Systematic Review and/or Meta-analysis

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The safety and efficacy between remimazolam and propofol in intravenous anesthesia of endoscopy operation: a systematic review and meta-analysis

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Background: Propofol is the most widely used intravenous anesthetic in endoscopic surgery, but is associated with several adverse reactions. Public research has shown that remimazolam, a safe general anesthetic, is increasingly being used as a substitute for propofol in clinical operations. Our meta-analysis aimed to analyze whether the adverse reaction rate of remimazolam in endoscopic surgery is acceptable and whether the surgical success rate is not lower than that of propofol.

Aim: This meta-analysis examined the adverse events and efficacy of remimazolam vs. propofol during endoscopic surgery.

Method: MEDLINE, Embase, ClinicalTrials.gov, and Google Scholar were comprehensively searched. Seven studies comparing remimazolam and propofol were included in our meta-analysis. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and Cochrane manual were used to assess the quality of the results published in all included studies to ensure that our meta-analysis results are reliable and worthwhile.

Results: Compared to propofol, the use of remimazolam reduced postoperative injection pain [relative risk (RR) = 0.06, 95% confidence interval (CI): 0.03–0.12, $P < 0.00001$], postoperative hypotension (RR = 0.45, 95% CI: 0.28–0.73, $P = 0.001$), and postoperative respiratory depression (RR = 0.20, 95% CI: 0.08–0.47, $P = 0.0002$); however, it also slightly reduced the success rate of the operation [risk difference (RD) = −0.02, 95% CI: −0.04 to −0.01, $P = 0.0007$]. There were no significant differences in the occurrence of bradycardia symptoms after the operation (RD = −0.01, 95% CI: −0.03 to 0.01, $P = 0.35$), recovery time after the operation [standardized mean difference (SMD) = 0.68, 95% CI: −0.43 to 1.80, $P = 0.23$] or discharge time (SMD = 0.17, 95% CI: −0.58 to 0.23, $P = 0.41$). We also performed a subgroup analysis of each corresponding outcome.

Conclusion: Our analysis showed that remimazolam may be a safer shock option than propofol for endoscopic surgery. However, further research is required to determine their utility.

Keywords: adverse events, anesthesia, endoscopy, propofol, remimazolam, sedation

Introduction

Endoscopic surgery under sedation is the current standard[1]. This is because, during endoscopy, patients may be less cooperative due to anxiety, pain, fear, and gastrointestinal reactions, which may even induce adverse cardiovascular events[2]. Endoscopic surgery under sedation has become the preferred choice for an increasing number of patients.

The most common endoscopic procedures include noninvasive ones such as upper gastrointestinal (GI) endoscopy, colonoscopy, and hysteroscopy. The incidence of GI disorders increases with age, and many of these conditions require GI endoscopy and colonoscopy for detection and treatment[3]. Hysteroscopy is performed to enter and observe the uterine cavity through the cervix with an elongated inspection tube. It is used not only to examine the condition of the uterine cavity but also for minimally invasive diagnosis and surgical management of cervical and

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intrauterine pathology. Direct visualization of the uterine cavity allows direct biopsy and prevents missing organic lesions[4]. For some people, GI endoscopy and hysteroscopy under general anesthesia are more appropriate.

Therefore, various sedatives such as benzodiazepines, opioids (pethidine and fentanyl), propofol, ketamine, and haloperidol are used during endoscopy[5]. Propofol is a phenolic derivative with the properties of γ-aminobutyric acid (GABA) receptor-mediated sedative and hypnotic effects. Owing to its rapid onset and short half-life, propofol has become the first choice of the European Society of Gastrointestinal Endoscopy for performing endoscopies, and there are many reports on its safety when used by gastroenterologists rather than by anesthesiologists[6]. In Australia, anesthesiologists performing sedation for endoscopy favored propofol-based deep sedation[7]. In China, propofol is the most popular sedative used by anesthesiologists and endoscopists during endoscopic procedures[8]. Not only does propofol have the widespread side effects of injection pain, but respiratory and circulatory depression is not uncommon. This also increases the incidence of unexpected risks of intraoperative and postoperative hypoxemia, hypotension, and cardiac arrest in patients sedated with propofol during endoscopic procedures[9]. We found that the clinical application of remimazolam has gradually become popular.

