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Original Article

Efficacy and adverse reactions of remimazolam and propofol in patients undergoing gastrointestinal endoscopy: a systematic review and meta-analysis

Rong Wang[1], Weiwei Peng[2], Juncai Li[3], Fan Xiao[4], Xuefen Yuan[5], Salman Khan[6]

[1]School of Medicine and Pharmacy, Hunan Vocational College of Electronic and Technology, Changsha 410200, Hunan, China; [2]School of Medicine and Pharmacy, Hunan Vocational College of Electronic and Technology, Changsha 410200, Hunan, China; [3]Hunan Vocational College of Electronic and Technology, No. 158 Wangwang West Road, Wangcheng District, Changsha 410200, Hunan, China; [4]Department of Thoracic and Cardiovascular Surgery, The First Hospital of Hunan University of Chinese Medicine, Changsha 410007, Hunan, China; [5]Department of Rehabilitation Medicine, Changde Rehabilitation Hospital, Changde 415000, Hunan, China; [6]District Headquarter Teaching Hospital, Gomal Medical College, Dera Ismail Khan, 29111, Pakistan

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Abstract: Background: Gastrointestinal (GI) endoscopy is crucial for detecting suspicious gastric lesions, screening for gastric cancer, and providing early diagnosis. With an aging population, an increasing number of elderly individuals require gastrointestinal endoscopy. Methods: Four databases were searched to acquire controlled clinical trials on the effects of remimazolam and propofol in patients undergoing GI endoscopy. A meticulous evaluation of the literature quality and data was then performed using Stata software. Results: Seventeen studies reported significantly lower respiratory depression in the experimental group compared to the control group (odds ratio: OR 0.28; 95% confidence interval (CI): 0.18-0.45; P<0.01). Injection pain (OR: 0.11; 95% CI: 0.06-0.20; P<0.01), hypotension (OR: 0.41; 95% CI: 0.33-0.52; P<0.01), and hypoxemia (OR: 0.38; 95% CI: 0.22-0.63; P<0.01) were also significantly lower in the experimental group. However, propofol was associated with improved sedation success (OR: 0.99; 95% CI: 0.98-1.00; P=0.048) and longer sedation time (SMD: 24.19; 95% CI: 14.60-33.79; P<0.01). Recovery time showed no significant difference between groups (SMD: -0.27; 95% CI: -1.46-0.92; P=0.657). Conclusion: This study suggests that both remimazolam and propofol are efficacious in patients undergoing gastrointestinal endoscopy. Remimazolam significantly reduces complications such as respiratory depression, injection pain, hypotension, and hypoxemia. However, propofol has advantages in improving sedation success and sedation time. These findings are supported by high-quality randomized controlled trials.

Keywords: Remimazolam, propofol, gastrointestinal endoscopy, meta-analysis

Introduction

Gastrointestinal diseases are common and frequently occurring among the elderly [1]. Gastrointestinal dysfunction is an inevitable phenomenon in the elderly population. Aging leads to reduced digestive enzyme activity and delayed gastric emptying, resulting in impaired digestion and food intolerance in elderly individuals. Digestive enzyme deficiency, gastric emptying disorders, and decreased gastrointestinal motility are common in the elderly and contribute to malnutrition, anemia, and related complications. Gastrointestinal endoscopy is crucial for detecting suspicious gastric lesions, screening for gastric cancer, and providing early diagnosis. With the acceleration of social aging, more and more elderly people need to undergo GI endoscopy. Previously, due to technological limitations, GI endoscopy was often performed while patients remained conscious. Although local anesthesia with lidocaine in the throat can to some extent reduce the throat reflexes during endoscopy, GI endoscopy, as an invasive examination, can cause anxiety, fear, and discomfort in patients. This decreases patient compliance and compromises the quality of the procedure. In addition, GI endoscopy under local anesthesia increases the adverse events risks [2].

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In 2020, remimazolam became the only benzodiazepine-type anesthetic approved for clinical use, which binds to high affinity benzodiazepine γ-aminobutyric acid (GABA) receptors [3], and has many advantages. Compared with midazolam, remimazolam is metabolized through nonspecific cholinesterase, with small individual differences. The metabolites do not have activity [4], and the metabolic rate is fast. Its effect can be fully antagonized and reversed by flumazenil, and there will be no sedation. It is equally effective for anesthesia induction and maintenance compared to propofol, but it causes less intravenous pain and has less hemodynamic effects, including thoes upon blood pressure and heart rate [5]. Under the anesthesia maintenance regimen with routine antagonism of flumazenil, the remimazolam recovery time is faster than the propofol [6]. Compared with volatile anesthetics, the use of remimazolam does not pollute the air in the operating room. Additionally, it does not cause malignant high fever and it also reduces the incidence of malignant high fever.

Currently, propofol is the most commonly used short-acting intravenous anesthetic, activated by the GABA receptor, which inhibits the central nervous system and produces sedative and hypnotic effects [7]. Propofol also has certain immune regulatory effects, but there are still adverse reactions in clinical applications, such as obvious injection pain, significant respiratory and circulatory inhibition, metabolic acidosis, propofol infusion syndrome, etc. [8], and its respiratory and circulatory inhibition is dose-dependent, which is more pronounced in elderly patients with poor cardiovascular regulation ability or patients with cardiovascular diseases. Intraoperative tissue hypoperfusion and hypoxia can increase the risk of cerebrovascular complications [9]. Therefore, in general anesthesia where the surgical time is long and the patient's overall condition is poor, propofol may not be conducive to improving anesthesia recovery and promoting postoperative outcomes. Hence, we directed a meta-analysis to investigate the remimazolam and propofol effects and adverse reactions in patients undergoing GI endoscopy. This study innovatively compared remimazolam and propofol, focusing on their safety and efficacy profiles in elderly patients, a group particularly vulnerable to anesthetic complications.

Materials and methods

Studies selection

Design of the study: Controlled trials assessing the effects of remimazolam and propofol in patients undergoing GI endoscopy. Preclinical trials were exempt.

