/388	130/311	0.15 [0.06, 0.35]	66 %	0.66	
	low	7	38/673	215/572	0.18 [0.12, 0.28]	36 %		
Hypoxia								
All trials	–	9	43/792	48/623	0.79 [0.46, 1.37]	30 %	N/A	Moderate
Body movement								
All trials	–	7	75/745	79/667	0.89 [0.67, 1.18]	0 %	N/A	Moderate
Respiratory depression								
All trials	–	7	23/630	83/631	0.29 [0.15, 0.56]	38 %	N/A	Moderate
Dizziness								
All trials	–	6	44/697	48/629	0.81 [0.49, 1.33]	26 %	N/A	Low
Rash								
All trials	–	4	5/318	0/226	1.95 [0.41, 9.28]	0 %	N/A	Very low
Prolonged QT interval								
All trials	–	4	26/328	16/238	1.06 [0.61, 1.83]	0 %	N/A	Very low

the sensitivity analysis based on the low bias risk test were consistent with the preliminary analysis (Table 2, Fig. 3B, eFigure21-23), and no positive results were found in the age-based meta-regression (p = 0.079, eFigure3B). Although the TSA's cumulative Z-curve shows that the amount of information required is insufficient, the Z-curve crosses traditional and hazard boundaries and indicates a true positive outcome for the use of ciprofol (Fig. 4B). According to Egger's test, this analysis did not show any publication bias (p = 0.801, Fig. 5B).

