BMJ Open Ciprofol versus propofol for sedation in gastrointestinal endoscopy: protocol for a systematic review and meta-analysis

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To cite: Qin X, Lu X, Tang L, *et al.* Ciprofol versus propofol for sedation in gastrointestinal endoscopy: protocol for a systematic review and meta-analysis. *BMJ Open* 2023;**13**:e071438. doi:10.1136/ bmjopen-2022-071438

Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/ bmjopen-2022-071438).

Received 27 December 2022 Accepted 17 May 2023

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ABSTRACT

Introduction Painless gastrointestinal endoscopy is being increasingly practised in the clinical field. The management and choice of sedation are important during the endoscopy procedure to reduce patient discomfort and facilitate high disease detection rates. Ciprofol is principally an agonist of the γ -aminobutyric acid type A receptor; it comprises the active ingredient HSK3486, which is similar to the currently used intravenous anaesthetic propofol in clinical practice. A systematic review and meta-analysis comparing ciprofol and propofol will be conducted to assess their efficacy and safety during endoscopy. Before starting the study, we describe the specific protocol of this systematic review.

Methods and analysis This protocol was prepared in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols 2015. The following databases will be searched: Embase. Cochrane Library, PubMed, Web of Science, Chinese Biomedical Literature Service System, China National Knowledge Infrastructure, Wanfang Database, China Science and Technology Journal Database and a clinical trial registry. The database search strategy will adopt a combination of subject words and free words. Randomised controlled trials related to ciprofol use for sedation during gastrointestinal endoscopy will also be included. Based on the inclusion and exclusion criteria, two researchers will independently screen the articles and extracted data. Following the qualitative evaluation of each study, analysis will be conducted using Review Manager software. Ethics and dissemination The protocol for this systematic review and meta-analysis involves no individual patient data: thus, ethical approval is not required. This will be the first meta-analysis to assess the sedation efficacy of ciprofol and provide evidence to clinicians for decision-making. The results will be disseminated through conference presentations and publications in peer-review journals related to this field.

PROSPERO registration number CRD42022370047.

INTRODUCTION

Gastrointestinal endoscopy is a minimally invasive procedure for the diagnosis and treatment of gastrointestinal pathologies. However, the procedure may be uncomfortable and stressful for most patients. With the continuous development in medical technology, painless gastrointestinal endoscopy

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This review will use a rigorous methodology following the Cochrane guidelines and the Preferred Reporting Items for Systematic Review and Meta-Analysis checklist.
- \Rightarrow The study will search Chinese and English literature and will be a comprehensive review.
- ⇒ We will use subgroup analysis to explore the heterogeneity and sensitivity analysis to ensure the stability of the results.
- ⇒ The main limitation of our study protocol is that some studies may not be of high quality, because all original randomised controlled trials in English and Chinese that fulfil the inclusion criteria will be included.

is being increasingly practiced in the clinical field. Most low-risk endoscopic procedures are performed under some form of sedation.¹ Adequate sedation during endoscopy can improve patient experience, influence the quality of the procedure, and result in high detection rates of gastrointestinal diseases.²

≥ Propofol (2,6-diisopropyl phenol), an training ultrashort-acting sedative agent with a rapid recovery profile, has been used extensively for gastrointestinal endoscopy.³ Propofol has significant advantages over other sedative agents. It has no active metabolites and <u>s</u> is cleared efficiently and quickly by the liver.⁴ Despite these desirable features, propofol does have some disadvantages, such as weak analgesic effect, hypotension, bradycardia and injection site pain. Administration of propofol alone for adequate sedation may lead to significant haemodynamic instability, **3** unmanageable dosage and increased risk of deep sedation, which directly or indirectly affects the stability of the sedation regimen.⁵ These adverse effects are significantly associated with the dose and speed of propofol injection^b and can have serious consequences for the patients.

Ciprofol, a novel intravenous general anaesthetic independently developed by Haisco

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Pharmaceutical Group, was approved in China in 2020.⁷ Ciprofol is principally an agonist of the y-aminobutyric acid type A (GABA_A) receptor. Its active ingredient, HSK3486, is a propofol analogue, which is a single diastereomer and contains an R-shaped hand centre. The chemical name of ciprofol is 2-[(1R)-1-cyclopropyl ethyl]-6-isopropylphenol.⁸ It has been shown to have a high affinity towards the GABA, receptor, and its hypnotic potency is approximately 4-5 fold higher than that of propofol.⁹ A phase 1 clinical trial on healthy individuals reported¹⁰ that the safety and tolerability parameters of ciprofol were similar to those of propofol, and all treatment-emergent adverse events were mild. The incidence of injection site pain and respiratory depression was lower in patients administered with ciprofol than in those administered with propofol.