Benzodiazepines enhance the neuroinhibitory effects mediated by GABA[10]. The main effects of benzodiazepines are sedation, hypnosis, anxiety reduction, paracrine amnesia, centrally mediated muscle relaxation, and anticonvulsant activity[11]. Currently, most benzodiazepines are used as adjuncts to sedatives and general anesthetics rather than as primary inducers. However, some benzodiazepines still have important advantages when used as intravenous inducers or sedatives[12]. Remimazolam is a new short-acting benzodiazepine in the final stage of clinical development and is believed to have sedative/anesthetic effects by promoting GABA binding to GABA receptors through the benzodiazepine-binding site of the receptor[13,14]. Remimazolam was first used in Japan and has since been used under supervision in other countries[15].

Currently, remimazolam is gradually becoming the mainstream anesthetic used for sedation in endoscopic surgery. Remimazolam was shown to be efficacious in three phase III trials in patients requiring endoscopy[16]. Although some conclusions have been drawn[17,18], we conducted a rare meta-analysis to evaluate the sedative effects of remimazolam vs. propofol in endoscopic surgery. Our main objective was to determine the risk of adverse reactions of remimazolam compared with propofol through randomized controlled trials (RCTs) and to further explore the sedative effects of both.

HIGHLIGHTS

- The use of remimazolam reduces adverse reactions after endoscopic surgery.
- The probability of remimazolam and propofol causing bradycardia is similar.
- In endoscopic surgery, the use of remimazolam is safer than propofol.
- Remimazolam and propofol have similar surgical success rates and discharge times.
- When clinical doctors perform endoscopic surgery, they can prioritize remimazolam.

Methods

Search strategy

This meta-analysis followed the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement, an updated guideline for reporting systematic reviews[19], and A MeaSurement Tool to Assess systematic Reviews (AMSTAR) 2 guidelines[20]. Ethical approval was not required because this was a meta-analysis of previously published literature. All studies in the literature were identified from different electronic-based searches, including MEDLINE, Embase, ClinicalTrials.gov, and Google Scholar. The final search or review was performed on 30 September 2022. The following keywords, together with grid terms and their combinations, were used to maximize the search accuracy: 'remimazolam, propofol, endoscopy, hysteroscopy, gastrointestinal endoscopy, and colonoscopy'. The search keywords used were MeSH (Medical Subject Headings) terms (remimazolam and propofol) AND (endoscopy, hysteroscopy, gastrointestinal endoscopy or colonoscopy). This study included only human randomized controlled trials (RCTs). A PRISMA flowchart is shown in Figure 1.

Inclusion and exclusion criteria

Participants/population

The inclusion criteria were as follows: (a) patients aged 18–95 years, (b) patients with a body mass index (BMI) within 18–30 kg/m^2, (c) patients who underwent endoscopic surgery in outpatient operating rooms, (d) patients with an American