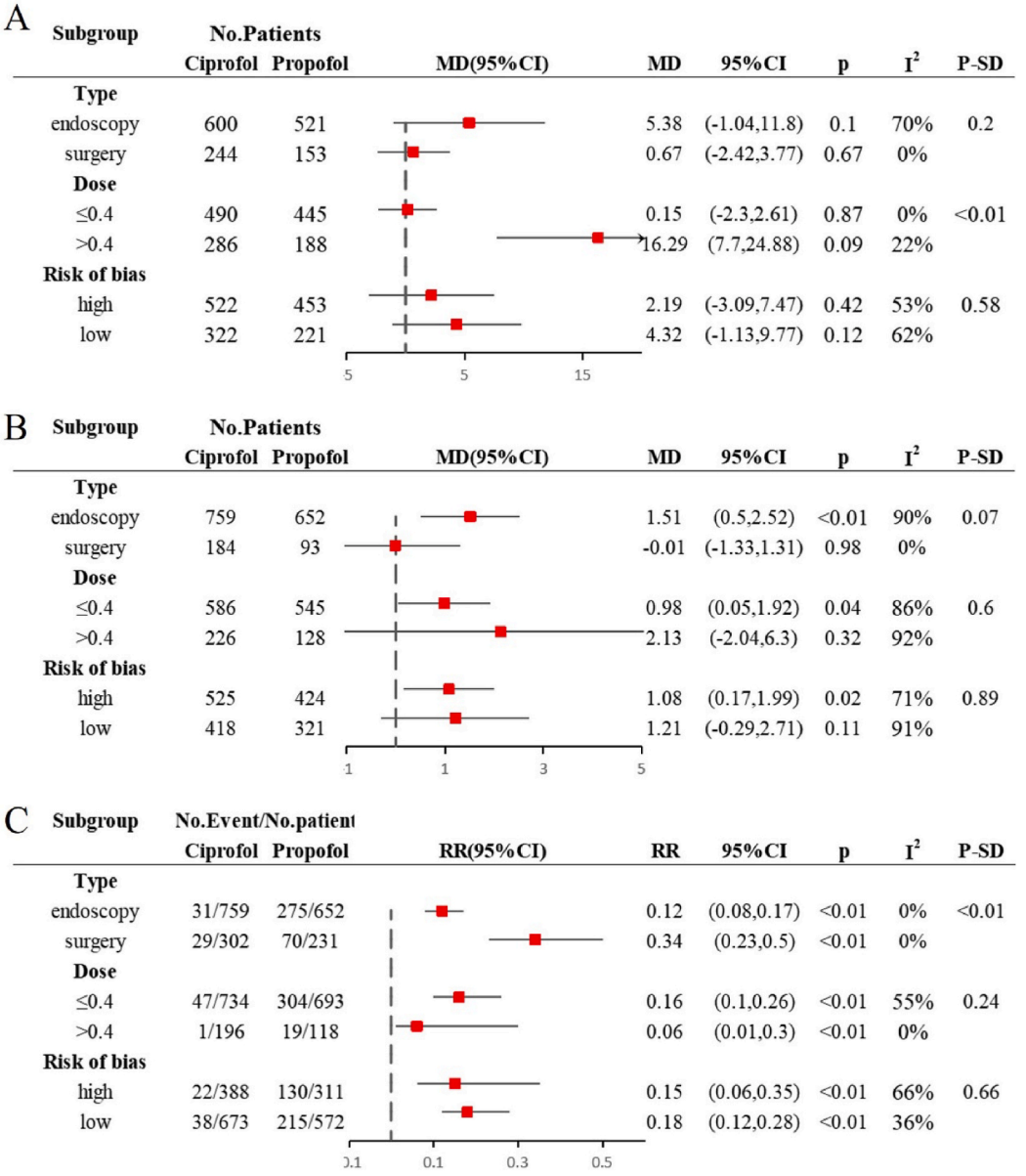


(A) Time to successful anesthesia induction (B) Time to fully alertness (C) Pain on injection

Fig. 2. Forest Plot of Primary Outcomes
(A) Time to successful anesthesia induction (B) Time to fully alertness (C) Pain on injection.

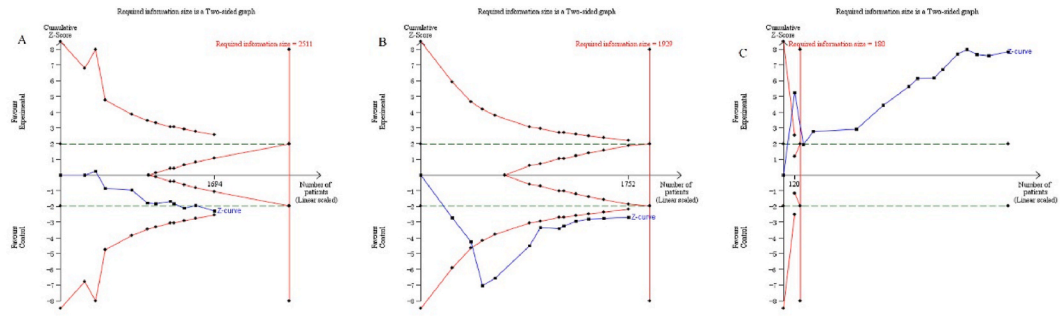
3.4.3. Injection pain

Injection pain from the two anesthetics was compared in 13 trials (1944 patients). I2 was 49 % (p = 0.02). This indicates significant heterogeneity. Our analysis revealed that propofol was associated with fewer injection pain (RR = 0.17, 95 % CI = 0.12, 0.26, p < 0.00001, low certainty, Table 2, eTable3, Fig. 2C). In the subgroup analysis, we determined that, in the subgroup of application



Explanations: (A) Time to successful anesthesia induction (B) Time to fully alertness (C) Pain on injection; CI = Confidence interval, N/A = Not applicable, RR = Relative risk, P-SD = P for subgroup differences.

Fig. 3. Subgroup Analysis for Primary Outcomes
Explanations: (A) Time to successful anesthesia induction (B) Time to fully alertness (C) Pain on injection; CI = Confidence interval, N/A = Not applicable, RR = Relative risk, P-SD = P for subgroup differences.



(A) Time to successful anesthesia induction (B) Time to fully alertness (C) Pain on injection

Fig. 4. Trial Sequential Analysis
(A) Time to successful anesthesia induction (B) Time to fully alertness (C) Pain on injection.

procedures, the heterogeneity within both subgroups was 0 %. The difference between the groups was 93.3 %. No effect modifications were observed in the dose subgroups. Sensitivity analysis did not change this conclusion (Table 2, Fig. 3C, eFigure24-26). The meta-regression analysis did not reveal an association between injection pain and age (p = 0.595, eFigure3C). AIS was significantly higher than RIS, and TSA was decisive and supported ciprofol (Fig. 4C). Egger's test showed no evidence of publication bias (p = 0.134, Fig. 5C).