Participant selection

Patients undergoing gastrointestinal endoscopy.

Intervention types

The experimental group received remimazolam or a combination involving remimazolam, while the control group received propofol or a combination involving propofol for gastrointestinal endoscopy.

Types of results

The efficacy parameters for patients undergoing gastrointestinal endoscopy were as follows. According to the research, the assessment tools for the remimazolam and propofol effects in patients undergoing GI endoscopy were: ① Respiratory depression; ② Injection pain; ③ Hypotension; ④ Hypoxemia; ⑤ Sedation success; ⑥ Sedation time; ⑦ Recovery time. Using any one of the above given scales, the efficacy parameters in the present study were assessed.

Research approaches

A comprehensive literature search was conducted in four major electronic databases: PubMed, EMBASE, Cochrane Library, and Web of Science, covering studies published up to June 2023. The objective was to identify controlled clinical trials comparing the efficacy and safety of remimazolam versus propofol in patients undergoing gastrointestinal endoscopy.

The search strategy combined both Medical Subject Headings (MeSH) and free-text terms, adjusted for each database. The primary keywords and Boolean operators used were: ("remimazolam" OR "remimazolam tosilate" OR "CNS 7056") AND ("propofol") AND ("gastrointestinal endoscopy" OR "gastroscopy" OR "colonoscopy" OR "GI endoscopy" OR "diges-

tive endoscopy") AND ("sedation" OR "anesthesia" OR "procedural sedation").

An example search string used in PubMed was: ("Remimazolam"[Mesh] OR remimazolam[tiab] OR CNS 7056[tiab]) AND ("Propofol"[Mesh] OR propofol[tiab]) AND ("Endoscopy, Digestive System"[Mesh] OR gastrointestinal endoscopy[tiab] OR gastroscopy[tiab] OR colonoscopy[tiab]) AND ("Anesthesia"[Mesh] OR sedation[tiab] OR procedural sedation[tiab]).

In EMBASE, equivalent Emtree terms and syntax were applied. No restrictions were applied on publication status, but only studies published in English were included. Reference lists of retrieved articles were also hand-searched to identify any additional relevant studies.

Duplicates were removed using EndNote software. After initial screening of titles and abstracts, full-text reviews were conducted independently by two reviewers to determine eligibility. Disagreements were resolved by discussion or by consulting a third reviewer.

Data retrieval and qualitative evaluation

Initially, abstracts were screened, followed by full-text assessments to acquire relevant literature. The screening reports were exchanged, unconventional literature was discussed or a consult with a third researcher occurred untill the reports were affirmed. The extracted data contained: fundamental data of the literature, study type, object of the study, size of the sample, and content of the intervention, result indicators, etc.

Statistical analysis

This meta-analysis was conducted using Stata software. (1) Combined effects: All result indicators were continuous variables, and the assessment tools varied across studies. There were variations among counts. The standardized mean difference (SMD) and 95% confidence intervals (CIs) were used as summary statistics as an effective measure. (2) Heterogeneousness test: Chi-square tests were used to determine whether there was heterogeneousness among studies. If $P>0.1$, $I^2<50\%$, the included studies were considered to be more analogous, and we proceed with a fixed-effects model systematic review; if $P<0.1$, $I^2\geq50\%$, heterogeneousness was represented in the included studies, heterogeneousness sources analysis, and if there was no medical heterogeneousness, a random-effects model was employed with meta analyses. Sensitivity analysis was performed by excluding individual studies to assess the robustness of the pooled results and identify potential sources of heterogeneity.

Results

Search results

According to research strategies, 197 references were recognized. Apart from duplicate studies, 61 studies were analyzed depending upon abstract and title. Then, 20 articles were assessed in full text. After full text assessment, 3 records were exempted for the following reasons: Lack of data (n=3). Ultimately, 17 studies [10-26] were added in this meta-analysis (**Table 1**). The PRISMA statement flow chart displayed this process (**Figure 1**).

Respiratory depression

Eight studies reported the respiratory depression of the experimental and the control group. A systematic review demonstrated significantly lower respiratory depression in the experimental group (OR: 0.28; 95% CI: 0.18, 0.45; P<0.01, **Figure 2**) compared to the control. The funnel plot is relatively symmetrical (**Figure 3**). In contrast to the control group, remimazolam in the treatment of patients undergoing gastrointestinal endoscopy decreased the level of respiratory depression. The Begg's Test result (P=0.063) indicates that the findings are stable with no significant publication bias.

Injection pain

Tweleve studies reported the Injection pain of the experimental and the control group. A systematic review revealed that injection pain was significantly lower in the treatment group (OR: 0.11; 95% CI: 0.06, 0.20; P<0.01, **Figure 4**) compared to control group. The funnel plot is relatively symmetrical (**Figure 5**). In contrast to the control group, remimazolam in the treatment of patients undergoing gastrointestinal endoscopy decreased the Injection pain level. The Begg's Test was 0.945, so the research

