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REVIEW

Ciprofol Versus Propofol for Sedation in Gastrointestinal Endoscopy: A Systematic Review and Meta-Analysis in a Chinese Population

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Purpose: Ciprofol (HSK3486) is a novel intravenous anesthetic structurally similar to propofol; however, its advantages over propofol remain unclear. This study aimed to compare the safety, efficacy, and satisfaction outcomes of ciprofol and propofol during gastrointestinal endoscopy.

Patients and Methods: This systematic review incorporated all available comparative trials assessing ciprofol versus propofol for endoscopic sedation following a comprehensive search strategy across eight biomedical databases—Web of Science, Embase, PubMed, and Cochrane Library, along with major Chinese repositories (CNKI, Wanfang, CBM, and VIP)—through September 2023. Evidence synthesis was conducted per PRISMA guidelines, with methodological rigor enhanced through prospective trial registry screening and implementation of GRADE framework for evidence grading.

Results: This systematic review included 45 randomized controlled trials involving 6884 patients who met predefined methodological and clinical eligibility thresholds. Very low to moderate certainty evidence showed that ciprofol induced sedation or anesthesia comparable to that of propofol (relative risk [RR]: 1.00, 95% confidence interval [CI]: 1.00 to 1.01), with both agents demonstrating similar procedural efficiency. Furthermore, ciprofol was associated with a reduced incidence of complications, including hypotension (RR: 0.60, 95% CI: 0.51 to 0.70), bradycardia (RR: 0.69, 95% CI: 0.56 to 0.85), nausea and vomiting (RR: 0.67, 95% CI: 0.54 to 0.84), hypoxia (RR: 0.38, 95% CI: 0.31 to 0.48), respiratory depression (RR: 0.39, 95% CI: 0.28 to 0.56), apnea (RR: 0.35, 95% CI: 0.23 to 0.53), and injection pain (RR: 0.13, 95% CI: 0.09 to 0.17), while also enhancing patient and anesthesiologist satisfaction.

Conclusion: Ciprofol-induced sedation or anesthesia was comparable to propofol, with both drugs demonstrating similar procedural efficiency. However, ciprofol was associated with lower risk of adverse reactions and higher satisfaction among patients and anesthesiologists. Ciprofol may represent a superior sedative option for gastrointestinal endoscopy.

Keywords: sedation, systematic review, gastrointestinal endoscopy

Introduction

Gastrointestinal endoscopy is a minimally invasive method for diagnosing and treating gastrointestinal tract diseases; however, it can cause discomfort and stress in some patients. With advancements in medical technology, painless gastrointestinal endoscopy is more frequently used in clinical settings, and sedation is typically employed in low-risk procedures.[1]

Propofol, known chemically as 2,6-diisopropyl phenol, is a sedative with an ultrashort duration of action and quick recovery, and is widely utilized in gastrointestinal endoscopy.[2] Unlike other sedatives, propofol lacks active metabolites

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and is rapidly and efficiently cleared by the liver.[3] Ciprofol, an innovative intravenous general anesthetic, was independently developed by the Haisco Pharmaceutical Group and approved in China in 2020.[4] As a GABAA receptor agonist, ciprofol primarily acts through its active ingredient, HSK3486, a propofol analog with a single diastereomer and an R-shaped chiral center.

The increasing application of ciprofol necessitates evaluation of its safety and benefits in gastrointestinal endoscopy. Several investigations have analyzed the hypnotic potency and safety of ciprofol compared with propofol for anesthesia induction, procedural sedation in surgical patients, and sedation beyond the operating room.[5–8] Nonetheless, the current evidence is limited by small number of included studies, lack of specificity, and inconsistent findings. Consequently, the advantages of ciprofol over the commonly used sedative propofol remain unclear. An up-to-date summary and analysis of the existing studies will assist in making clinical decisions.

Materials and Methods

Protocol Registration

This systematic review was prospectively registered with PROSPERO (CRD42022370047), with previously published protocol details.[9,10] The methodology was conducted in strict adherence to the AMSTAR 2 criteria for quality assessment and PRISMA 2020 reporting standards,[11,12] as detailed in Tables S1, Supplementary Material 1 and Tables S2, Supplementary Material 2, respectively.

Search Strategy

A preliminary keyword search was conducted in PubMed to gain an understanding of the literature on propofol. Subsequently, two researchers systematically searched the Web of Science, Embase, PubMed, Cochrane Library, Wanfang Database, China National Knowledge Infrastructure Database (CNKI), Chinese Biomedical Literature Database (CBM), China Science and Technology Journal Database (VIP), and North American Clinical Trial Registry (www.clinicaltrials.gov) without language restrictions from inception to September 2023. The last search update was conducted in May 2024 to ensure the comprehensiveness of the retrieval. Searches across all databases were conducted using a blend of subject-specific and free-form words customized for each database (Table S3, Supplementary Material 3). In addition, we carefully and manually examined the reference lists to identify any pertinent studies that the electronic search might have missed.

Eligibility Criteria

Eligibility was restricted to randomized controlled trials (RCTs) evaluating ciprofol versus propofol for endoscopic sedation. Combination protocols involving propofol and adjunctive agents (eg, opioid analgesics) were included only if adjunctive medication were standardized across study arms. Exclusion criteria encompassed: (1) preclinical investigations; (2) non-randomized studies assessing therapeutic interventions; (3) secondary publications (conference abstracts, reviews, letters, and protocols); (4) case reports; and (5) duplicate datasets.

Study Screening

EndNote software version X9 (Thomson Corp., Stanford, CT, USA) was used to import all retrieved records, and duplicate entries were deleted. The literature was screened by the researchers using predetermined criteria for inclusion and exclusion. Prior to the official screening, all team members involved in the review were trained using the EndNote software. Furthermore, an initial screening was performed to prevent bias and refine screening criteria. Any disagreements among the reviewers were resolved through consensus or group discussions, if needed. The reasons for the exclusion of each study was recorded.

Data Extraction

After the training and calibration exercises, pairs of reviewers independently used a standardized data extraction form to gather data for each eligible trial. Before merging, extracted data were converted and standardized when necessary. For

documents providing data in a chart format, we contacted the corresponding authors. If contact failed, Engauge Digitizer software version 9.8 (Markmitch, Torrance, CA, USA) was used to extract data.[13] Initially, continuous data shown as medians or interquartile ranges were transformed into means and standard deviations.[14,15] Discrepancies between reviewers were resolved through discussion by the an arbitrators.

Risk of Bias Assessment

The Risk of Bias Tool 2 (RoB2), detailed in the Cochrane Handbook for Systematic Reviews of Interventions (version 6.4), was used to assess the methodological quality of each study.[16] This tool assesses the risk of bias across five areas: randomization process, deviations from planned interventions, missing outcome data, outcome measurements, and selection of reported results. Any disagreements between reviewers were discussed and resolved by consensus following a full-text review.

Certainty of the Evidence

The authors and guidelines panel agreed to classify the certainty of evidence for all reported outcomes as high, moderate, low, or very low using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) method.[17] The certainty of the evidence was downgraded because of several factors: imprecision, characterized by insufficient sample sizes falling below the optimal information size (OIS) needed to identify meaningful differences; broad confidence intervals; inconsistency, marked by significant statistical heterogeneity; and risk of bias stemming from issues such as inadequate sequence generation, lack of blinding, and baseline imbalances.[18,19] Additionally, we used the GRADEpro software (version 3.6) to generate a summary of the findings.

Statistical Analysis

A random-effects model was used for meta-analysis. The relative risk (RR) and 95% confidence interval (CI) were determined for categorical outcomes. Given the low event rates in many trials, we used the Mantel-Haenszel (MH) odds ratio (OR) method as the primary analysis for single-arm zero-event studies.[20] For double-arm zero-event studies, we used the MH absolute risk difference (ARD) method to pool effect estimates across studies.[21] We calculated the ARD for all adverse events to aid in result interpretation. When discrepancies arose between RR and ARD for the same result, RR was preferred due to its greater reliability, particularly for interventions designed to prevent negative events.[16,22,23] For continuous outcomes (eg, procedural efficiency), weighted mean difference (WMD) and 95% CI were calculated. When scales differed (eg, patient, anesthesiologist, and endoscopist satisfaction), data were pooled using the standardized mean difference (SMD).