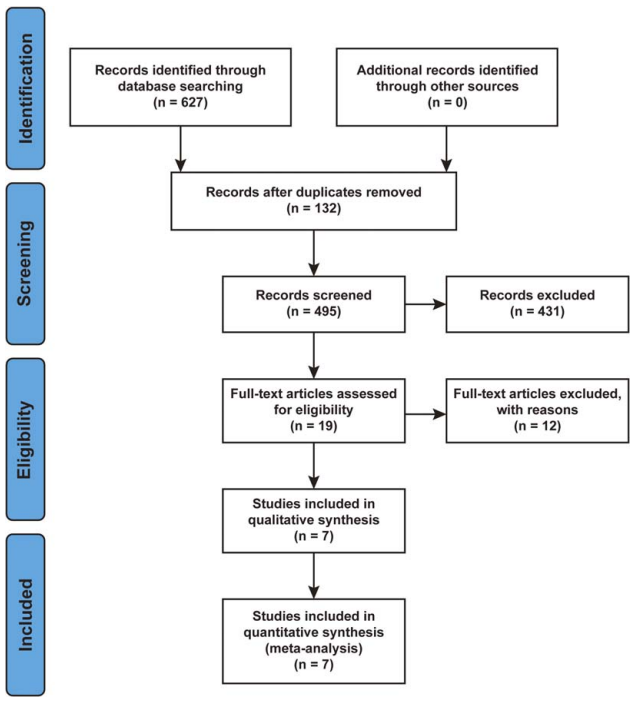

Figure 1. The selection of literature for the included studies. (*From*: Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol. 2009 Oct;62(10):1006–12. doi: 10.1016/j.jclinepi.2009.06.005. Epub 2009 Jul 23. PMID: 19631508.)

Table 1

The characteristics of included studies.

Clinical trials	Age (years)	Sex (M/F)	ASA (I/II)	BMI (kg/m^2)	Number of patients	Dose of opioids (μg/kg)
Chen *et al.*,[26]						
Remimazolam	40.78 ± 11.10	78/111	161/28	23.00 ± 3.05	189	0.5
Propofol	41.69 ± 10.48	69/120	155/34	23.15 ± 2.88	189	0.5
Dai *et al.*,[27]						
Remimazolam (0. 2mg/kg)	53.4 ± 14.6	29/17	16/30	25.3 ± 3.5	46	0.3–0.5
Remimazolam (0.3 mg/kg)	47.9 ± 13.6	31/20	21/30	24.8 ± 3.7	51	0.3–0.5
Remimazolam (0.4 mg/kg)	46.9 ± 12.7	26/18	14/30	23.4 ± 1.9	44	0.3–0.5
Propofol	52.0 ± 13.7	26/22	15/33	24.6 ± 3.7	48	0.3–0.5
Liu *et al.*,[29]						
Remimazolam	68.87 ± 2.58	54/61	37/78	25.35 ± 2.07	111	0.5 (+0.5)
Propofol	69.12 ± 2.75	58/59	46/71	24.75 ± 2.16	117	0.5 (+0.5)
Tan *et al.*,[30]						
Remimazolam (0.1 mg/kg)	66.4 ± 4.8	19/14	18/15	22.7 ± 3.0	33	0.01
Remimazolam (0.2 mg/kg)	65.5 ± 5.2	22/11	24/9	23.4 ± 3.9	33	0.01
Propofol	66.2 ± 5.0	21/12	18/15	23.2 ± 3.0	33	0.01
Xiaoqiang Zhang *et al.*,[32]						
Remimazolam	43.8 ± 8.0	–	28/13	24.7 ± 2.7	41	1.5 ± 0.5 ng/ml
Propofol	45.2 ± 7.0	–	34/7	24.1 ± 2.8	41	1.5 ± 0.5 ng/ml
Shuoya Zhang *et al.*,[31]						
Remimazolam (0.48 mg/kg/h)	32.60 ± 5.06	–	–	23.58 ± 3.48	30	0.1
Remimazolam (0.6 mg/kg/h)	31.13 ± 3.95	–	–	22.50 ± 2.64	30	0.1
Propofol	32.70 ± 5.25	–	–	23.70 ± 2.73	30	0.1
Guo *et al.*,[28]						
Remimazolam	70.4 ± 3.9	25/14	7/32	23.0 ± 3.0	39	5 (+2)
Propofol	69.1 ± 4.0	22/16	7/31	23.0 ± 3.4	38	5 (+2)

ASA, American Society of Anesthesiologists Score; BMI, body mass index, weight/height^2.

Society of Anesthesiologists (ASA-PS) score of Grade I or II, and (e) patients who provided signed informed consent.