Given the gradual increase in the use of ciprofol, it is essential to evaluate the actual benefits and safety of ciprofol sedation during gastrointestinal endoscopy. Several studies have compared the hypnotic potency and safety of ciprofol with those of propofol in patients undergoing gastrointestinal endoscopy. Their findings revealed improved patient satisfaction, decreased sedation and recovery times, and lower rates of cardiorespiratory adverse events with ciprofol use.^{11 12} However, comparison of the two sedatives in several other studies presented contradictory results and safety profiles.^{13 14} Thus, the advantages of ciprofol as an alternative to the most common sedative, propofol, remain unclear. An up-to-date summary and analysis of the existing literature will aid clinical decision-making. This systematic review will lay the foundation for future research on this novel intravenous general anaesthetic.

Objectives

This systematic review aims to compare the efficacy and safety of the new intravenous anaesthetic ciprofol with the commonly used anaesthetic propofol during gastrointestinal endoscopy. Furthermore, it aims to clarify whether ciprofol is as effective as propofol with fewer adverse effects.

MATERIALS AND METHODS Protocol and registration

The Cochrane Handbook for Systematic Reviews of Interventions was used as guidance for the protocol.¹⁵ The protocol was based on the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRIS-MA-P) checklist guidelines.¹⁶ The completed PRISMA-P checklist can be found in online supplemental file 1. In accordance with the guidelines, our systematic review protocol was registered with the International Prospective Register of Systematic Reviews on 24 December 2022 (Registration number: CRD42022370047). Ethical approval and patient consent are not required, because this study will be based on published studies. We will submit our results to a peer-review journal for publication.

The planned start and end dates of the study are 1 March 2023 and 30 August 2023, respectively.

Patient and public involvement

No patient involved.

Eligibility criteria

Study designs

All published randomised controlled trials (RCTs) comparing the use of ciprofol and propofol for sedation in gastrointestinal endoscopy will be included. Animal otected by copyright, studies, meeting notes, literature studies, letters, study protocols, case reports, duplicate literature and nonrandomised studies on the effects of interventions will be excluded.

Participants

We will include studies that recruited patients of all ages who had undergone gastrointestinal endoscopy. Studies that included patients with severe circulatory disorders (uncontrolled hypertension, severe arrhythmia, chronic heart failure, Adams-Stokes syndrome, unstable angina, cardiac infarction within 6 months, third degree atrioventricular block, or QTcF interval \geq 450 ms), respiratory uve pulmonary disease, bronchospasm requiring treat-ment within the last 3 months or acute respiratory tract infection with obvious fever, wheeze, rhinobuor cough within 1 week at bear " abuse or allergy will be excluded. Studies that included text and patients with difficult airways or respiratory sleep apnoea syndrome will also be excluded.

Interventions

Interventions using ciprofol alone or in combination with other drugs to achieve sedative effects are of interest. Regarding the interventions used in the studies, no d restrictions have been set with respect to the dose admin-⋗ istered, injection speed, additional doses or interval between each additional dose.

Comparators

training, and We will include RCTs on propofol sedation as the control for gastrointestinal endoscopy. If propoloi sedation as the control **a** with other drugs (eg, opioid analgesics) for sedation in the study, the same combination regimen must be used in the intervention. Outcomes The primary outcomes in this study will be the success rate of the gastrointestinal endoscopy procedure and safety endpoints (complication events) because these

safety endpoints (complication events), because these are usually prioritised by researchers. The secondary outcomes will be satisfaction and efficacy measures. Original studies that do not provide relevant data required for this meta-analysis will be excluded.

Information sources

To ascertain all relevant studies regardless of the publication status, we will systematically search the following

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electronic databases: Embase, Cochrane Library, PubMed, Web of Science, Chinese Biomedical Literature Service System, China National Knowledge Infrastructure, Wanfang Database, China Science and Technology Journal Database, and ClinicalTrials.gov (until May 2023). To ensure completeness of the literature search, we will scan the list of references identified for inclusion in the study or relevant reviews. The literature search will be limited to articles published in English and Chinese.

Search strategy

All database searches will be based on a combination of subject words and free words and will be adjusted according to the specific database. Specific search strategies will be created by a Health Sciences librarian with expertise in systematic review searching. The database will be searched periodically prior to the systematic review and meta-analysis, and a final search will be performed to update the results before the full text is completed. The specific search strategy applied to the PubMed database is presented in table 1. The full planned search strategy can be found in online supplemental file 2.