Statistical heterogeneity was quantified using χ^2 testing with I^2 statistics, interpreted as: 0–40% (negligible), 30–60% (moderate), 50–90% (substantial), and 75–100% (considerable). Endoscopic procedures require special techniques and longer operation time,[24] therefore we categorized all qualifying trials into endoscopic treatment and endoscopic examination groups and conducted a subgroup analysis.

To assess the robustness of our findings, we conducted sensitivity analyses using diverse effect measures (RR, OR, and ARD) and statistical models (fixed versus random effects). For studies with single- or double-arm zero events, we applied the Mantel-Haenszel OR or ARD method, respectively, as an alternative to exclude such studies.[21,25] Leave-one-out meta-analyses were conducted to evaluate result stability.

Publication bias was evaluated by visually examining funnel plot asymmetry, applying Egger's test, and using the trim-and-fill method,[26] provided that the meta-analysis included at least 10 studies.

The OIS was estimated using PASS software version 15 (NCSS, LLC, Kaysville, UT, USA), while all statistical analyses were performed using Review Manager (RevMan) version 5.4 (The Nordic Cochrane Centre, Rigshospitalet, Copenhagen, Denmark) and Stata version 18.0 (StataCorp, College Station, Texas, USA). OIS calculations were derived with a power of ≥ 0.80 and a two-tailed significance level of $\alpha = 0.05$. All statistical comparisons were two-tailed, with a threshold for significance set at $P \leq 0.05$.

Results

Study Selection

The study selection process is illustrated in the PRISMA flow diagram (Figure 1). From an initial pool of 293 citations, duplicate and ineligible studies were removed, resulting in the inclusion of 45 RCTs encompassing 6884 patients for meta-analysis.[27–71]

Study and Patient Characteristics

The patient characteristics are presented in Table 1. Further details of sedative administration are provided in Table S4 and Supplementary Material 4. All included studies were published between 2021 and 2024 and were conducted in China. Of these, 10 studies[27,28,30,35,40,59,61,63,67,71] were published in English and 35[29,31–34,36–39,41–58,60,62,64–66,68–70] in Chinese. The sample sizes ranged from 50[49] to 368 patients.[40] Two studies were multicenter RCTs,[27,30] whereas the remaining 43[28,29,31–71] were monocentric. Forty studies involved endoscopic examination (5852 patients),[27–53,55–57,60,61,63–67,69–71] while five focused on endoscopic treatment (1032 patients).[54,58,59,62,68]

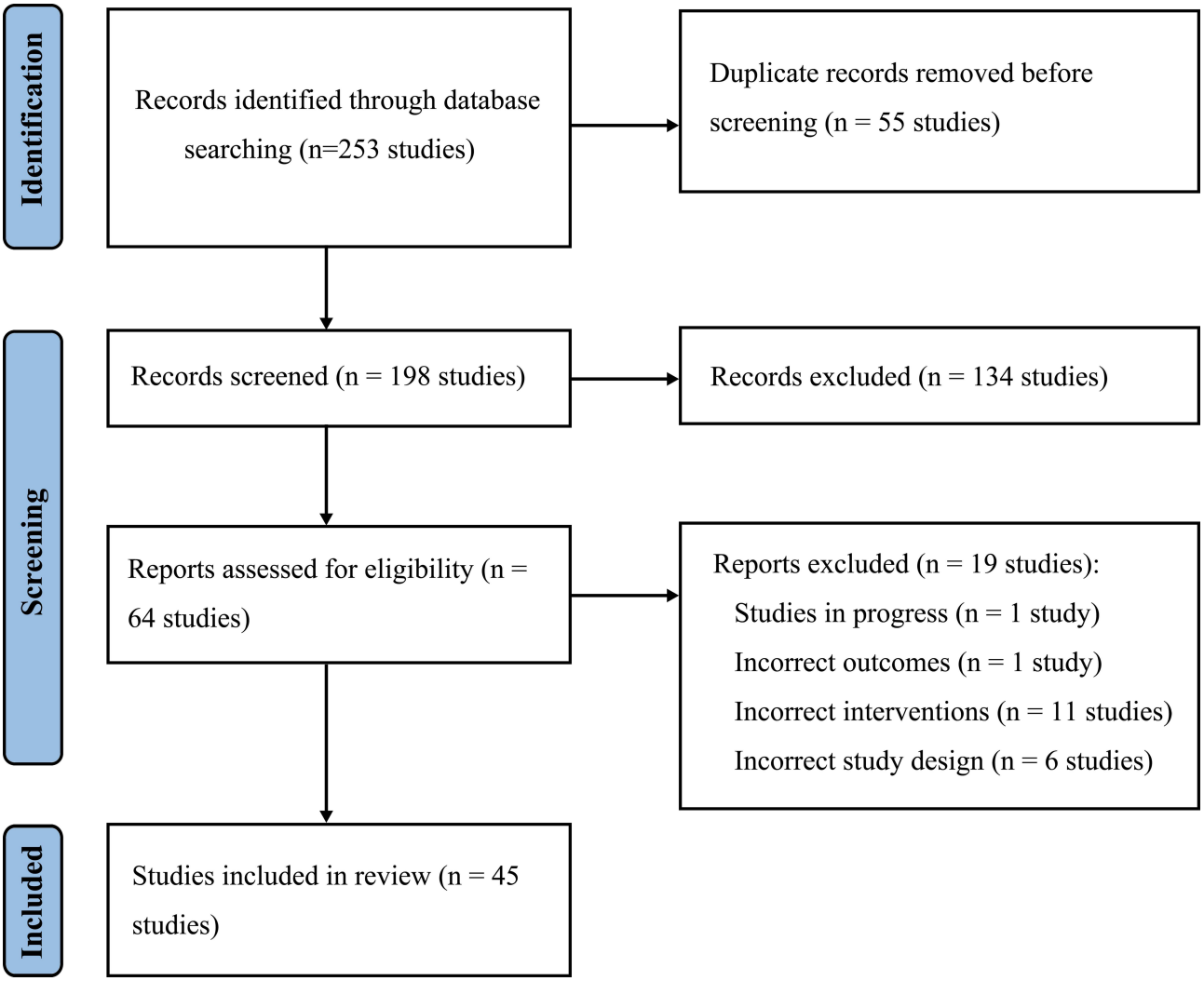

Figure 1 Flow diagram of the study selection process.