Table 1. The basic characteristics of the included studies

Study (ref.)	Sample Size (T/C)	Age (years) (T/C)	Male/Female	T	C	Main Outcomes
Zhang, 2023 [10]	131/130	45 (39-50)/44 (37-49)	139/122	RE+Es	P+Es	③, ④
Liu, 2023 [11]	107/109	67.6±5.7/67.5±4.9	102/114	RE	P	③, ④
Ye, 2023 [12]	64/65	68 (66-72)/68 (66-71)	75/54	RE	P	②, ③, ④
Wang, 2023 [13]	83/90	46.37±12.48/49.19±11.39	None	RE	P	①, ②, ③, ⑤, ⑥, ⑦
Wei, 2023 [14]	111/97	44±13/46±13	98/110	RE	P	②, ④, ⑥
Yao, 2022 [15]	66/66	49 (41-56)/48 (39-56)	63/69	RE	P	②, ③, ④
Xin, 2022 [16]	29/27	52.24±9.80/56.00±10.13	36/20	RE+Al	P+Al	②, ③, ④, ⑦
Tan, 2022 [17]	33/33	65.5±5.2/66.2±5.0	43/23	RE	P	③, ④, ⑦
Cao, 2022 [18]	74/74	47.6±5.8/48.5±7.1	87/61	RE	P	①, ③, ⑥
Wang, 2022 [19]	357/119	44.3 (33.0-54.0)/46.4 (37.5-56.0)	210/266	RE	P	②, ③, ④
Shi, 2022 [20]	81/80	42.03±10.51/45.45±11.75	78/83	RE+Al	P+Al	①, ②, ③, ④, ⑤
Lu, 2022 [21]	200/200	70.6±4.7/70.1±4.5	161/239	RE	P	①, ②, ③, ④, ⑦
Guo, 2022 [22]	39/38	70.4±3.9/69.1±4.0	47/30	RE	P	①, ②, ⑤, ⑦
Xu, 2022 [23]	457/457	52.69±13.12/52.56±12.69	420/494	RE+Al	P+Al	①, ②, ③
Hu, 2022 [24]	173/173	70.11±7.37/69.92±7.57	141/205	RE	P	①, ②, ③, ④, ⑤, ⑦
Chen (1), 2020 [25]	189/189	40.78±11.10/41.69±10.48	147/230	RE	P	①, ②, ③, ⑤, ⑥
Chen (2), 2020 [26]	194/190	44.47±11.67/44.43±11.37	161/223	RE	P	①, ②, ③, ④

T: trial group; C: control group; RE: remimazolam; P: propofol; Es: esketamine; Al: alfentanil; ① Respiratory depression; ② Injection pain; ③ Hypotension; ④ Hypoxemia; ⑤ Sedation success; ⑥ Sedation time; ⑦ Recovery time.

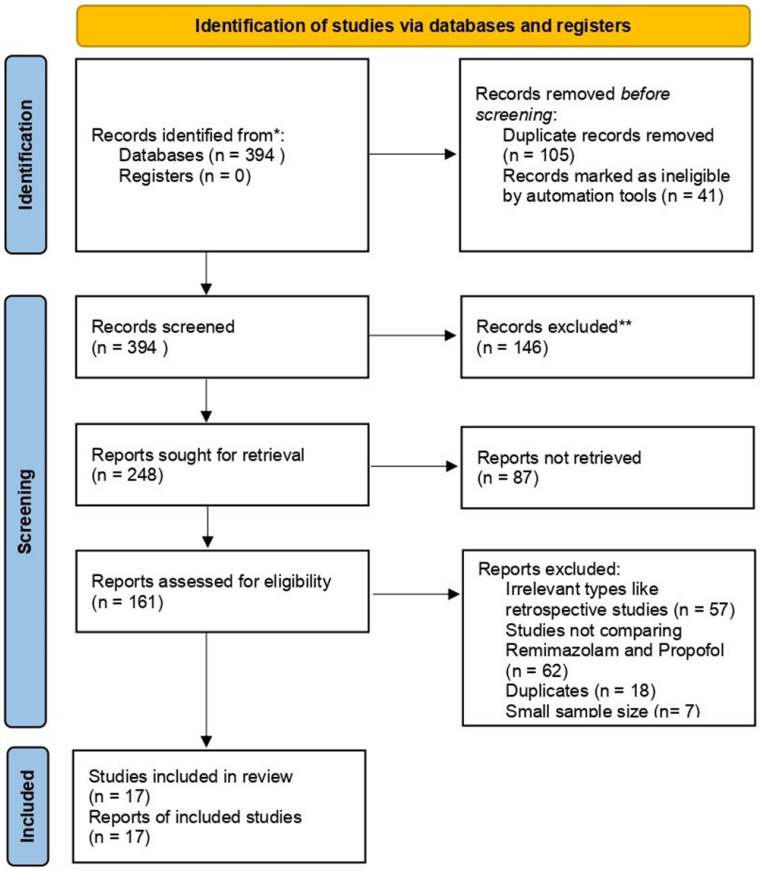

Figure 1. Flow Chart of Meta-analysis.

results are relatively constant and there is no obvious file drawer effect.

Hypotension

Fifteen studies reported the hypotension of the experimental and the control group. A systematic review revealed that hypotension in the experimental group was significantly lower (OR: 0.41; 95% CI: 0.33, 0.52; P<0.01, **Figure 6**) compared to control group. In contrast to the control group, remimazolam in the treatment of patients undergoing gastrointestinal endoscopy decreased the level of hypotension. The Begg's Test was 0.235, so the research results are relatively constant and there is no obvious file drawer effect.

Hypoxemia

Eleven studies reported the hypoxemia of the experimental and the control group. A systematic review revealed that hypoxemia of the experimental group was significantly lower (OR: 0.38; 95% CI: 0.22, 0.63; P<0.01, **Figure 7**) compared to control group. In contrast to the control group, remimazolam in the treatment of patients undergoing gastrointestinal endoscopy decreased the level of hypoxemia. The Begg's Test was 0.087, so the research results are relatively constant and there is no file drawer effect.

Sedation success

Five studies reported the sedation success of the experimental and the control group. A systematic review revealed that sedation success in the experimental group was slightly lower (OR: 0.99; 95% CI: 0.98, 1.00; P=0.048, **Figure 8**) compared to control group. In contrast to the control group, remimazolam in the treatment of patients undergoing gastrointestinal endoscopy did not increase the level of sedation success. The Begg's Test was 0.806, so the research results are relatively constant and there is no file drawer effect.

Sedation time

Four studies reported the sedation time of the experimental and the control group. A systematic review revealed that the sedation time of the experimental group was remarkably greater (SMD: 24.19; 95% CI: 14.60, 33.79; P<0.01, **Figure 9**) in contrast to control group. In contrast with control group, remimazolam in the treatment of patients undergoing gastrointestinal endoscopy prolonged sedation time. The Begg's Test was 1.000, so the research results are relatively constant and there is no file drawer effect.