3.5. Secondary outcomes

3.5.1. Procedure success

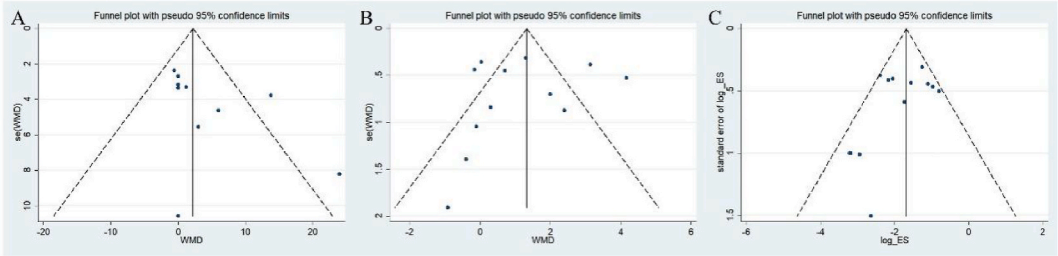
Based on data pooled from 15 trials with 2444 participants, our analysis showed no difference in the success rate of anesthesia induction between patients using ciprofol and propofol (RR = 1.00, 95 % CI 0.99, 1.01, p = 0.95, moderate certainty, Table 2, eFigure4).

3.5.2. Time to leaving operation room

Pooled estimates of 10 RCTS (n = 1278 patients) showed that compared with propofol, ciprofol was associated with longer operating room stays (MD = 1.22, 95%CI = 0.32, 2.11, p = 0.008, low certainty, Table 2, eFigure5). There was a high inter-study heterogeneity (I2 = 70 %, p = 0.001). No effect correction was found in the subgroup and sensitivity analysis (Table 2, eFigure27-29), or meta-regression (p = 0.095, eFigure3D). Although the cumulative Z-curve does not reach the required amount of information, it crosses both the routine and hazard boundaries to arrive at a TSA conclusion (eFigure15A). Egger's test showed no publication bias (p = 0.548, eFigure17A).

3.5.3. Adverse events

In 11 studies (n = 1633), the total number of patients with adverse events were included in the evaluation. Inter-study heterogeneity was observed (I2 = 84 %, p < 0.00001). Meta-analysis showed that ciprofol did not increase the risk of adverse events compared with propofol (RR = 0.88, 95%CI = 0.78, 1.00, p = 0.05, very low certainty, Table 2, eFigure6). Neither the subgroup analysis nor the sensitivity analysis changed the main conclusions (Table 2, eFigure30-32). Meta-regression analysis also showed no significant results (p = 0.609, eFigure3E). The TSA conclusion is inconclusive because the cumulative Z-curve does not cross any boundaries and the AIS is smaller than the RIS; therefore, further research is needed to find conclusive evidence (eFigure15B). The



(A) Time to successful anesthesia induction (B) Time to fully alertness (C) Pain on injection

Fig. 5. Funnel plot
(A) Time to successful anesthesia induction (B) Time to fully alertness (C) Pain on injection.

Egger's test (p = 0.042) showed no publication bias (eFigure17B).

To investigate the difference in the incidence of bradycardia between ciprofol and propofol, we comprehensively analyzed 13 studies (n = 1888 patients) with low heterogeneity (I2 = 0 %, p = 0.55). Our analysis showed that ciprofol did not increase the risk of bradycardia in patients (RR = 0.96, 95%CI = 0.77, 1.21, p = 0.76, high certainty, Table 2, eFigure7). The TSA's conclusion is definitive. The Z-curve crossed the invalid boundary (eFigure15C), the conclusion was deterministic despite the fact that the AIS was smaller than the RIS. Based on the Egger's test (p = 0.589), no publication bias was detected (eFigure17C). These trials also assessed the incidence of hypotension; however, there was heterogeneity in the assessment of this outcome (I2 = 51 %, p = 0.02). Therefore, subgroup analysis and meta-regression were performed, but no credible subgroup effects were observed in both the procedure-based and dose-based subgroup and age-based meta-regression (p = 0.415, eFigure3F), whereas sensitivity analysis based on a low-bias risk trial showed the opposite result, proving that there may be an underlying bias (Table 2, eFigure33-35). Results from these 13 trials showed that ciprofol reduced the incidence of hypotension compared with propofol (RR = 0.77, 95%CI = 0.63, 0.94, p = 0.01, low certainty Table 2, eFigure8). The TSA results suggest that further trials are necessary (eFigure15D). Publication bias was also detected (p = 0.097, eFigure17D).