Table 1 The Characteristics of Included Studies

Study	Procedure	Sedation	Sample Size	Age (years)	Gender (M/F)	BMI (kg/m^2)	ASA (I/II/III)
Teng Y 2021[27]	CS	Ciprofol (0.4 mg/kg)+fentanyl	31	46.2±13.0	12/19	NR	25/6/0
		Ciprofol (0.5 mg/kg)+fentanyl	32	47.5±15.2	14/18	NR	25/7/0
		Propofol+fentanyl	31	48.4±13.7	16/15	NR	25/6/0
Chen XQ 2022[28]	EGD/CS	Ciprofol	47	41.22±11.63	22/25	25.22±10.12	43/4/0
		Propofol	49	43.20±12.29	17/32	23.46± 3.43	43/6/0
Huang FN 2022[29]	EGD/CS	Ciprofol+sufentanil	82	47±13	37/45	22.0±2.4	10/72/0
		Propofol+sufentanil	82	46±10	45/37	23.0±2.7	11/71/0
Li JX 2022[30]	EGD/CS	Ciprofol+fentanyl	144	43.8±11.8	55/89	23.2±2.5	115/29/0
		Propofol+fentanyl	145	44.1±11.3	63/82	23.4±2.6	118/27/0
Xia LQ 2022[31]	EGD/CS	Ciprofol	144	40.12±2.11	77/67	22.11±2.35	NR
		Propofol	145	40.04±2.13	79/67	NR	NR
Yi QL 2022[32]	EGD	Ciprofol+sufentanil	79	69.6±2.8	40/39	23.2±3.0	6/73/0
		Propofol+sufentanil	80	70.1±2.9	43/37	24.1±3.1	14/66/0
Zhang JW 2022[33]	EGD/CS	Ciprofol	50	58.12±4.26	28/22	NR	NR
		Propofol	50	58.44±4.25	27/23	NR	NR
Zhuang XY 2022[34]	EGD/CS	Ciprofol+dezocine	44	56.39±1.38	24/20	24.29±1.49	34/10/0
		Propofol+dezocine	44	56.98±2.19	22/22	24.56±2.10	33/11/0
Chen LN 2023[35]	EGD/CS	Ciprofol (0.2 mg/kg)+fentanyl	38	52.03±13.54	22/16	23.41±2.77	12/12/14
		Ciprofol (0.3 mg/kg)+fentanyl	36	45.58±17.04	12/24	22.65±3.53	15/10/11
		Ciprofol (0.4 mg/kg)+fentanyl	31	47.45±11.90	11/20	22.99±3.01	14/12/5
		Propofol+fentanyl	44	43.55±16.19	18/26	22.16±3.06	19/19/6
Gao ZW 2023[36]	EGD/CS	Ciprofol+dexamethasone+palonosetron+nalbuphine	61	68.03±4.91	24/37	24.40±3.32	13/48/0
		Propofol+dexamethasone+palonosetron+nalbuphine	60	67.32±3.02	25/35	24.76±2.98	17/43/0
He YS 2023[37]	EGD	Ciprofol+alfentanyl	44	53±13	22/22	24±3	I–II
		Propofol+alfentanyl	44	54±12	21/23	24±3	I–II
Li HB 2023[38]	EGD/CS	Ciprofol	43	65.1±10.4	NR	NR	NR
		Propofol	43	66.7±9.8	NR	NR	NR
Liang WB 2023[39]	EGD	Ciprofol (0.4 mg/kg)	40	41.3±9.5	21/19	21.8±2.6	18/22/0
		Ciprofol (0.5 mg/kg)	40	42.2±8.9	20/20	22.2±3.1	18/22/0
		Ciprofol (0.6 mg/kg)	40	43.1±9.3	18/22	21.8±3.3	19/21/0
		Propofol	39	42.1±7.8	18/21	22.5±2.9	20/19/0
Liao JS 2023[40]	EGD/CS	Ciprofol+sufentanil	185	44.98±11.74	87/98	23.07±2.28	79/106/0
		Propofol+sufentanil	183	45.35±11.12	77/106	23.13±2.23	62/121/0
Liu X 2023[41]	EGD/CS	Ciprofol+alfentanyl	49	49.02±10.42	26/23	23.90±2.87	37/12/0
		Propofol+alfentanyl	49	50.78±10.43	27/22	24.73±2.69	38/11/0
Liu XY 2023[42]	EGD	Ciprofol+sufentanil	175	39.81±5.25	90/85	24.53±1.22	87/88/0
		Propofol+sufentanil	175	39.76±5.20	89/86	24.65±1.33	85/90/0
Ma C 2023[43]	EGD/CS	Ciprofol	73	41.49±5.76	36/37	NR	48/25/0
		Propofol	73	42.07±5.29	38/35	NR	45/28/0
Ma JN 2023[44]	EGD	Ciprofol+sufentanil	40	65.35±2.46	19/21	NR	20/20/0
		Propofol+sufentanil	40	65.22±2.35	20/20	NR	25/15/0
Shi XH 2023[45]	EGD/CS	Ciprofol+sufentanil	100	58.40±6.25	57/43	NR	I–II
		Propofol+sufentanil	100	59.13±6.47	54/46	NR	I–II
Su GW 2023[46]	EGD	Ciprofol+sufentanil	46	51.83±10.95	30/16	31.16±1.77	0/46/0
		Propofol+sufentanil	46	51.46±8.52	28/18	31.51±3.30	0/46/0
Sun LL 2023[47]	EGD/CS	Ciprofol+sufentanil	30	40.56±4.36	18/12	30.04±2.86	I–II
		Propofol+sufentanil	30	40.39±4.38	17/13	29.88±2.97	I–II
Tang M 2023[48]	EGD/CS	Ciprofol+butorphanol	50	48.60±6.55	27/23	23.00±1.15	I–II
		Propofol+butorphanol	50	48.65±6.58	28/22	23.02±1.02	I–II
Tang ST 2023[49]	EGD/CS	Ciprofol	25	53.0 (45.0, 57.5)	15/10	29.0 (28.3, 30.3)	15/10/0
		Propofol	25	50.0 (44.5, 58.0)	16/9	28.7 (28.4, 29.6)	18/7/0
Wang C 2023[50]	CS	Ciprofol+alfentanyl	49	76.6±4.6	27/22	24.4±3.0	25/24/0
		Propofol+alfentanyl	50	76.2±3.5	27/23	24.1±2.8	29/21/0
Wang J 2023[51]	EGD/CS	Ciprofol+esketamine	50	49.47±11.45	21/29	23.61±3.15	23/27/0
		Propofol+esketamine	50	50.22±11.71	18/32	23.82±3.20	22/28/0
Xiang L 2023[52]	EGD	Ciprofol+sufentanil	104	42.79±10.70	48/56	22.82±2.93	94/10/0
		Propofol+sufentanil	96	42.97±11.54	42/54	23.57±3.31	84/12/0

(*Continued*)

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Table 1 (Continued).

Study	Procedure	Sedation	Sample Size	Age (years)	Gender (M/F)	BMI (kg/m^2)	ASA (I/II/III)
Xing CB 2023[53]	EGD	Ciprofol+sufentanil	40	70.55±5.2	16/24	23.12±2.78	13/19/8
		Propofol+sufentanil	40	69.78±4.45	19/21	23.13±2.82	11/21/8
Xu M 2023[54]	CP	Ciprofol+sufentanil	164	69.6±3.6	89/75	24.5±2.9	25/139/0
		Propofol+sufentanil	166	68.9±3.3	90/76	24.4±2.8	27/139/0
Zhai XQ 2023[55]	EGD	Ciprofol+remifentanil	38	49.01±5.15	20/18	NR	NR
		Propofol+remifentanil	38	48.25±5.17	21/17	NR	NR
Zhang JW 2023[56]	EGD	Ciprofol+remifentanil	52	62.02±4.29	29/23	22.25±1.56	34/18/0
		Propofol+remifentanil	52	61.15±4.62	24/28	22.53±1.97	39/13/0
Zhang X 2023[57]	EGD	Ciprofol+sufentanil	50	70.5±5.0	27/23	22.8±2.7	5/36/9
		Propofol+sufentanil	50	70.4±5.0	30/20	22.7±2.8	1/35/14
Zhao WT 2023[58]	ERCP	Ciprofol+sufentanil	142	73.6±7.1	73/69	23.1±2.7	0/36/106
		Propofol+sufentanil	142	73.6±7.2	72/70	22.3±2.7	0/39/103
Zhong J 2023[59]	ESD	Ciprofol (6 mg/kg/h)+remifentanil	23	57.1±11.1	13/10	22.5±2.7	7/15/1
		Ciprofol (8 mg/kg/h)+remifentanil	23	58.0±11.6	14/9	23.2±2.2	4/18/1
		Propofol+remifentanil	23	56.7±13.2	15/8	23.2±3.1	6/16/1
	ERCP	Ciprofol (6 mg/kg/h)+esketamine	23	59.0±12.5	13/10	23.0±2.6	4/15/4
		Ciprofol (8 mg/kg/h)+esketamine	23	59.3±11.6	11/12	22.3±2.8	4/16/3
		Propofol+esketamine	23	58.2±14.1	15/8	21.5±4.0	4/16/3
Zhu JL 2023[60]	EGD/CS	Ciprofol+sufentanil	100	61.1±9.6	54/46	NR	31/69/0
		Propofol+sufentanil	100	62.1±8.4	45/55	NR	25/75/0
Gao SH 2024[61]	CS	Ciprofol	82	54 (42, 63)	34/48	23.4±3.0	16/66/0
		Propofol	82	54 (44, 63)	32/50	23.7±3.0	20/62/0
He K 2024[62]	ERCP	Ciprofol (0.4 mg/kg)+sufentanil	50	50.0±11.8	22/28	22.6±2.5	33/17/0
		Ciprofol (0.5 mg/kg)+sufentanil	50	52.1±9.6	24/26	23.0±2.6	33/17/0
		Propofol+sufentanil	50	51.4±11.7	25/25	23.5±3.1	31/19/0
Li T 2024[63]	EGD	Ciprofol	108	46.36 ± 12.33	48/60	23.19 ± 3.01	70/38/0
		Propofol	109	47.34 ± 11.20	49/60	23.42 ± 2.79	71/38/0
Li XJ 2024[64]	EGD/CS	Ciprofol	60	48.17±5.23	34/26	NR	I–II
		Propofol	60	48.22±5.16	32/28	NR	I–II
Li YF 2024[65]	EGD/CS	Ciprofol	45	55.11±1.65	25/20	NR	I–II
		Propofol	45	56.25±1.24	23/22	NR	I–II
Tang EH 2024[66]	CS	Ciprofol+sufentanil	56	45.28±9.17	31/25	20.82±1.48	I–II
		Propofol+sufentanil	56	45.72±8.91	29/27	20.47±1.21	I–II
Zhang JQ 2024[67]	EGD/CS	Ciprofol+alfentanyl	93	54 ± 11.1	52/41	23.4 ± 3.3	75/18/0
		Propofol+alfentanyl	92	51.6 ± 11.1	52/40	23.3 ± 3.2	69/23/0
Zhang XD 2024[68]	ESD	Ciprofol	64	71.6±4.2	40/24	22.3 ± 4.4	0/52/12
		Propofol	66	72.0±3.4	37/29	24.7 ± 3.1	0/54/12
Zhang ZG 2024[69]	EGD/CS	Ciprofol	36	65.02±4.71	22/14	NR	NR
		Propofol	36	65.83±4.56	21/15	NR	NR
Zheng LB 2024[70]	EGD	Ciprofol+sufentanil	132	49.8±3.0	73/59	31.7 ± 2.9	50/82/0
		Propofol+sufentanil	135	51.1±3.1	73/62	32.9 ± 3.1	55/80/0
Zhou R 2024[71]	EGD/CS	Ciprofol+sufentanil	120	48.02±12.05	52/68	NR	NR
		Propofol+sufentanil	120	48.72±9.97	66/54	NR	NR