Recovery time

Six studies described the recovery time of the experimental and the control group. A system-

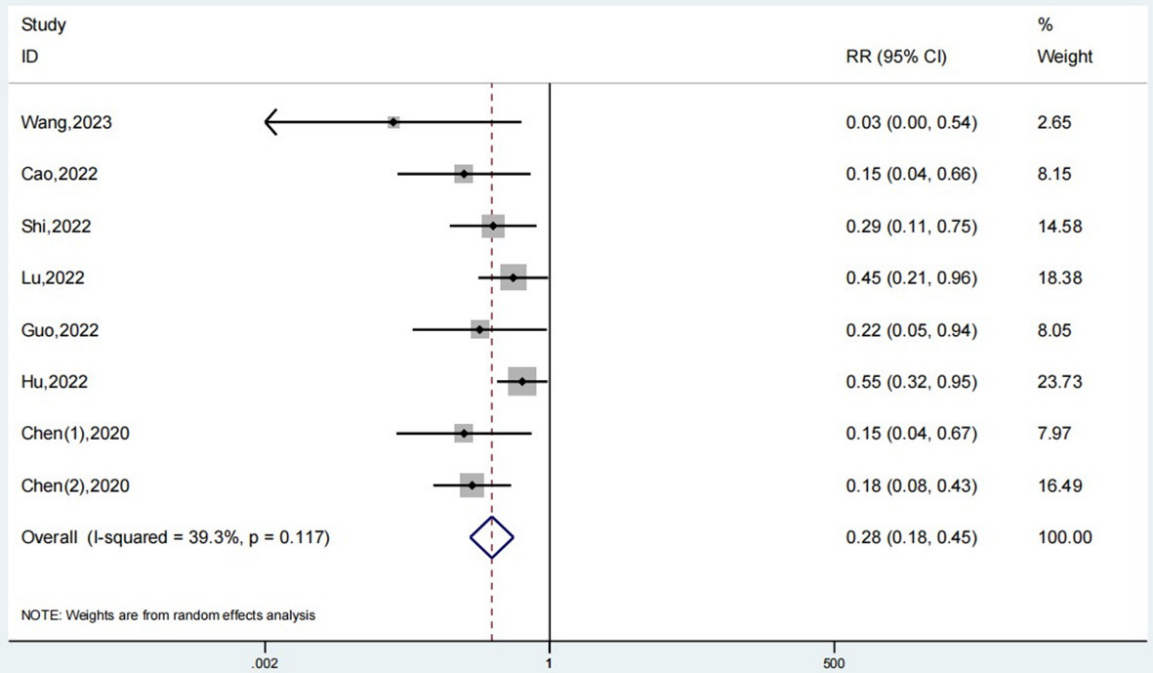

Figure 2. Forest plot illustrating respiratory depression.

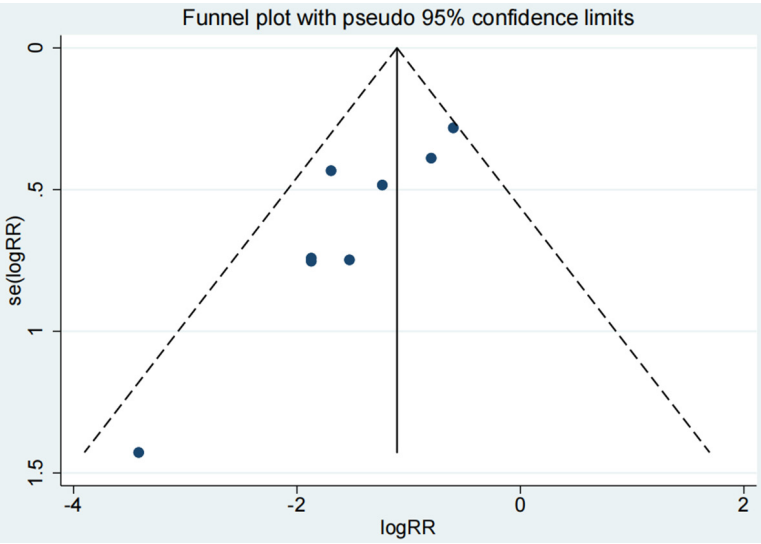

Figure 3. Funnel plot illustrating respiratory depression.

atic review revealed that recovery time did not differ significantly (SMD: -0.27; 95% CI: -1.46, 0.92; P=0.657, **Figure 10**) compared to control group. In contrast to control group, remimazolam in the treatment of patients undergoing gastrointestinal endoscopy did not increase the level of recovery time. The Begg's Test was 0.452, so the research results are relatively constant and there is no file drawer effect.

Literature quality evaluation

The quality of the 17 included studies was assessed using Cochrane Risk of Bias Tool. Of these, 10 studies were rated as high-quality (low risk of bias), while 7 had moderate risk due to issues like unclear randomization methods or incomplete outcome data. No studies were excluded based on quality (**Table 2**). The overall quality supports the reliability of the findings.

Publication bias

Publication bias was assessed using Funnel plots and Begg's tests.

Respiratory depression: Symmetrical Funnel plot with no bias (*P*=0.063; **Figure 3**).

Injection pain: No bias detected (*P*=0.945; **Figure 5**).

Hypotension: Symmetrical Funnel plot (*P*= 0.235).

Hypoxemia: No significant bias (*P*=0.087).