The exclusion criteria were as follows: (a) patients with respiratory or cardiac dysfunction, (b) patients with abnormal routine blood or biochemical tests before endoscopy, (c) patients hospitalized after endoscopic surgery, (d) patients who took benzodiazepines or opioids every day within 1 month or intermittently within the past 3 months, and (e) patients with allergies or contraindications to benzodiazepines, opioids, propofol, flumazenil, or naloxone.

Interventions and exposures

The inclusion criterion was endoscopic surgery using remimazolam or propofol for sedation.

Types of studies included

The inclusion criteria were as follows: (a) RCT for clinical trials must have been published, (b) the follow-up rate of the study was at least 80% and there was at least one primary outcome, (c) the study had a complete treatment outcome, (d) the study reported at least one of the following: the amount of remimazolam or propofol administered during the surgery, incidence of adverse reactions, or the success rate of the surgery.

The exclusion criteria were as follows: Review articles, animal studies, case studies that were not relevant to the question, and non-extractable were excluded.

The authors independently evaluated all eligible literature and resolved any differences between them through discussion with the co-first author. The risk of bias was assessed using the Cochrane Collaboration tool, and the quality of the RCTs was assessed using funnel plots[21].

Data extraction

The following data were extracted and analyzed: the name of the first author, the year of publication, number of patients, success rate of surgery, time to full alertness or discharge, and adverse reactions. The following data were extracted but not analyzed: patient age and sex, anesthesia classification (ASA), BMI, and dosage of opioids. We only analyzed and integrated the data in RCT and did not analyze the missing research data. The author independently extracted the data of all eligible studies and resolved any differences between them through discussion with the co-first author; if no consensus was reached, the second author, as the defender, made the final decision.

Statistical analysis

Pooled data were analyzed using Revman 5.4 (Cochran Cooperation Nordic Cochran Center, Copenhagen, Denmark). After the chi-square (χ^2) test, heterogeneity was assessed with I^2 and P values; $I^2 < 50\%$ and $P = 0.1$ were considered to have no substantial heterogeneity[22]. When there was a high degree of heterogeneity, we used the random effects model analysis; otherwise, we used the fixed effects model for analysis[23,24]. For continuous variables, the standardized mean difference (SMD) and 95% confidence interval (CI) were used to represent the results[25]. Relative risk (RR), risk difference (RD), and 95% CI were calculated for dichotomous variables.

Table 2

Significant features of each group.

Groups	Number of patients	Adverse reactions				Number of operations completed	Time for fully alert (min)	Time for discharge (min)
		Injection pain	Hypotension	Respiratory depression	Bradycardia			
Chen *et al.*,[26]								
Remimazolam	189	0	24	2	0	184	NM	NM
Propofol	189	31	81	13	0	189	NM	NM
Dai *et al.*,[27]								
Remimazolam (0.2 mg/kg)	46	0	6	NM	NM	41	NM	NM
Remimazolam (0.3 mg/kg)	51	0	12	NM	NM	48	NM	NM
Remimazolam (0.4 mg/kg)	44	0	15	NM	NM	44	NM	NM
Propofol	48	12	21	NM	NM	48	NM	NM
Liu *et al.*,[29]								
Remimazolam	115	4	15	0	6	111	3 (2–4)[a]	13.92 ± 1.57
Propofol	117	15	12	0	9	117	4 (3–4)[a]	14.57 ± 1.64
Tan *et al.*,[30]								
Remimazolam (0.1 mg/kg)	33	NM	1	NM	NM	NM	3.82 ± 2.49	NM
Remimazolam (0.2 mg/kg)	33	NM	7	NM	NM	NM	6.85 ± 4.29	NM
Propofol	33	NM	16	NM	NM	NM	4.33 ± 2.97	NM
Xiaoqiang Zhang *et al.*,[32]								
Remimazolam	41	1	1	NM	0	41	199.0 ± 76.9 (s)	5.44 ± 1.0
Propofol	41	33	5	NM	1	41	59.7 ± 1.2 (s)	6.3 ± 1.9
Shuoya Zhang *et al.*,[31]								
Remimazolam (0.48 mg/kg/h)	30	0	NM	1	NM	30	NM	28.67 ± 3.37
Remimazolam (0.6 mg/kg/h)	30	0	NM	1	NM	30	NM	26.33 ± 3.73
Propofol	30	7	NM	4	NM	30	NM	26.67 ± 4.77
Guo *et al.*,[28]								
Remimazolam	39	0	NM	2	NM	35	12.3 ± 3.2	NM
Propofol	38	5	NM	9	NM	36	12.9 ± 4.2	NM