Abbreviations: CS, colonoscopy; EGD, esophagogastroduodenoscopy; CP, colonoscopic polypectomy; ERCP, endoscopic retrograde cholangiopancreatography; ESD, endoscopic submucosal dissection; M, male; F, female; BMI, body mass index; NR, not reported; ASA, American Society of Anesthesiologists.

Quality Assessment

The risk of bias assessments per outcome and for each study is presented in Table S5 and Supplementary Material 5. Overall, 34 studies were identified as having a high risk of bias,[28,31–35,37–39,41–53,55–58,60,62,64–66,68–70] while 11 studies were categorized as having some concerns.[27,29,30,36,40,54,59,61,63,67,71] The main study limitations included the lack of allocation sequence concealment, blinding of patients and outcome assessors, and absence of a study protocol.

Primary Outcomes

Success Rate of Gastrointestinal Endoscopy

Data on the success rate of gastrointestinal endoscopy were available from 28 studies,[27,29–33,36–39,41,42,44–48,50,54,56–58,60–62,64,65] allowing the analysis of 4310 patients. Overall, no statistical difference was observed between the ciprofol and propofol group regarding the success rate of gastrointestinal endoscopy (RR: 1.00, 95% CI: 1.00 to 1.01, I^2 = 43%; 28 studies, n = 4310) (Figure 2).

Complication Events

Compared with propofol, ciprofol was associated with a lower incidence of hypotension (RR: 0.60, 95% CI: 0.51 to 0.70, I^2 = 56%; OR: 0.46, 95% CI: 0.37 to 0.58; ARD: −0.10, 95% CI: −0.14 to −0.07; 33 studies, n = 5259)[27,29,30,32,33,36–38,40–42,44,46–48,50,52–54,56–59,61–68,70,71] (Figure S1 and Supplementary Material 6), bradycardia (RR: 0.69, 95% CI: 0.56 to 0.85, I^2 = 15%; ARD: −0.03, 95% CI: −0.06 to −0.01; 26 studies, n = 4149)[27,30,32–34,36–38,40–42,46,48,50,54,56,57,59,61–68,70] (Figure S2 and Supplementary Material 6), nausea and vomiting (RR: 0.67, 95% CI: 0.54 to 0.84, I^2 = 0%; ARD: −0.02, 95% CI: −0.03 to −0.01; 24 studies, n = 3925)[29,32,34–37,40–43,45,46,48,50,54,55,61–63,66–70] (Figure S3 and Supplementary Material 6), hypoxia (RR: 0.38, 95% CI: 0.31 to 0.48, I^2 = 42%; OR: 0.31, 95% CI: 0.24 to 0.39; ARD: −0.13, 95% CI: −0.17 to −0.09; 29 studies, n = 4883)[29,30,32,37–42,44,46,49–54,56–59,61–63,66–68,70,71] (Figure S4 and Supplementary Material 6), respiratory depression (RR: 0.39, 95% CI: 0.28 to 0.56, I^2 = 0%; OR: 0.35, 95% CI: 0.23 to 0.52; ARD: −0.05, 95% CI: −0.07 to −0.02; 18 studies, n = 2168)[27,30,33,35,36,38,44,45,47,48,53,57,64–69] (Figure S5 and Supplementary Material 6), apnea (RR: 0.35, 95% CI: 0.23 to 0.53, I^2 = 0%; ARD: −0.06, 95% CI: −0.10 to −0.01; 10 studies, n = 1613)[27,30,34,43,52,53,57,61,67,70] (Figure S6 and Supplementary Material 6), injection pain (RR: 0.13, 95% CI: 0.09 to 0.17, I^2 = 38%; OR: 0.07, 95% CI: 0.05 to 0.11; ARD: −0.28, 95% CI: −0.35 to