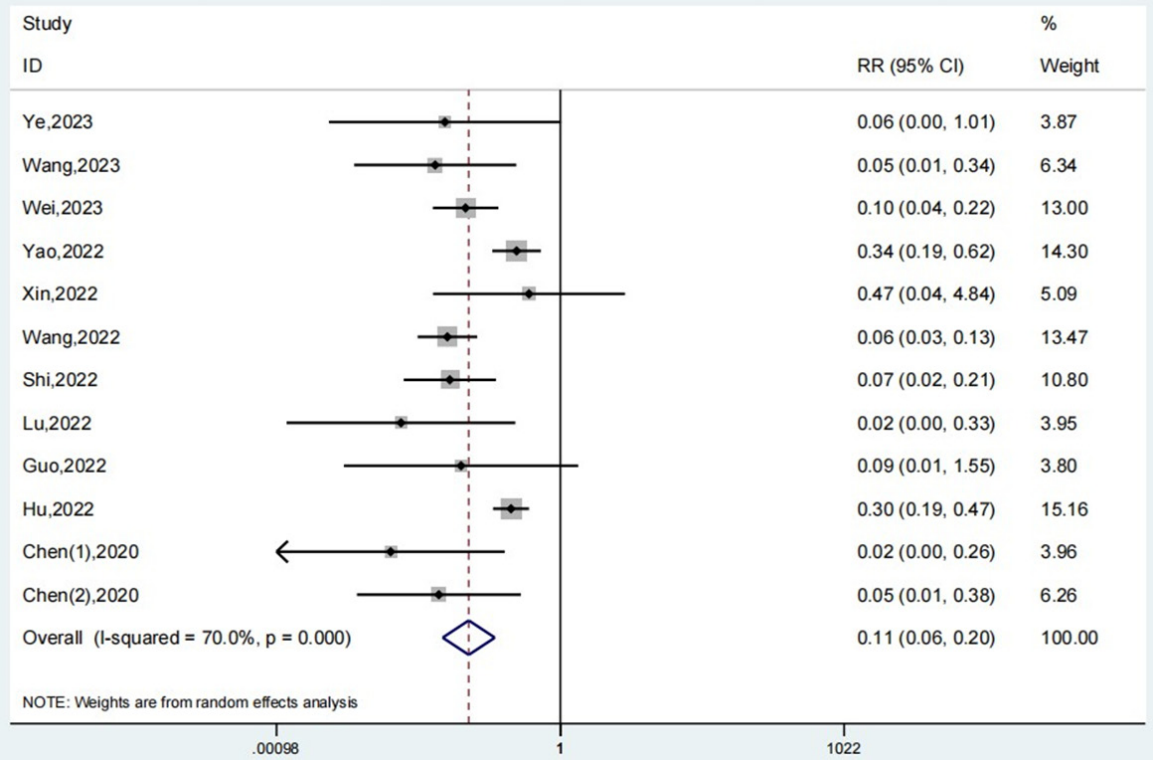

Figure 4. Forest illustration of the injection pain.

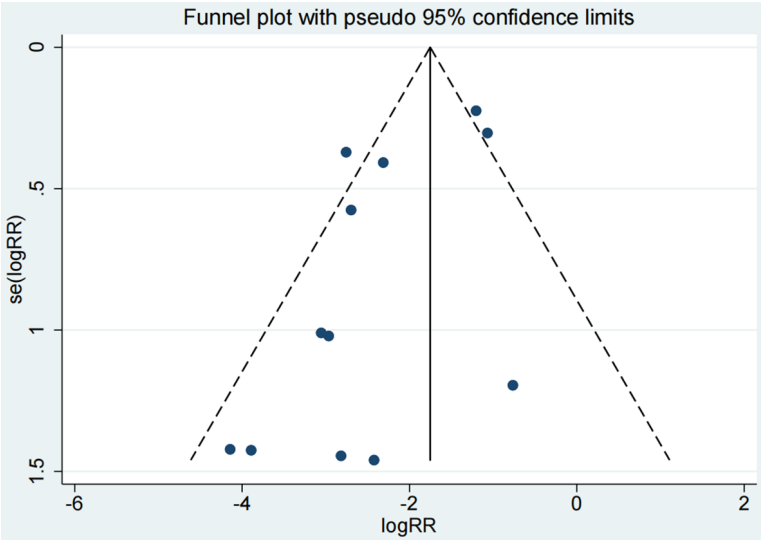

Figure 5. Funnel plot of the injection pain.

Discussion

This study provides a direct comparison of remimazolam and propofol, highlighting their differential impact on safety and efficacy in elderly patients undergoing GI endoscopy. The findings supported tailored anesthetic approaches to minimize complications in this high-risk population.

An alkyl phenol intravenous anesthetic (short-acting), propofol has an onset of time about 0.5-1 minutes and a maintenance time of about 5-10 minutes. Propofol is known for its rapid distribution and elimination, making it widely used in short-duration procedures such as painless gastroscopy. However, due to the lack of analgesic properties, large doses are often required when used alone. Higher propofol doses are associated with increased risks of cardiovascular suppression, respiratory depression, injection site pain, and delayed awakening [27, 28]. Opioid drug effects are synergistic to propofol effects, improving the effect of anesthetic while also decreasing drugs dosages.