NM, not mentioned.
[a]Median (data range).

Results

Literature search

Through an electronic-based search, a total of 627 potential articles were identified, including 132 duplicate articles. After the initial screening, 489 unrelated articles were excluded, and the remaining seven RCTs met the selection criteria[26–32]. A total of 1147 patients were included, and the study period was between 2017 and 2022. Among them, in three trials, the experimenters conducted a grouping study on the dose of remimazolam[27,30,31], whereas the other four trials were not grouped[26,28,29,32]. In all the pooled literatures, 'Dai 2020 (0.2 mg/kg)', 'Dai 2020 (0.3 mg/kg)', and 'Dai 2020 (0.4 mg/kg)' were the same trial; therefore, we divided this trial into three different dose comparisons (0.2 mg/kg remimazolam vs. propofol, 0.3 mg/kg remimazolam vs. propofol, and 0.4 mg/kg remimazolam vs. propofol). 'Tan 2022 (0.1 mg/kg)' and 'Tan 2022 (0.2 mg/kg)' were the same trial as well; therefore, we divided this trial similarly into two different dose comparisons (0.1 mg/kg remimazolam vs. propofol and 0.2 mg/kg remimazolam vs. propofol). 'Zhang 2021 (0.48 mg/kg/h)'and 'Zhang 2021 (0.6 mg/kg/h)' also belonged to one trial; to investigate the influence of the dose, this trial was divided into two different comparisons (0.48 mg/kg/h remimazolam vs. propofol and 0.6 mg/kg/h remimazolam vs. propofol).

Study characteristics

The key characteristics of the studies on remimazolam and propofol are shown in Table 1. The sample size of each relevant study ranged from 30 to 189 patients. Statistically significant features were extracted from the two groups (Table 2). The literature included in the study has heterogeneity: the results of awakening and discharge times were highly subjective, which resulted in high heterogeneity.

Risk of bias assessment

The Cochrane Collaboration tool was used to assess the risk of bias in all the included RCTs. A quality assessment of the methodology is shown in Figure 2. In the studies by Guo *et al.*[28] and Zhang *et al.*[31,32], we found a high-risk bias,. However, Dai *et al.*[27] found two high-risk biases in their research. There was no high-risk bias in the other studies.

Outcomes of intervention

Adverse events

Injection pain: Six trials reported details regarding the injection pain caused by remimazolam and propofol in patients after endoscopic surgery[26–29,31,32]. A meta-analysis showed that remimazolam had a lower risk of causing injection pain than propofol (RR = 0.06, 95% CI: 0.03–0.12, $P < 0.00001$). No significant heterogeneity was observed among the included studies ($\chi^2 = 9.01$, df = 8, $I^2 = 11\%$, $P = 0.34$; Fig. 3).