Nine trials (n = 1415) included the outcome of hypoxia, and the heterogeneity between the trials was relatively insignificant (I2 = 30 %, p = 0.18). There was no difference in the risk of hypoxia between the ciprofol and propofol groups (RR = 0.79, 95%CI = 0.46, 1.37, p = 0.40, moderate certainty, Table 2, eFigure9). The Z-curve did not cross any boundaries, suggesting that further testing is essential (eFigure16A). The risk of respiratory depression with ciprofol was lower than that with propofol (RR = 0.29, 95%CI = 0.15, 0.56, p = 0.0002, moderate certainty, Table 2, eFigure10), and seven trials (n = 1301, I2 = 38 %, p = 0.14) confirmed this, and the TSA results were positive (eFigure16B). Seven trials (n = 1412, I2 = 0 %, p = 0.78) included body movement, and there was no difference between the two anesthetics in this outcome (RR = 0.89, 95%CI = 0.67, 1.18, p = 0.41, moderate certainty, Table 2, eFigure11), while six trials (n = 1326, I2 = 26 %, p = 0.24) reported dizziness (RR = 0.81, 95%CI = 0.49, 1.33, p = 0.4, low certainty, Table 2, eFigure12); however, TSA results for both outcomes were negative (eFigure16C, 16D). Four trials (n = 1412, I2 = 0 %, p = 0.97) reported rashes (RR = 1.95, 95%CI = 0.41, 9.28, p = 0.4; very low certainty, Table 2, eFigure13) and four trials (n = 1412, I2 = 0 %, p = 0.65) reported prolonged QT intervals in patients (RR = 1.06, 95%CI = 0.61, 1.83, p = 0.83, very low certainty, Table 2, eFigure14). There was no significant difference in the incidence of adverse events between the two drugs.

4. Discussion

Our meta-analysis evaluated the use of ciprofol for programmed sedation and anesthesia induction in combination with 15 recent clinical trials. We analyzed 14 outcome indicators to compare the advantages of ciprofol and propofol, and the results showed that the success rate of induction of anesthesia with ciprofol was consistent with that of propofol. Although there was no significant difference in induction time between the two drugs, ciprofol was associated with longer awakenings. This was confirmed by the longer stay in the operating room. The greatest advantage of ciprofol over propofol is its significant reduction of pain during injection. In terms of adverse events, ciprofol did not differ from propofol in the total number of adverse events or several common sedative adverse events, including bradycardia, hypoxia, vertigo, body movement, rash, and prolonged QT interval. However, the incidence of hypotension and respiratory depression was significantly lower than that with propofol.

In terms of programmed sedation and anesthetic effects, both drugs were 100 % effective in most trials. Only two trials involved patients in whom anesthesia was not induced and required additional anesthetics. The concentration of ciprofol used in these two trials was 0.3 mg/kg [28] and 0.2 mg/kg [31] respectively, the propofol concentration was relatively low. We believe that the researchers preferred to use lower concentrations of drugs, which may have caused failure in the induction of anesthesia. In terms of induction time, the two drugs showed similar effects, and the heterogeneity in the results was mainly due to differences in drug concentration. In the subgroup with ciprofol >0.4 mg/kg, the induction time was longer than that of propofol. Huang et al. [30] pre-pumped remifentanil 0.5 μg/kg in the propofol group, while the ciprofol group did not. Zhong et al. [33] divided their study into three subgroups, and combined the results of these three subgroups in our analysis [36]. In their study, the only statistically significant patient in the flexible bronchoscopy (FB) group was administered a higher dose of remifentanil. The synergistic effect of propofol and remifentanil may have led to a shorter induction time for propofol[[37,38]]. However, patients in the propofol group had an extended awakening time, leaving the recovery room time. The average awakening time of propofol was 1.84 min longer than that of propofol. The reasons may be as follows: the elimination half-life of ciprofol is approximately 1.58–2.47 h, slightly longer than the 1.5 h of propofol [39]. However, propofol is known for its rapid onset, rapid and complete recovery, and lack of accumulation after continuous infusion. As an emerging sedative, ciprofol has almost the same effect as propofol on procedural sedation and anesthesia; therefore, ciprofol is an ideal candidate for procedural sedation and anesthesia.