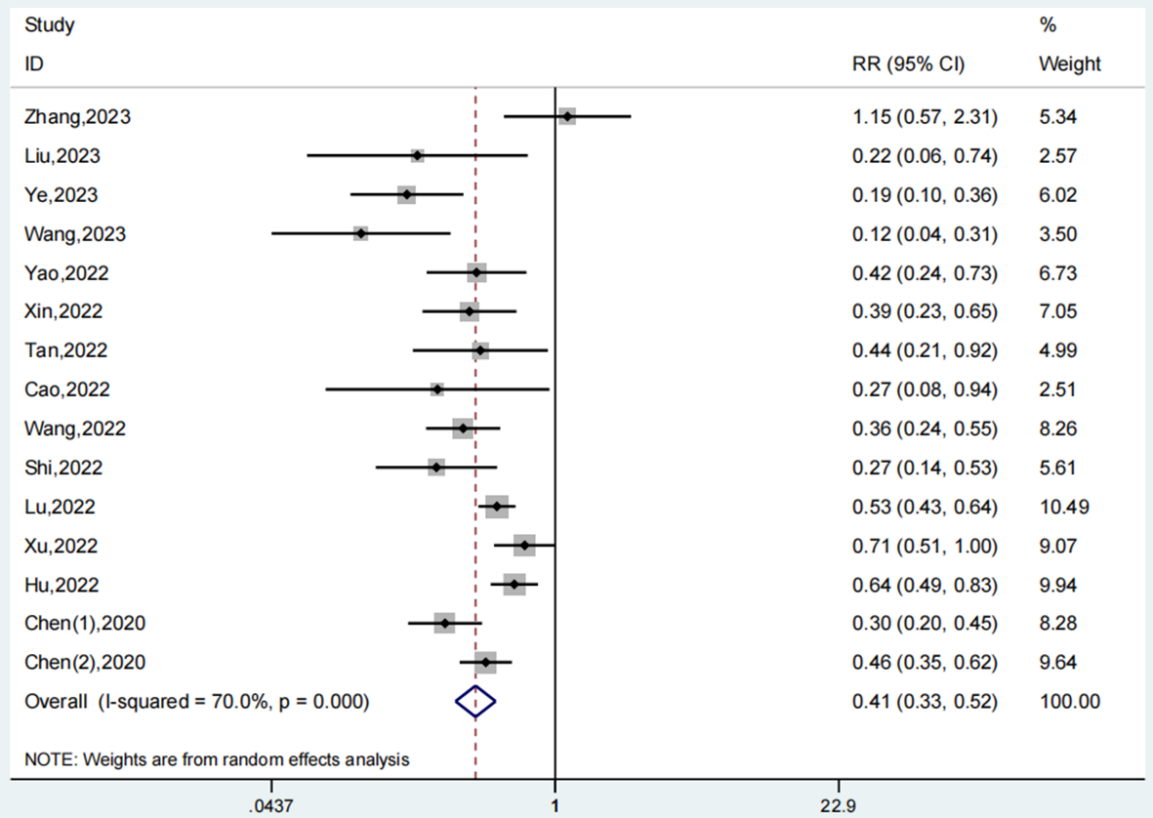

Figure 6. Forest illustration of the hypotension.

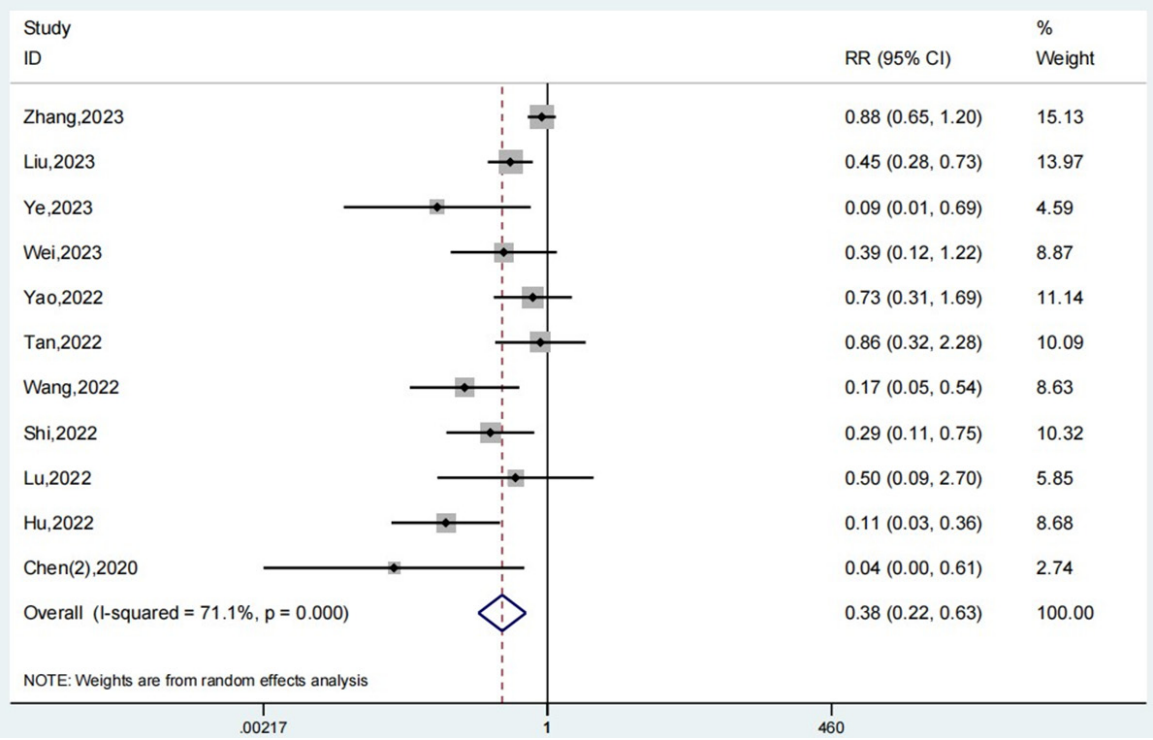

Figure 7. Forest illustration of the hypoxemia.