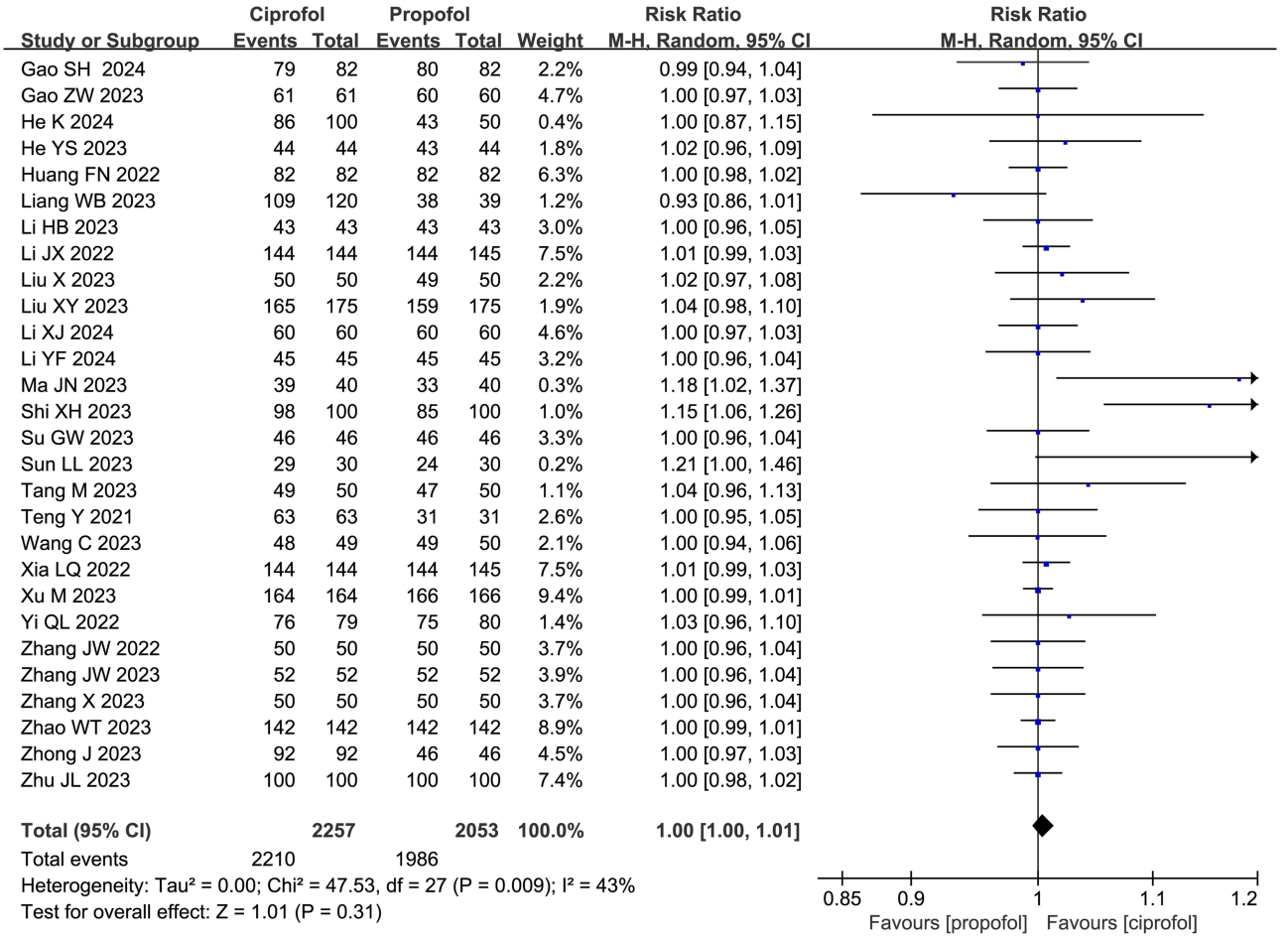

Figure 2 Forest plot of the success rate of gastrointestinal endoscopy.

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−0.20; 35 studies, n = 5526)[27–33,35–42,44–48,50,51,53–56,58,59,61,63–65,67,68,70] (Figure S7 and Supplementary Material 6), and pain scores (SMD: −1.85, 95% CI: −3.10 to −0.61, I^2 = 97%, 3 studies, n = 457)[52,67,69] (Figure S8 and Supplementary Material 6) during gastrointestinal endoscopy. No significant difference was found in body movement (RR: 0.82, 95% CI: 0.64 to 1.06, I^2 = 30%; ARD: −0.03, 95% CI: −0.05 to 0.00; 18 studies, n = 2862)[29,32,39–41,44,46,51,52,54–56,59,62,63,66–68] (Figure S9 and Supplementary Material 6) when pooling the results for these two groups.

Secondary Outcomes

Procedural Efficiency

No significant differences were observed between the ciprofol and propofol groups in terms of time to achieve adequate sedation (WMD: 0.03 min, 95% CI: −0.04 to 0.09, I^2 = 99%; 34 studies, n = 5483)[28–32,34–38,41–46,48,50–54,57–61,63,66–71] (Figure S10 and Supplementary Material 7), procedure duration (WMD: −0.11 min, 95% CI: −0.37 to 0.15, I^2 = 52%; 27 studies, n = 4057)[27–29,31,35,36,38–40,43,44,46,48–50,52,56–58,60,62,63,66–69,71] (Figure S11 and Supplementary Material 7), recovery time (WMD: −0.02 min, 95% CI: −0.31 to 0.27, I^2 = 94%; 42 studies, n = 6466)[27–32,34–38,41–46,48,50–54,56–68,70] (Figure S12 and Supplementary Material 7), and discharge time (WMD: 0.32 min, 95% CI: −0.63 to 1.28, I^2 = 97%; 23 studies, n = 3964)[27,28,30–32,36–40,42–44,48,52,53,57–61,63,67] (Figure S13 and Supplementary Material 7).

Patient, Anesthesiologist, and Endoscopist Satisfaction

Nineteen studies (3244 patients) assessed patient satisfaction between the ciprofol and propofol groups. Meta-analysis revealed that patients receiving ciprofol anesthesia exhibited a significantly higher satisfaction rate (RR: 1.04, 95% CI: 1.00 to 1.09, I^2 = 72%; 7 studies, n = 1439)[29,31,32,42,46,52,67] (Figure S14 and Supplementary Material 8) and satisfaction score (SMD: 0.27, 95% CI: 0.05 to 0.49, I^2 = 79%; 10 studies, n = 1632)[28,30,37,50,53,59,60,63,67,71] (Figure S15 and Supplementary Material 8) compared with the propofol group. Although the studies conducted by Gao et al[61] and Teng et al[27] provided data on patient satisfaction scores, we were unable to meta-analyze the outcome because of an SD of zero for the ciprofol/propofol group (Figure S15 and Supplementary Material 8). However, upon reviewing the original data, Gao et al[61] reported higher patient satisfaction scores with ciprofol, whereas Teng Y et al[27] found no statistically significant difference between the groups. In addition, one study[57] found no statistically significant difference in patient satisfaction scores between groups but failed to present specific data.

Nine studies (1255 patients) assessed anesthesiologist satisfaction in the ciprofol versus propofol groups. The consolidated research findings indicated a higher satisfaction scores among anesthesiologists regarding the efficacy of ciprofol anesthesia (SMD: 0.74, 95% CI: 0.34 to 1.14, I^2 = 83%; 5 studies, n = 666)[27,37,50,60,67] (Figure S16 and Supplementary Material 8), although no significant difference was observed in satisfaction rate between the two groups (RR: 1.04, 95% CI: 0.98 to 1.11, I^2 = 56%; 4 studies, n = 636)[32,46,52,67] (Figure S17 and Supplementary Material 8). Zhong et al[59] provided data on anesthesiologist satisfaction scores, we were unable to meta-analyze the outcome owing to an SD of zero for both groups (Figure S16 and Supplementary Material 8). Their raw data suggested no statistically significant difference between the two groups.

Twelve studies (1696 patients) assessed endoscopist satisfaction between the ciprofol and propofol groups. Meta-analysis revealed no difference in endoscopist satisfaction rate (RR: 1.02, 95% CI: 0.99 to 1.06, I^2 = 26%; 4 studies, n = 600)[29,32,46,67] (Figure S18 and Supplementary Material 8) and satisfaction scores (SMD: 0.22, 95% CI: −0.11 to 0.55, I^2 = 84%; 7 studies, n = 979)[27,28,37,50,60,63,67] (Figure S19 and Supplementary Material 8) between the two groups. Although the studies conducted by Gao et al[61] and Zhong et al[59] provided data on endoscopist satisfaction scores, we were unable to meta-analyze the outcome because of an SD of zero for the ciprofol/propofol group (Figure S19 and Supplementary Material 8). Examination of their raw data indicated that satisfaction scores of anesthesia from the endoscopists were comparable across the two groups.