Injection pain, the most common adverse reaction of propofol, has been widely reported. Compared with other intravenous anesthetics, the pain rate associated with propofol injection is higher, reaching 28–90 %[[40,41]]. Some patients even say that the induction of anesthesia is the most painful stage of surgery. Pain associated with injections not only affects patients' hemodynamics during induction, but also their physical and psychological health. Anesthesiologists have made many efforts to reduce propofol injection pain[[42–45]]. There were no concerns regarding the use of ciprofol. In our meta-analysis, we found that propofol significantly reduced injection pain. Although the results were heterogeneous, the subgroup analysis revealed that the source of heterogeneity was different from that of the surgical procedures. More patients who underwent endoscopic procedures experienced injection pain than those who underwent conventional surgery. Pain as an unpleasant feeling and emotional experience are personal experiences influenced by psychological and social factors [46]. We believe that pain from the injection is less intense in situations where traditional surgery is more traumatic and painful than an endoscopic procedure. The reduction in injection pain by ciprofol may be related to the

following factors: the aqueous-phase concentration of propofol may be a major variable of pain related to propofol injection[[3,47]], and the effective concentration of ciprofol is only 20 % of that of propofol [48]. In addition, propofol has higher fat solubility than propofol. The concentration of free molecules in the emulsion was significantly lower than that in propofol, and a lower concentration of aqueous free drugs reduced the stimulation of the veins [49].

In our analysis, which evaluated the safety of both drugs, we found that the incidence of adverse events with ciprofol (67.8 %) was lower than that with propofol (75.2 %), although this difference was not statistically significant. For the majority of adverse events, no significant difference was observed between the two drugs. We believe that, as a GABAA receptor inhibitor similar to propofol, most of the undesirable reactions of ciprofol were not different from those of propofol. The difference was likely due to hypotension and respiratory depression, because of the eight common adverse events that we summarized; only these two were statistically significant. Hypotension is caused by diastolic peripheral arterial vessels [50], decreased venous smooth muscle tone [51], and reduced myocardial contractility by decreasing the concentration of free Ca2+ in cardiomyocytes via its action on protein kinase C [52]. The mechanism by which ciprofol causes hypotension in patients may be similar to that of propofol alone. We found that the proportion of hypoxia between the two groups was slightly lower than that with propofol, but the difference was not statistically significant. There are several causes of hypoxia, including respiratory depression. Surprisingly, we found that ciprofol significantly reduced the incidence of respiratory depression compared to propofol. The inhibitory effect of propofol on the respiratory system has been troubling for users, and is the most common adverse event of propofol. Therefore, ciprofol may be superior to propofol in terms of hemodynamic stability [53]. As an analog of propofol, ciprofol may have the same mechanism of causing hypotension and respiratory depression as propofol. The tighter binding force of the GABAA receptor compared to that of propofol may be a potential reason for the lower incidence of hypotension and respiratory depression, which requires further research. In addition, rash cases were reported in four trials in the ciprofol group and none in the propofol group. Rash may be related to anaphylaxis, and the incidence of propofol allergy is approximately 1–2% [54]. Although the result was not statistically significant, it suggests that attention should be paid to allergic reactions to ciprofol, which may be a more intense allergen.

Our study summarizes recent trials of ciprofol for anesthesia induction. In our study, subgroup analysis, sensitivity analysis, trial sequence analysis, and Egger's test were used to comprehensively check whether our outcomes were stable. Our study had some limitations. First, all the trials were conducted in China, and the results may not be universally applicable. Further trials are needed worldwide in the future to determine the general suitability of ciprofol. Second, in the sensitivity analysis, the outcome of hypotension changed only after maintaining the low-bias test. For some outcome indicators of adverse events, we reached conclusions based on trials with high or uncertain bias, indicating that these results may lack stability. We included low-quality and small studies, which also lowered our confidence in the robustness of our findings. Further RCTs with sufficient sample sizes must be designed and conducted. Third, in terms of the total number of adverse reactions and cases of hypotension, we found publication bias using the Egger's test. This reduced the evidence grades for the two outcome indicators. However, the mechanism by which ciprofol reduces the incidence of blood pressure and respiratory depression remains unknown. Although we have proposed some hypotheses, the corresponding basic research evidence is lacking. Therefore, further high-quality trials are warranted. In addition, some outcome indicators showed significant heterogeneity. Although we conducted a subgroup analysis of the outcome indicators with high heterogeneity, no clear source of heterogeneity was found for some outcome indicators.