Study records

Data management

The literature search results will be uploaded to EndNote software, a literature management software. The researchers will screen the literature based on the predetermined inclusion and exclusion criteria. Prior to the formal screening process, all review team members participating in the screening will receive training in using EndNote software. Moreover, a pilot screening will be conducted to avoid any bias and refine the screening questions.

Selection process

All retrieved records will be imported into EndNote software, and duplicates will be removed. Two researchers will independently screen the titles and abstracts obtained by the search against the inclusion criteria. Full articles will be obtained if the literature meets the inclusion criteria or if a decision cannot be made from the title/abstract alone. The review authors will resolve disagreements through a consensus-based decision or through discussions within the group if necessary. Additionally, we will record the specific reasons for the exclusion of each study. The flow diagram of the screening of the selected studies is shown in figure 1.

Data collection process

Two researchers will use Microsoft Excel data extraction form to extract data independently from each eligible study. To ensure consistency between the reviewers, we will perform a calibration exercise on the forms. All personnel involved in the data extraction should have practised using the form before starting the audit, and the data extractors should be given appropriate training if necessary. All tables will be pretested using representative evaluation studies to identify missing or redundant

Table 1	Search strategy for PubMed
Number	Search terms
#1	"proctoscopes" (MeSH] OR "gastroscopes" (MeSH] OR "colonoscopy" (MeSH] OR "endoscope" (MeSH] OR "endoscopes, gastrointestinal" (MeSH] OR "endoscopes, gastrointestinal/adverse effects" (MeSH] OR "endoscopy, gastrointestinal" (MeSH)
#2	"gastroscope"(Title/Abstract) OR "gastroscopes"(Title/Abstract) OR "colonoscopy"(Title/Abstract) OR "enteroscopy"(Title/Abstract) OR "proctoscope"(Title/Abstract) OR "proctoscopes"(Title/Abstract)OR "gastrointestinal endoscope"(Title/Abstract)OR "gastrointestinal endoscope"(Title/Abstract)OR "gastrointestinal endoscopes"(Title/Abstract)OR "gastrointestinal endoscopes"(Title/Abstract)OR "gastrointestinal endoscopes"(Title/Abstract)OR "endoscope"(Title/Abstract)OR "coloscopy"(Title/ Abstract)OR "proctoscope"(Title/Abstract)OR "gastrointestinal endoscopies"(Title/Abstract)OR "gastrointestinal endoscopies"(Title/Abstract) OR "endoscopic gastrointestinal surgical procedures"(Title/Abstract)OR "gastrointestinal endoscopic surgical procedure"(Title/ Abstract)OR "endoscopic gastrointestinal surgery"(Title/Abstract)OR "endoscop*"(Title/ Abstract)OR "gastroscop*"(Title/Abstract) OR "colonoscop*"(Title/Abstract)OR "proctoscop*"(Title/Abstract)OR
#3	#1 OR #2
#4	"ciprofol"(Title/Abstract)OR "hsk3486"(Title/ Abstract)
#5	"propofol"(MeSH)
#6	"propofol" (Title/Abstract)OR "disoprofol" (Title/ Abstract)OR "diprivan" (Title/Abstract)OR "disoprivan" (Title/Abstract)OR "fresofol" (Title/ Abstract)OR "ivofol" (Title/Abstract)OR "recofol" (Title/Abstract)OR "aquafol" (Title/ Abstract)
#7	#5 OR #6
#8	#3 AND #4 AND #7

elements in the data extraction tables. The two reviewers will resolve their differences through discussion, and unresolved differences will be solved by arbitrators. In case of missing data or uncertainties, we will attempt to contact the corresponding author of the original report to obtain the missing data or reasons for exclusion of the data.

Data items

The main information that we will collect includes research characteristics (eg, study design, author information, year of publication, number of publications, location and source of funding), population characteristics (eg, sample size, age, sex, body mass index, American Society of Anesthesiologists classification, and history of disease and treatment), intervention details and comparators' characteristics (eg, drugs used, dose, frequency,





Figure 1 Flow diagram of the study selection process. RCTs, randomised controlled trials.

time point of administration and duration of treatment) and results of interest (eg, definitions and criteria for the primary and secondary outcomes, reported time points, and type of questionnaires used to assess physician and patient satisfaction).