Subgroup Analysis

Table S6, Supplementary Material 9 summarizes the results of the subgroup analysis. Forest plots for the subgroup analysis are presented in the Supplementary Data online, Figures S20–S50. Subgroup analysis, based on intervention types, indicated that ciprofol reduced the risk of bradycardia (RR: 0.63, 95% CI: 0.49 to 0.81, I^2 = 11%; 22 studies, n =

3401)[27,30,32–34,36–38,40–42,46,48,50,56,57,61,63,64,66,67,70] (Figure S20 and Supplementary Material 9) and nausea and vomiting (RR: 0.66, 95% CI: 0.52 to 0.84, I^2 = 0%; 21 studies, n = 3315)[29,32,34–37,40–43,45,46,48,50,55,61,63,66,67,69,70] (Figure S21 and Supplementary Material 9), and improved patient (SMD: 0.29, 95% CI: 0.05 to 0.53, I^2 = 81%; 9 studies, n = 1494)[28,30,37,50,53,60,63,67,71] (Figure S22 and Supplementary Material 9) and anesthesiologist (SMD: 0.74, 95% CI: 0.34 to 1.14, I^2 = 83%; 5 studies, n = 666[27,37,50,60,67] (Figure S23 and Supplementary Material 9) satisfaction scores compared to propofol in the endoscopic examination group. However, no difference was observed in the endoscopic treatment group. Subgroup analysis also showed that ciprofol shortened discharge time (WMD: −3.91 min, 95% CI: −5.09 to −2.74, I^2 = 0%; 2 studies, n = 422)[58,59] (Figure S24 and Supplementary Material 9) compared to propofol in the endoscopic treatment group, but no difference was found in the endoscopic examination group. The subgroup analysis did not show any significant differences within subgroups based on endoscopic examination or treatment in the success rate of gastrointestinal endoscopy, hypotension, hypoxia, respiratory depression, injection pain, body movement, time to achieve adequate sedation, procedure time, recovery time, or endoscopist satisfaction scores (Table S6, see Supplementary Data online, Figures S25–S34). Subgroup analyses were not conducted for apnea, injection pain score, and satisfaction rate (patient, anesthesiologist, and endoscopist) because of the limited number of studies included.

Subgroup analysis based on the dose of ciprofol used during endoscopic examination showed that ciprofol reduced the risk of bradycardia (RR: 0.59, 95% CI: 0.45 to 0.76, I^2 = 7%; 17 studies, n = 2780)[22,27,30,32,33,36,40,42,46,50,56,57,61,64,66,67,70] (Figure S35 and Supplementary Material 9), respiratory depression (RR: 0.41, 95% CI: 0.28 to 0.62, I^2 = 0%; 13 studies, n = 1548)[27,30,33,35,36,44,47,53,57,64–67] (Figure S36 and Supplementary Material 9) and apnoea (RR: 0.36, 95% CI: 0.23 to 0.54, I^2 = 0%; 9 studies, n = 1493)[27,30,43,52,53,57,61,67,70] (Figure S37 and Supplementary Material 9), and improved patient satisfaction scores (SMD: 0.44, 95% CI: 0.28 to 0.60, I^2 = 38%; 9 studies, n = 1263)[27,30,43,52,53,57,61,67,70] (Figure S38 and Supplementary Material 9) compared to propofol when the dose of ciprofol was 0.4 mg/kg or lower. However, no differences were observed between the two groups when the dose of ciprofol exceeded 0.4 mg/kg. Subgroup analysis also showed that patients experienced longer discharge times (WMD: 1.46 minutes, 95% CI: 0.49 to 2.42, I^2 = 67%; 5 studies, n = 585)[27,38,39,48,63] (Figure S39 and Supplementary Material 9) when ciprofol was administered at doses greater than 0.4 mg/kg compared to propofol. In contrast, no differences in discharge time were observed when the dose was 0.4 mg/kg or lower. The subgroup analysis did not reveal any significant differences between dose-based subgroups in success rate of gastrointestinal endoscopy, hypotension, nausea and vomiting, hypoxia, injection pain, injection pain score, body movement, time to achieve adequate sedation, procedure time, recovery time, or endoscopist satisfaction score (Table S6, see Supplementary Data online; Figures S40–S50). Subgroup analyses were not conducted for patient, anesthesiologist, and endoscopist satisfaction rates due to the limited number of studies included.

Sensitivity Analysis

Table S7 and Supplementary Material 10 summarizes the results of the sensitivity analysis. Sensitivity analysis using alternative effect measure (RR, OR, or ARD), statistical models (fixed versus random effects), pooling with the Mantel–Haenszel OR method for single-arm-zero-events studies or the ARD method for double-arm-zero-events studies (versus excluding zero-events studies), and leave-one-out meta-analysis showed similar results for bradycardia, nausea and vomiting, hypoxia, respiratory depression, apnea, injection pain, anesthesiologist satisfaction rate, anesthesiologists satisfaction score, and endoscopist satisfaction rate.

Publication Bias

Funnel plot analyses and statistical tests showed no evidence of publication bias for bradycardia (P = 0.17, Figure S51 and Supplementary Material 11), nausea and vomiting (P = 0.25, Figure S52 and Supplementary Material 11), respiratory depression (P = 0.27, Figure S53 and Supplementary Material 11), body movement (P = 0.19, Figure S54 and Supplementary Material 11), procedure time (P = 0.37, Figure S55 and Supplementary Material 11), discharge time (P = 0.49, Figure S56 and Supplementary Material 11), and recovery time (P = 0.71, Figure S57 and Supplementary Material 11). However, publication bias was found for the success rate of gastrointestinal endoscopy

($P = 0.02$, Figure S58 and Supplementary Material 11), hypotension ($P = 0.00$, Figure S59 and Supplementary Material 11), hypoxia ($P = 0.02$, Figure S60 and Supplementary Material 11), injection pain ($P = 0.00$, Figure S61 and Supplementary Material 11), and time to achieve adequate sedation ($P = 0.02$, Figure S62 and Supplementary Material 11), as indicated by the asymmetrical funnel plot and Egger's test results. Except for the time to achieve adequate sedation, the effect size estimates obtained using the trim-and-fill method did not differ significantly from those obtained in the original meta-analysis, indicating that the results were reliable (Figures S63–S67 and Supplementary Material 11).

Grading the Quality of Evidence

Table 2 summarizes the GRADE findings.

Discussion

Summary of Main Findings

We found evidence of very low-to-moderate certainty that ciprofol-induced sedation or anesthesia was equivalent to propofol (97.9% vs 96.7%), with both agents showing similar procedural efficiencies. Additionally, ciprofol reduced the incidence of complications, including hypotension, bradycardia, nausea and vomiting, hypoxia, respiratory depression, apnea, and injection pain, while also improving patient and anesthesiologist satisfaction. In summary, our findings indicate that ciprofol could be a safer option than propofol in the context of gastrointestinal endoscopic anesthesia. The study was conducted in strict accordance with the established international guidelines for systematic reviews and meta-analyses.[72]

Relevant Evidence

The results of this review differ from those of recent systematic reviews.[5,7,8] Currò JM et al[8] retrieved 14 RCTs, with 8 focusing on patients receiving sedation and 6 on general anesthesia. They concluded that ciprofol, whether used for sedation or general anesthesia, might be safer than propofol. However, the authors conducted only a literature review without a meta-analysis. Yang YN et al revealed that ciprofol, in comparison to propofol, markedly decreased the occurrence of injection pain (RR: 0.12, 95% CI: 0.08 to 0.19, $I^2 = 0$) and respiratory depression in non-operating room settings. Ciprofol was associated with a reduction in induction time (SMD: −0.65, 95% CI: −1.37 to 0.07, $I^2 = 96\%$) and lower incidence of hypotension (RR: 0.79, 95% CI: 0.42 to 1.49, $I^2 = 86\%$) and bradycardia (RR: 0.89, 95% CI: 0.61 to 1.29, $I^2 = 33\%$), though these effects did not reach statistical significance.[5] Hung et al performed a systematic review and meta-analysis of 12 clinical trials evaluating ciprofol versus propofol for anesthesia induction and non-intensive care unit sedation.[7] Aggregated data showed non-significant intergroup differences in procedural success rates (RR: 1.00, 95% CI: 0.99 to 1.01, $I^2 = 0\%$) and time-to-effect metrics (MD: 7.95 s, 95% CI: −1.09 to 16.99, $I^2 = 97\%$), with the latter demonstrating substantial heterogeneity. Comparative analysis revealed similar outcomes between groups for bradycardia (RR: 0.94, 95% CI: 0.73 to 1.23, $I^2 = 0\%$), hypoxemia/pulmonary depression (RR: 0.78, 95% CI: 0.51 to 1.19, $I^2 = 0\%$), postoperative nausea/vomiting (RR: 0.85, 95% CI: 0.35 to 2.06, $I^2 = 0\%$), discharge time (MD: 1.39 min, 95% CI: −0.45 to 3.22, $I^2 = 80\%$), and satisfaction scores (SMD: 0.23, 95% CI: −0.10 to 0.56, $I^2 = 74\%$). Notably, ciprofol demonstrated reduced risks of hypotension (RR: 0.85, 95% CI: 0.73 to 0.98, $I^2 = 24\%$) and injection pain (RR: 0.17, 95% CI: 0.11 to 0.27, $I^2 = 56\%$) relative to propofol. Although propofol showed a statistically significant 0.66-min advantage in time to full alertness, this difference lacked clinical significance. However, the authors recognized that their results should be interpreted with caution because of the limited and low-quality evidence available at that time. Notably, in the study by Yang et al, only five of the included studies were related to gastrointestinal endoscopy, whereas the study by Hung et al included only three such studies. Thus, the risk of spurious results is likely to be significant. Therefore, the inconsistent results between our study and previous meta-analyses may be primarily due to the smaller sample sizes in the earlier studies. Our study incorporated data from 45 RCTs involving 6884 patients to compare the safety, efficiency, and satisfaction outcomes of ciprofol and propofol in gastrointestinal endoscopy. The incorporation of these trials