Hypotension: Five trials reported details concerning the hypotension caused by remimazolam and propofol in patients after endoscopic surgery[26,27,29,30,32]. Compared to the propofol

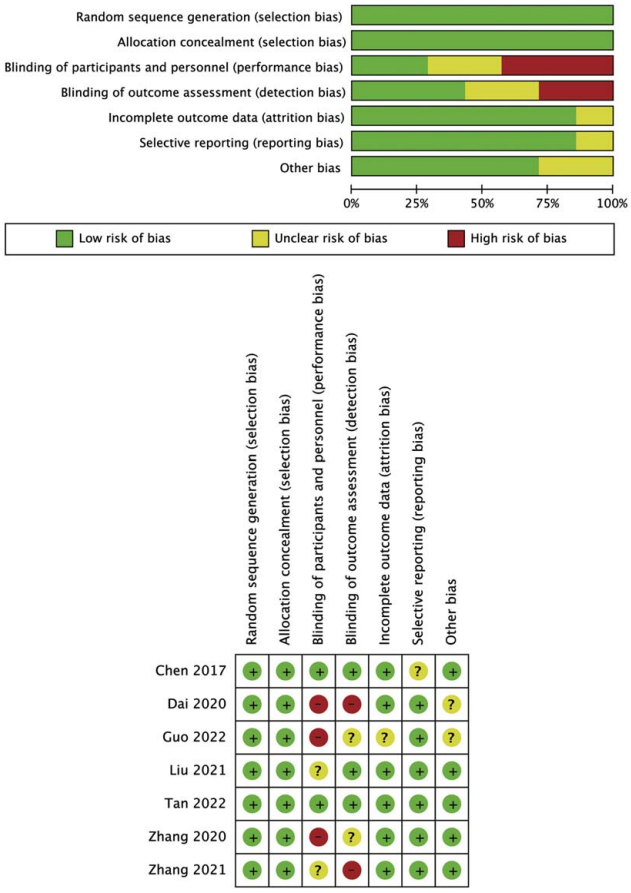

Figure 2. The graph and summary of risk bias of randomized controlled trials.

group, the patients experienced less hypotension during and after endoscopic surgery when sedated with remimazolam (RR = 0.45, 95% CI: 0.28–0.73, $P = 0.001$). These studies had slightly higher heterogeneity; therefore, we used a random effects model for the analysis ($\chi^2 = 22.77$, df = 7, $I^2 = 69\%$, $P = 0.002$; Fig. 4).

Respiratory depression: Four trials reported the occurrence of respiratory depression in patients after the use of two sedatives during endoscopic surgery[26,28,29,31]. However, one trial was excluded because of its high heterogeneity[29]. In the remaining three trials, we concluded that remimazolam caused less respiratory depression (RR = 0.20, 95% CI: 0.08–0.47, $P = 0.0002$). Moreover, these three trials have low heterogeneity ($\chi^2 = 0.22$, df = 3, $I^2 = 0\%$, $P = 0.97$; Fig. 5).

Bradycardia: Three trials reported bradycardia caused by two sedatives[26,29,32]. In the limited trials, we concluded that there was no significant difference in bradycardia caused by the sedative effects of remimazolam and propofol during endoscopic surgery (RD = −0.01, 95% CI: −0.03 to 0.01, $P = 0.35$). There were moderate differences in heterogeneity among the trials ($\chi^2 = 4.87$, df = 2, $I^2 = 59\%$, $P = 0.09$; Fig. 6).

Secondary outcome

Operation completion rate: The number of endoscopic procedures that achieved the primary endpoint was recorded in six trials[26–29,31,32]. This shows that the two sedatives successfully completed their respective missions during endoscopic surgery. Patients in both the remimazolam and propofol groups had good operation completion rates (RD = −0.03, 95% CI: −0.05 to −0.01, $P = 0.0005$). However, these trials exhibited moderate heterogeneity ($\chi^2 = 9.47$, df = 8, $I^2 = 15\%$, $P = 0.30$; Fig. 7).

Time for fully alert: The time for fully alert of the patients after the operation was recorded in detail in three trials[28,30,32]. Because the time measurement units used in the three trials were inconsistent, we adopted the SMD for evaluation. Although these three trials have high heterogeneity ($\text{Tau}^2 = 1.22$, $\chi^2 = 59.84$, df = 3, $I^2 = 95\%$, $P < 0.0001$), they still revealed that the time for patients to become fully alert after remimazolam sedation is longer than that after propofol sedation (SMD = 0.68, 95% CI: −0.43 to 1.80, $P = 0.23$; Fig. 8). We used the random effect model to analyze this trial.