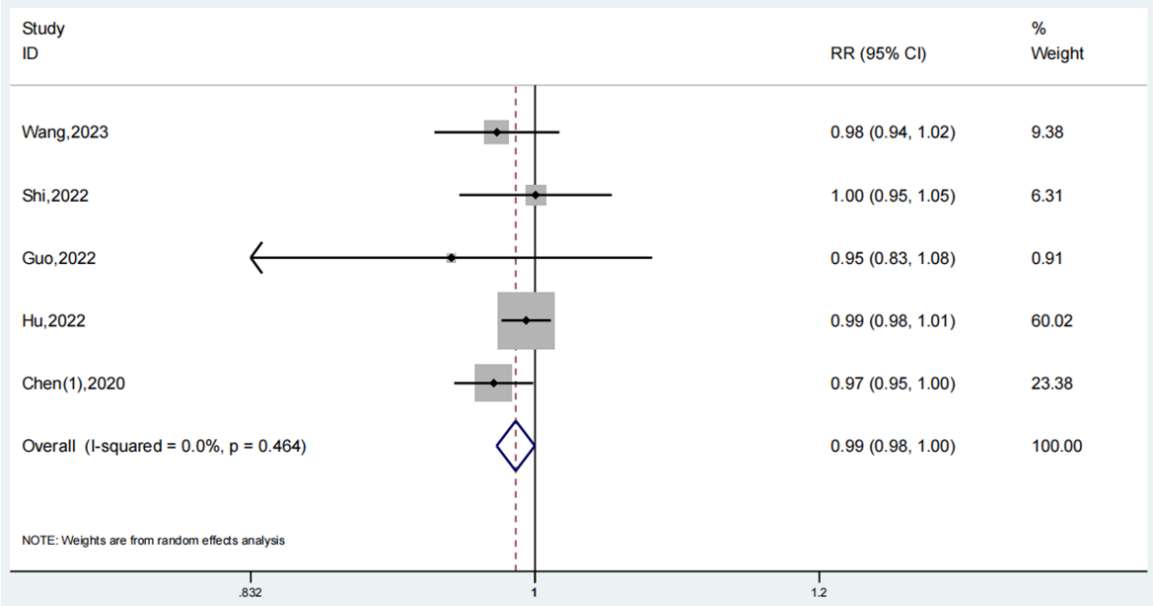

Figure 8. Forest illustration of the sedation success.

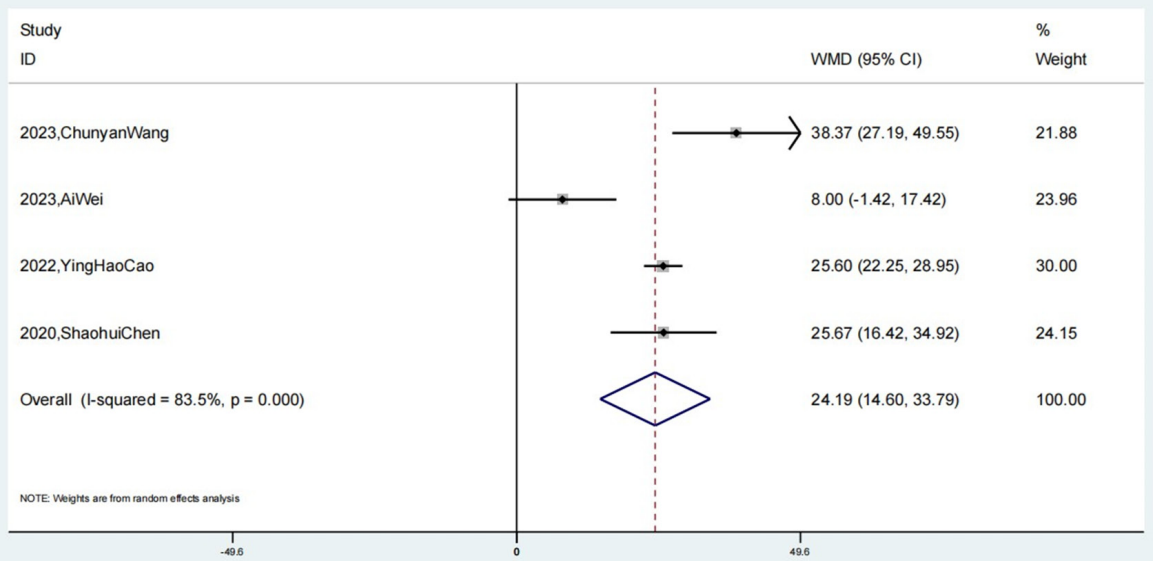

Figure 9. Forest illustration of the sedation time.

Correspondingly, the adverse effects of drugs are minimized, and combination use has many benefits [29, 30]. Although these opioid drugs have significantly improved the quality of anesthesia, there are still certain shortcomings. Painless gastroscopy has a large surgical volume, short duration, strong stimulation, no airway protection during anesthesia, and high risk. Further research is needed to optimize anesthesia effectiveness, safety, and strategies for faster postoperative recovery.

Remimazolam has a short half-life in body tissues. It can quickly degrade into inactive metabolites. It has characteristics such as fast onset of effect, no impact on the body after long-term use, and less cardiorespiratory inhibition, and it can be reversed by flumazenil [31]. Compared to another similar drug midazolam, its sedation depth is dose-dependent and can achieve the required anesthesia depth for surgery. Compared with propofol, remimazolam has significant advantages in maintaining