Table 2 GRADE (Grading of Recommendations, Assessment, Development and Evaluation) Evidence Profile

Outcomes	Number of participants (studies)	Quality assessment					Effect		Quality
		Risk of bias	Inconsistency	Indirectness	Imprecision	Publication Bias*	Relative (95% CI)	Absolute (95% CI)	
Success rate of gastrointestinal endoscopy	4310 (28 RCTs)	Serious[a]	Not serious	Not serious	Serious[b]	Serious[c]	RR 1 (1 to 1.01)	0 fewer per 1000 (from 0 more to 10 more)	⊕◯◯◯Very low
Hypotension	5259 (33 RCTs)	Serious[a]	Serious[d]	Not serious	Not serious	Serious[c]	RR 0.60 (0.51 to 0.7)	115 fewer per 1000 (from 86 fewer to 141 fewer)	⊕◯◯◯Very low
Bradycardia	4149 (26 RCTs)	Serious[a]	Not serious	Not serious	Not serious	Not serious	RR 0.69 (0.56 to 0.85)	41 fewer per 1000 (from 20 fewer to 58 fewer)	⊕⊕⊕◯Moderate
Nausea and vomiting	3925 (24 RCTs)	Serious[a]	Not serious	Not serious	Not serious	Not serious	RR 0.67 (0.54 to 0.84)	31 fewer per 1000 (from 15 fewer to 43 fewer)	⊕⊕⊕◯Moderate
Hypoxic	4883 (29 RCTs)	Serious[a]	Not serious	Not serious	Not serious	Serious[c]	RR 0.38 (0.31 to 0.48)	135 fewer per 1000 (from 113 fewer to 150 fewer)	⊕⊕◯◯Low
Respiratory depression	2168 (18 RCTs)	Serious[a]	Not serious	Not serious	Not serious	Not serious	RR 0.39 (0.28 to 0.56)	59 fewer per 1000 (from 43 fewer to 70 fewer)	⊕⊕⊕◯Moderate
Apnea	1613 (10 RCTs)	Serious[a]	Not serious	Not serious	Not serious	Not serious	RR 0.35 (0.23 to 0.53)	68 fewer per 1000 (from 49 fewer to 80 fewer)	⊕⊕⊕◯Moderate
Injection pain	5526 (35 RCTs)	Serious[a]	Not serious	Not serious	Not serious	Serious[c]	RR 0.13 (0.09 to 0.17)	287 fewer per 1000 (from 274 fewer to 300 fewer)	⊕⊕◯◯Low
Injection pain score	457 (3 RCTs)	Serious[a]	Serious[d]	Not serious	Not serious	Not serious	–	SMD 1.85 lower (3.1 to 0.61 lower)	⊕⊕◯◯Low
Body movement	2862 (18 RCTs)	Serious[a]	Not serious	Not serious	Serious[b]	Not serious	RR 0.82 (0.64 to 1.06)	28 fewer per 1000 (from 57 fewer to 9 more)	⊕⊕◯◯Low
Time to achieve adequate sedation	5362 (33 RCTs)	Serious[a]	Serious[d]	Not serious	Not serious	Serious[c]	–	MD 0.03 higher (0.04 lower to 0.1 higher)	⊕◯◯◯Very low
Procedure time	4057 (27 RCTs)	Serious[a]	Serious[d]	Not serious	Serious[b]	Not serious	–	MD 0.11 lower (0.37 lower to 0.15 higher)	⊕◯◯◯Very low
Recovery time	6466 (42 RCTs)	Serious[a]	Serious[d]	Not serious	Serious[b]	Serious[c]	–	MD 0.02 lower (0.31 lower to 0.27 higher)	⊕◯◯◯Very low
Discharge time	3964 (23 RCTs)	Serious[a]	Serious[d]	Not serious	Not serious	Not serious	–	MD 0.32 higher (0.63 lower to 1.28 higher)	⊕⊕◯◯Low
Patient satisfaction rate	1439 (7 RCTs)	Serious[a]	Serious[d]	Not serious	Not serious	Not serious	RR 1.04 (1 to 1.09)	36 more per 1000 (from 0 more to 81 more)	⊕⊕◯◯Low
Patient satisfaction score	1890 (12 RCTs)	Serious[a]	Serious[d]	Not serious	Not serious	Not serious	–	SMD 0.27 higher (0.05 to 0.49 higher)	⊕⊕◯◯Low
Anesthesiologist satisfaction rate	636 (4 RCTs)	Serious[a]	Serious[d]	Not serious	Serious[b]	Not serious	RR 1.04 (0.98 to 1.11)	35 more per 1000 (from 17 fewer to 96 more)	⊕◯◯◯Very low
Anesthesiologists satisfaction score	804 (6 RCTs)	Serious[a]	Serious[d]	Not serious	Not serious	Not serious	–	SMD 0.74 higher (0.34 to 1.14 higher)	⊕⊕◯◯Low
Endoscopist satisfaction rate	600 (4 RCTs)	Serious[a]	Not serious	Not serious	Serious[b]	Not serious	RR 1.02 (0.99 to 1.06)	18 more per 1000 (from 9 fewer to 55 more)	⊕⊕◯◯Low
Endoscopist satisfaction score	1281 (9 RCTs)	Serious[a]	Serious[d]	Not serious	Not serious	Not serious	–	SMD 0.22 higher (0.11 lower to 0.55 higher)	⊕⊕◯◯Low

Notes: * Publication bias was only considered for when more than 10 studies were included in a meta-analysis; [a] Quality was rated down for risk of bias due to inadequately generated randomization sequence, inadequate concealment and blinding, or selectively report of outcomes; [b] The total sample size is insufficient or the outcome is not robust; [c] Publication bias was detected using the asymmetrical funnel plot and Egger's test; [d] Moderate or severe heterogeneity (> 50% heterogeneity). GRADE Working Group grades of evidence: High quality, Further research is very unlikely to change our confidence in the estimate of effect; Moderate quality, Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; Low quality, Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; Very low quality, We are very uncertain about the estimate.

Abbreviations: CI, confidence interval; RCTs: randomized controlled trials; RR, relative risk; MD, mean difference; SMD: standardized mean difference.

significantly enhanced the precision of the effect size calculations, augmented analytical robustness through improved statistical power, and achieved balanced weighting across the included studies.

Meaning of the Study

Optimal endoscopic sedation optimizes patient comfort and tolerance, improves procedural efficiency, and increases the diagnostic yield for gastrointestinal pathologies.[73] The ideal sedative should be fast-acting, require a low dosage, be easy to regulate, have minimal adverse effects, and be cost-effective. Among currently used anesthetics, propofol has pharmacokinetic and pharmacodynamic properties closest to this ideal.[74,75] Ciprofol, (2-[(1R)-1-cyclopropylethyl]-6-isopropyl-phenol), a novel intravenous anesthetic agent,[76] demonstrates potent GABAA receptor binding affinity with 4–5-fold greater hypnotic efficacy than propofol.[77] Our pooled analysis revealed comparable procedural success rates for anesthesia and sedation between the two agents.