Time to discharge: Three trials recorded the time to discharge[29,31,32]. There was also the problem of inconsistent measurement units of time, and we still used the SMD assessment. In general, consistent with the time for fully alert, due to the difference in the sedation effect between the two agents, patients in the remimazolam group had a longer time to discharge than those in the propofol group (SMD = −0.17, 95% CI: −0.58 to 0.23, $P = 0.41$). However, the abovementioned trials had significant heterogeneity. ($\text{Tau}^2 = 0.12$, $\chi^2 = 11.31$, df = 3, $I^2 = 73\%$, $P = 0.01$; Fig. 9).

Subgroup analysis

Due to differences in the criteria for patients included in each of the included RCTs, the doses used to regard remimazolam varied

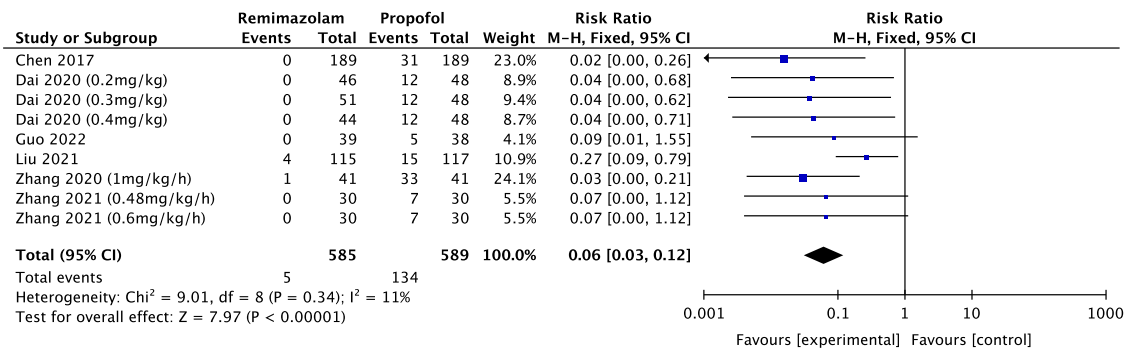

Figure 3. A forest plot of the injection pain after administration of remimazolam or propofol.

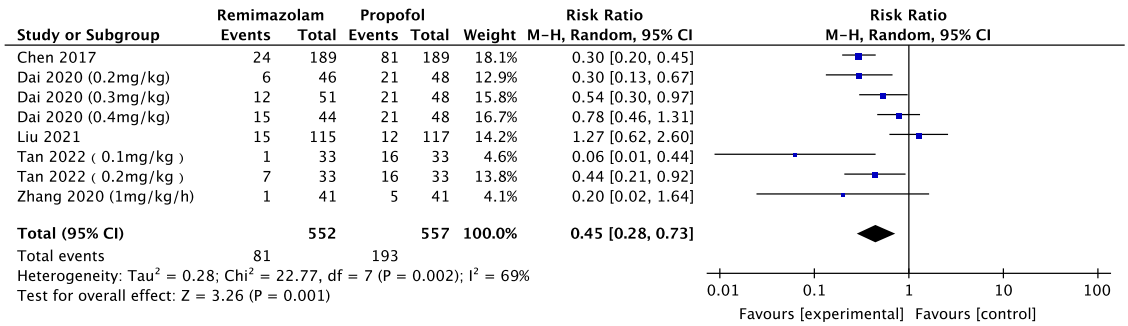

Figure 4. A forest plot of the hypotension after administration of remimazolam or propofol.

and different criteria were used. However, the initial dose of remimazolam for induction of anesthesia prior to the start of the endoscopic procedure was explicitly mentioned in each trial, although the subsequent procedure was performed with either continuous pump-in sedation or intermittent supplemental injections of sedation (Table 3). To explore the relationship between the dose of remimazolam on safety and efficacy, we performed a subgroup analysis on whether the initial anesthetic dose exceeded 0.2 mg/kg for each outcome (Fig. 10). One trial had a different initial dose calculation than several others and was excluded[26].