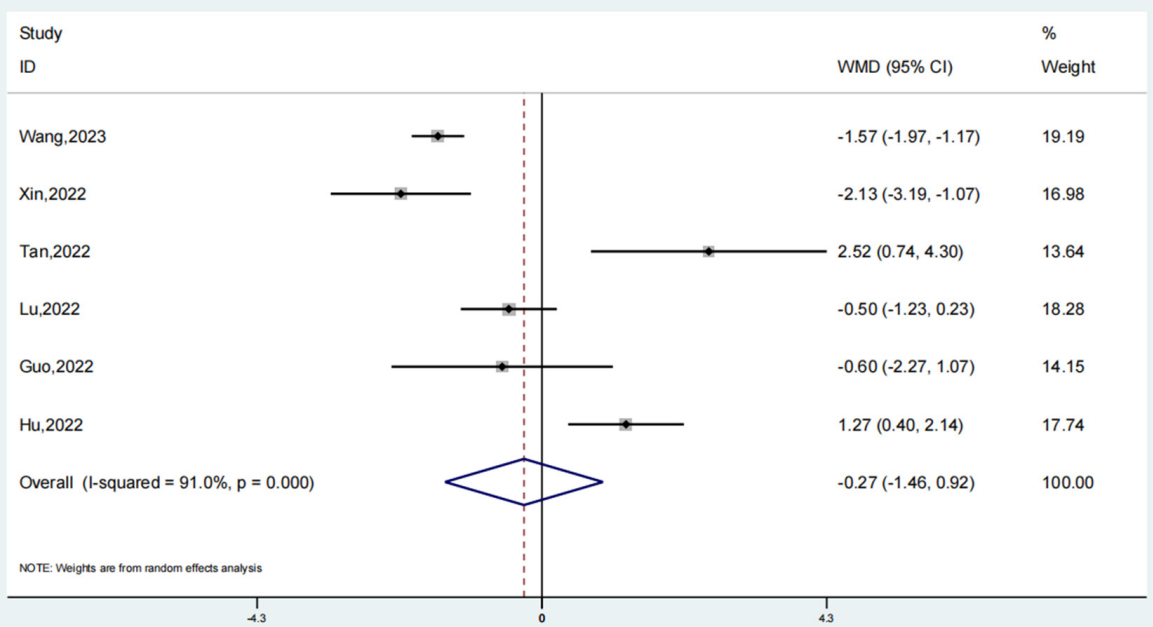

Figure 10. Forest illustration of the recovery time.

Table 2. Risk of bias assessment for included studies based on randomization, allocation concealment, blinding, and outcome completeness

Study	Randomization	Allocation Concealment	Blinding	Incomplete Outcome Data	Risk of Bias
Zhang, 2023 [10]	Low	Low	High	Low	Moderate
Liu, 2023 [11]	Low	Low	Low	Low	Low
Ye, 2023 [12]	Low	Low	Moderate	Low	Moderate
Wang, 2023 [13]	Low	Moderate	High	Moderate	Moderate
Wei, 2023 [14]	Low	Low	Moderate	Low	Moderate
Yao, 2022 [15]	Low	Low	Low	Low	Low
Xin, 2022 [16]	Low	Low	Moderate	Low	Moderate
Tan, 2022 [17]	Low	Moderate	High	Low	Moderate
Cao, 2022 [18]	Low	Low	Low	Low	Low

hemodynamic stability and reducing respiratory suppression events, which is closer to an ideal sedative drug and can meet the anesthesia needs of a large number of medical patients. Further research is needed to optimize remimazolam's anesthesia maintenance dosage and investigate its effects on inflammatory markers, oxidative stress, and immune response [32, 33].

Remimazolam is mostly administered intravenously, with the advantage of fast onset and recovery, as well as low susceptibility to injection pain. In clinical practice, it is recommended to configure remimazolam at 1 mg/ml, making it easy to administer with a syringe and injection pump, with a recommend initial dose of 12 mg/kg/h for inductive general anesthesia, and subsequently 1 mg/kg/h for maintenance of anesthesia. Taking into account the patient's age, general physical condition, and surgical needs, the drug infusion rate should be adjusted to maintain an appropriate depth of anesthesia, However, it is not recommended that the infusion rate exceed 2 mg/kg/h [34].

Overall 17 studies were included in the present research, consisting of 2,388 patients in the experimental group and 2,137 patients in the control group. A systematic review revealed

that patients undergoing GI endoscopy who received remimazolam had lower level of respiratory depression than the control group. The meta-analysis demonstrated a significant reduction in respiratory depression in the experimental group (OR: 0.28; 95% CI: 0.18, 0.45; P<0.01). In contrast to the control group, meta-analysis revealed that Injection pain in the experimental group was remarkably less (OR: 0.11; 95% CI: 0.06, 0.20; P<0.01). Meta-analysis revealed that the hypotension of experimental group was remarkably less than in the control group (OR: 0.41; 95% CI: 0.33, 0.52; P<0.01). In contrast to control group, meta-analysis revealed that hypoxemia of the experimental group was remarkably less (OR: 0.38; 95% CI: 0.22, 0.63; P<0.01).

The meta-analysis showed a slightly lower sedation success rate in the experimental group (OR: 0.99; 95% CI: 0.98-1.00; P=0.048). Meta-analysis revealed that sedation time of the experimental group was remarkably greater (SMD: 24.19; 95% CI: 14.60, 33.79). Meta-analysis revealed that the recovery time of the experimental group was not statistically significant compared to the control group (SMD: -0.27; 95% CI: -1.46, 0.92; P=0.657).

The findings of this study align with prior research highlighting remimazolam's advantages in maintaining hemodynamic stability and reducing respiratory depression during sedation. For instance, Doi et al. (2020) demonstrated that remimazolam had a significantly lower incidence of hypotension and hypoxemia compared to propofol, consistent with the present results showing reduced odds of these complications (OR: 0.41 and OR: 0.38, respectively) [6]. Similarly, Wang et al. (2023) noted reduced injection pain with remimazolam, which corresponds with the significant reduction observed in this meta-analysis (OR: 0.11; *P*<0.01) [13].

Sensitivity analyses confirmed the robustness of our findings, as no single study significantly impacted the pooled estimates. Subgroup analyses suggested that differences in procedural settings and patient demographics might contribute to observed heterogeneity.

Limitations

This study only included English-language literature, which may introduce selection bias and limit comprehensiveness. Therefore, more comphrensive Meta-analysis should be the objective.

Conclusion

This study confirms that both remimazolam and propofol are effective for sedation in GI endoscopy. Remimazolam significantly reduces complications such as respiratory depression, injection pain, hypotension, and hypoxemia. However, propofol offers advantages in sedation success and duration. These findings are supported by high-quality randomized controlled trials included in this meta-analysis.

Disclosure of conflict of interest

None.

Address correspondence to: Rong Wang, School of Medicine and Pharmacy, Hunan Vocational College of Electronic and Technology, Changsha 410200, Hunan, China. E-mail: zonghuaipan9@hotmail.com; Juncai Li, Hunan Vocational College of Electronic and Technology, No. 158 Wangwang West Road, Wangcheng District, Changsha 410200, Hunan, China. E-mail: 18570363999@163.com; Salman Khan, District Headquarter Teaching Hospital, Gomal Medical College, Dera Ismail Khan 29111, Pakistan. E-mail: salmankhn663@gmail.com

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