Currently, more studies on ciprofol have been designed and conducted, and more clinical trial protocols have been designed[[55–57]]. Ciprofol also performs well in ICU sedation [58]; however, it has not been reported whether long-term infusion of ciprofol causes infusion syndrome like propofol. Its application in cardiopulmonary bypass surgery has been reported [53]. Given its low injection pain and smoother hemodynamics, ciprofol has broad application prospects. Currently, trials have demonstrated the safety of ciprofol in elderly patients[[59,60]] and and patients with hepatic impairment [61]. No trials have been conducted to analyze the economics of ciprofol compared to other anesthetics. The current price of ciprofol is approximately three times that of propofol, but we believe that the price of ciprofol will decrease with the promotion of the drug. Ciprofol is a good alternative in the adult population, but has a possible beneficial effect if tested in children or patients with other special conditions. Further studies are needed to conclusively determine whether ciprofol has a wide range of uses, such as propofol, for treating seizures, as a neuroprotector, and as an antiemetic. Currently, ciprofol has received attention from researchers in other countries [62], and we believe that an increasing number of studies will be conducted.

5. Conclusion

In conclusion, we conclude that ciprofol performed as well as propofol for most outcomes. While the time to full alertness may be prolonged, injection pain was significantly relieved, and hypotension and respiratory depression were reduced when compared with propofol. We believe that ciprofol is an excellent alternative to intravenous anesthetic agents.

Ethical approval statement

Review and/or approval by an ethics committee was not needed for this study as it was a systematic review and meta-analysis.

Data availability statement

Data generated and utilized for analyses of results presented in this manuscript are available from the corresponding author on reasonable requests.

Funding statement

No funding supported this research.

Supporting information

eTable1: PRISMA checklist. eTable2: The Risk of Interventions (ROBINS-I) assessment. eTable3: Evidence Profile Table. eFigure1: Risk of bias graph. eFigure2: Risk of bias summary. eFigure3. Meta-regression based on the mean age of participants. eFigure4. The Forest Plot. of Procedure Success. eFigure5. The Forest Plot. of Time to leaving operation room. eFigure6. The Forest Plot. of Total number of patients with adverse events. eFigure7. The Forest Plot. of Bradycardia. eFigure8. The Forest Plot. of Hypotension. eFigure9. The Forest Plot. of Anoxia. eFigure10. The Forest Plot. of Respiratory depression. eFigure11. The Forest Plot. of Body movement. eFigure12. The Forest Plot. of Dizziness. eFigure13. The Forest Plot. of Rash. eFigure14. The Forest Plot. of Prolonged QT interval. eFigure15. Trial Sequential Analysis (A) Time to leaving operation room (B) Total number of patients with adverse events (C) Bradycardia (D) Hypotension eFigure16. Trial Sequential Analysis (A) Anoxia (B) Respiratory depression (C) Body moving (D) Dizziness eFigure17. Funnel Plot. (A) Time to leaving operation room (B) Total number of patients with adverse events (C) Bradycardia (D) Hypotension eFigure18. Induction Time Subgroup Analysis by procedure Forest Plot. eFigure19. Induction Time Subgroup Analysis by dose Forest Plot. eFigure20. Induction Time Sensitivity Analysis by risk of bias Forest Plot. eFigure21. Time to fully alert Subgroup Analysis by procedure Forest Plot. eFigure22. Time to fully alert Subgroup Analysis by dose Forest Plot. eFigure23. Time to fully alert Sensitivity Analysis by risk of bias Forest Plot. eFigure24. Injection pain Subgroup Analysis by procedure Forest Plot. eFigure25. Injection pain Subgroup Analysis by dose Forest Plot. eFigure26. Injection pain Sensitivity Analysis by risk of bias Forest Plot. eFigure27. Time to leaving operation room Subgroup Analysis by procedure Forest Plot. eFigure28. Time to leaving operation room Subgroup Analysis by dose Forest Plot. eFigure29. Time to leaving operation room Sensitivity Analysis by risk of bias Forest Plot. eFigure30. Total number of patients with adverse events Subgroup Analysis by procedure Forest Plot. eFigure31. Total number of patients with adverse events Subgroup Analysis by dose Forest Plot. eFigure32. Total number of patients with adverse events Sensitivity Analysis by risk of bias Forest Plot. eFigure33. Hypotension Subgroup Analysis by procedure Forest Plot. eFigure34. Hypotension Subgroup Analysis by dose Forest Plot. eFigure35. Hypotension Sensitivity Analysis by risk of bias Forest Plot.

CRediT authorship contribution statement

Jiaxuan Wen: Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **Chen Liu:** Data curation, Conceptualization. **Xueying Ding:** Data curation. **Zimeng Tian:** Methodology, Formal analysis, Data curation. **Wenyu Jiang:** Formal analysis. **Xiuhong Wei:** Supervision, Methodology. **Xin Liu:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The authors have no acknowledgments.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e22634.

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