Sedation during gastrointestinal endoscopy carries the risk of possible cardiorespiratory complications.[78] Although complete sedation can be achieved using a clinical dose of propofol alone, its potential to cause respiratory and cardiovascular depression remains a concern for clinicians.[79] This systematic evaluation quantified the cardiovascular risks in 2565 patients from 33 RCTs comparing propofol and ciprofol for gastrointestinal endoscopic sedation. Propofol demonstrated significantly higher hypotensive event rates (29%, n = 739; typically defined as systolic BP <90 mmHg) than ciprofol (18%), confirming its greater hemodynamic instability profile. Twenty-six reports comparing propofol with ciprofol included 4149 patients, of whom 190 (9%) in the ciprofol group and 265 (13%) in the propofol group developed bradycardia, based on the criteria defined by the authors. Although these differences were statistically significant, their clinical impact was minimal.

Hemodynamic stability and preserved ventilatory function are critical requirements for sedation. Gastrointestinal endoscopic procedures carry inherent risks of central respiratory depression and airway compromise,[80] necessitating prompt recognition and intervention to prevent hypoxic organ damage or mortality.[81] Both sedatives and centrally acting analgesics exhibit dose-dependent suppression of the respiratory drive. Ciprofol has demonstrated efficacy and safety in various clinical settings.[5] Our study found that the risks of hypoxia (8% vs 22%), respiratory depression (3% vs 10%), and apnea (3% vs 10%) during sedation were significantly lower in the ciprofol group than that in the propofol group. This difference may be related to their distinct interactions with GABAA receptor subunits. Propofol has relatively high affinity for the β2 and β3 subunits, with its sedative effects primarily mediated by these subunits. Respiratory depression induced by propofol is mainly mediated via the β3 subunit, suggesting that ciprofol may predominantly target different subunits, thereby resulting in milder respiratory depression.[82]

Although injection site discomfort is a non-life-threatening adverse event, it persists as a memorable patient experience during procedural sedation. Clinical surveys posit that propofol-induced injection pain is among the top ten concerns in contemporary anesthesia practice.[83] The underlying mechanisms involve phenol-mediated local irritation (affecting cutaneous, mucosal, and vascular endothelial) and kinin cascade activation through mediators, such as kininogen.[84] Our data demonstrated that ciprofol had a superior safety profile, exhibiting significantly lower injection-related adverse effects than propofol (4% vs 33%), consistent with observational evidence from clinical practice.

In addition to assessing cardiorespiratory and other complications, our study analyzed various aspects of the sedation profile and found no statistically significant differences between ciprofol and propofol in the time required to achieve adequate sedation, procedure duration, recovery time, or discharge time. Following intravenous administration, ciprofol demonstrates rapid tissue distribution kinetics, with preferentially accumulating in target organs accompanied by efficient systemic clearance. The compound undergoes hepatic biotransformation through Phase I oxidation and Phase II conjugation pathways (glucuronidation/sulfation), with more than 90% of the metabolites ultimately eliminated through the renal and fecal routes.[85,86] This investigation revealed comparable pharmacodynamic profiles between ciprofol and propofol, with both agents demonstrating equivalent temporal parameters for induction latency and post-procedural return to baseline consciousness.

Satisfaction metrics vary across studies and have been inconsistently reported; thus, the SMD is a more appropriate measure for comparing satisfaction scores. While endoscopists' procedural ratings showed parity between the groups, ciprofol demonstrated superior patient-reported satisfaction and anesthesiologist evaluations. This difference appears to

be driven by ciprofol's reduced incidence of injection pain (4% vs 33%), a key determinant of patient perception. Anesthesiologist assessments included five clinical parameters: induction latency, cardiopulmonary event rate, injection discomfort, intraprocedural rescue medication requirements, and recovery duration. Endoscopist evaluations focused solely on procedural feasibility and patient cooperation during the endoscopic maneuvers.

Although cost-effectiveness was not a direct focus of this study, a discussion of direct costs is warranted. Propofol, a classic intravenous anesthetic with a long history of clinical use, is inexpensive and widely accessible in most healthcare systems. In contrast, ciprofol—a novel sedative in the early stages of clinical dissemination—has a significantly higher cost per unit than propofol. However, it is noteworthy that the distinctive pharmacological characteristics of ciprofol may indirectly affect healthcare expenditures by reducing the incidence of respiratory depression and circulatory fluctuations, as well as lowering the intensity of perioperative monitoring and the costs associated with complication management. At the availability level, the fat-soluble carrier in propofol is prone to causing injection pain and lipid metabolism disorders, often requiring co-administration of analgesics or adjustments to the infusion regimen.[87] In contrast, ciprofol may avoid these issues through its optimized physicochemical properties, enhanced potency, improved molecular structure, and other mechanisms. This is particularly advantageous for patients requiring prolonged infusion or those at metabolic risk. Nevertheless, the current clinical experience with ciprofol remains limited, and evidence regarding its safety in special populations—such as those with hepatic or renal insufficiency—is still evolving. This may constrain its broader clinical application at present. It is imperative that future pharmacoeconomic studies incorporating real-world data be conducted to systematically quantify the comprehensive cost-effectiveness ratios of these two anesthetic agents across different clinical scenarios.

Strengths and Limitations

This study represents the most methodologically robust evaluation of the endoscopic sedation profile of ciprofol. To ensure methodological transparency, our PROSPERO-registered protocol was prospectively published before data extraction.[10] Using a predefined search strategy encompassing multiple languages and recent high-quality trials, we established a more representative evidence base than previous analyses. ARD calculations were systematically implemented for all safety endpoints to enhance clinical interpretability. GRADE evidence grading confirmed ciprofol's superior safety profile relative to that of propofol, with multiple outcomes demonstrating moderate-to-high certainty.

Several methodological constraints should be acknowledged when interpreting these findings. First, variations in dosing regimens (bolus vs infusion) and administration schedules existed between the study arms. Second, outcome definitions varied across included studies. Third, several pooled effect estimates showed significant unexplained heterogeneity, leading to substantial inconsistencies. Fourth, subgroup analysis revealed discrepancies in bradycardia, nausea and vomiting, time to discharge, and patient and anesthesiologist satisfaction scores between the endoscopic treatment and examination groups, reducing the credibility of the findings. Fifth, although our review included more trials than that in previous reviews,[5,7,8] the certainty of evidence ranged from moderate to very low. Sixth, the predominance of studies with a high risk of bias—primarily due to the absence of blinding and allocation concealment—may substantially compromise the certainty of the evidence. Furthermore, the quality of evidence ratings was largely subjective, and some readers may disagree with our assessments. Seventh, despite the inclusion of a large number of studies, the total sample sizes for several outcomes did not reach the optimal information size (OIS), thereby reducing the precision of the results. Finally, all included studies were conducted in China, which may limit the generalizability of our findings to other populations. Therefore, the results of the present study should be interpreted with caution.

Conclusion

This systematic review of RCTs found very low-to-moderate certainty evidence indicating that ciprofol-induced sedation or anesthesia is comparable to propofol, with both drugs showing similar procedural efficiency. Additionally, ciprofol reduced the incidence of complications, including hypotension, bradycardia, nausea and vomiting, hypoxia, respiratory depression, apnea, and injection pain, while enhancing patient and anesthesiologist satisfaction. As a novel sedative, ciprofol may offer a better safety profile compared with propofol. However, high-quality RCTs are needed to confirm

these findings and improve the precision of the effect estimates. Future investigations should prioritize establishing evidence-based dosing regimens for ciprofol, systematically evaluating its therapeutic index in vulnerable populations—particularly geriatric and pediatric cohorts—and expediting multinational clinical trials to validate the generalizability of these therapeutic strategies.

Data Sharing Statement

All data relevant to the study are included in the article or uploaded as online supplemental information.

Ethical Approval & Informed Consent

This meta-analysis was based on previously published studies; therefore, ethical approval and informed consent were not required.

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Disclosure

The authors declare no conflicts of interest in this work.

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