If the studies consist of multiple treatment groups, we will combine the groups from the multiple-arm studies. This will avoid the introduction of bias due to multiple statistical comparisons with one control group. Additionally, we will convert and unify the data units extracted from the same indicator prior to merging. For documents that provide data in a chart format, we will first attempt to contact the original authors for the relevant data. If this fails, the Engauge Digitizer software will be used to extract data. Data provided as medians or means±SEs will be converted to means±SDs before entering.¹⁷⁻¹⁹

Outcomes and prioritisation

Primary outcomes

The primary outcomes will be the success rate of gastrointestinal endoscopy and safety endpoints (complication events).

► The success rate of gastrointestinal endoscopy is defined as the completion of the procedure without

the use of alternative anaesthetic drugs or the administration of top-up dosages of the study drugs no more than five times within a 15 min period from the first administration to the completion of gastrointestinal endoscopy.²⁰

• Complication events: These include hypotension q, and similar (defined as intraprocedural systolic blood pressure <90 mm Hg, mean arterial pressure <60 mm Hg or $\geq 20\%$ decrease in the systolic blood pressure or mean arterial pressure from baseline values), bradycardia (heart rate <50 beats/min or $\geq 20\%$ decrease from baseline value), hypoxia (arterial saturation <90%), respiratory depression, apnoea (thoracic motion disappeared for >30 s), body movements, injection pain, and nausea and vomiting. These are the most common adverse events during gastrointestinal endoscopy. In cases where complication events are classified according to severity, we will identify and calculate the total number of patients for all degrees of severity.²¹

Secondary outcomes

Secondary outcomes include the satisfaction and efficacy measures.

- ► Satisfaction includes patient and physician satisfaction. We will follow the criteria established by the authors in each study, even if the content and format of the satisfaction questionnaires differ.
- Efficacy measures include the time to induction, time to sedation, total procedure time, time to waking after ceasing sedation and time to discharge.

Risk of bias individual studies

To facilitate the assessment of the possible risk of bias for each study, methodological quality assessment will be performed independently by two calibrated authors using the Cochrane risk of bias tool 2 (RoB2).¹⁵ RoB2 assesses the following seven possible sources of bias: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessments, completeness of outcome data, selective reporting and other biases (eg, baseline imbalances and conflicts of interest). Each item is scored as low risk, unclear risk or high risk of bias. Disagreements will be resolved by discussion or by consulting a third author for arbitration.

Data synthesis

RevMan software will be used for meta-analysis. We will calculate the mean difference (MD) and 95% CI for continuous data and the risk ratio and 95% CI for dichotomous data. Heterogeneity among the studies will be assessed using the χ^2 test and I^2 statistic. Meta-analysis will be performed using a fixed-effects model when there is insignificant heterogeneity ($I^2 < 50\%$), else it will be performed using a random-effects model. The standardised MD is used as a summary statistic in meta-analysis when all studies assess the same outcome but measure it in different ways (eg, all studies measure satisfaction but use different satisfaction rating scales). Furthermore, sensitivity analysis will be conducted to detect the sources of heterogeneity and evaluate the robustness of the findings. The endoscopic procedure or colonoscopy may require special procedures or longer operating times.²² Therefore, all eligible trials will be divided into the endoscopic therapy group and endoscopic examination group or into the gastroscopy group and colonoscopy group. Subgroup analysis will be performed separately. According to the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions,¹⁵ publication bias will be evaluated using the Stata software for Egger's test or Begg's test when more than 10 publications are included. Two-tailed tests with a significance threshold of p<0.05 will be used for all analyses.

ETHICS AND DISSEMINATION

The protocol for this systematic review and meta-analysis involves no individual patient data; thus, ethical approval is not required. This will be the first meta-analysis to assess the sedation efficacy of ciprofol and provide evidence to clinicians for decision-making. The results will be disseminated through conference presentations and publications in peer-review journals related to this field.

Contributors XQ contributed substantially to the design and conception of the study, registered in the PROSPERO database and drafted the manuscript. XQ developed the search criteria with input from XL and LT. XQ and XL contributed to the design of the statistical methods. XQ and CW coordinated the whole process. CW and JX supervised the protocol development process. All authors (XQ, XL, LT, CW and JX) revised the manuscript critically for important intellectual content, approved the final submission and agreed to be held accountable for all aspects of the work.

Funding This work was supported by the National Natural Science Foundation of China (No. 81760892, 82260973) and Science and Technology Project of Gansu Province (No. 20JR10RA435, 20YF3FA020).

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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