Injection pain: In the four trials where the initial dose did not exceed 0.2 mg/kg, remimazolam was more difficult to cause injection pain (RR = 0.09, 95% CI: 0.04–0.21, $P < 0.00001$)[27–29,32]. Similarly, the same conclusion was reached in the two trials with initial doses greater than 0.2 mg/kg (RR = 0.05, 95% CI: 0.01–0.20, $P < 0.00001$)[27,31]. The heterogeneity of both subgroup analyses was not high, so we used Fixed model for both ($\chi^2 = 5.47$, df = 3, $I^2 = 45\%$, $P < 0.00001$; $\chi^2 = 0.13$, df = 3, $I^2 = 0\%$, $P < 0.0001$; Fig. 10A).

Hypotension: The initial dose of remimazolam in the four trials did not exceed 0.2 mg/kg[27,29,30,32], and their results showed that remimazolam has a lower capacity to cause hypotension than propofol (RR = 0.38, 95% CI: 0.16–0.91, $P = 0.03$). But these trials have high heterogeneity ($\chi^2 = 13.77$, df = 4, $I^2 = 71\%$, $P = 0.008$). The results of the one trial with an initial dose of more than 0.2 mg/kg were not inconsistent and had low heterogeneity (RR = 0.66, 95% CI: 0.45–0.98, $P = 0.04$; $\chi^2 = 15.68$, df = 6, $I^2 = 0\%$, $P = 0.02$; Fig. 10B)[27].

Respiratory depression: Only one trial was conducted in conditions where the initial dose did not exceed 0.2 mg/kg and revealed that remimazolam was safer than propofol in terms of respiratory depression (RR = 0.22, 95% CI: 0.05–0.94, $P = 0.04$)[28]. The one remaining trial with initial doses above 0.2 mg/kg showed that remimazolam had an advantageous safety profile over propofol in terms of respiratory depression (RR = 0.25, 95% CI: 0.06–1.13, $P = 0.07$)[31]. However, the support of clinical evidence is not strong. And there was low heterogeneity ($\chi^2 = 0.00$, df = 1, $I^2 = 0\%$, $P = 1.00$; Fig. 10C). This was due to consistent results in both data sets.

Operation completion rate: Four of the trials that documented the successful completion of endoscopic procedures did not exceed 0.2 mg/kg of the initial anesthetic dose of remimazolam[27–29,32]. Compared with propofol, remimazolam also significantly supported the completion of surgery at low doses (RD = – 0.05, 95% CI: – 0.08 to – 0.01, $P = 0.007$). However, the heterogeneity of several tests is not low ($\chi^2 = 5.71$, df = 3, $I^2 = 47\%$, $P = 0.13$). And high doses of remimazolam were more likely to allow the procedure to be performed completely, even though the clinical evidence provided by the two trials was not sufficient (RD = – 0.02, 95% CI: – 0.05 to – 0.01, $P = 0.46$)[27,31]. However, heterogeneity was better ($\chi^2 = 2.60$, df = 3, $I^2 = 0\%$, $P = 0.46$; Fig. 10D).

Time to discharge: Compared with propofol, low-dose remimazolam has a slight advantage in discharge time (SMD = – 0.44, 95% CI: – 0.67 to – 0.22, $P = 0.0001$). These two trials reached this conclusion[29,32], and their heterogeneity is low ($Tau^2 = 0.00$, $\chi^2 = 0.36$, df = 1, $I^2 = 0\%$, $P = 0.55$). Under the condition of high dose, there was no significant difference in the time of discharge for patients undergoing endoscopic surgery sedated by remimazolam or propofol (SMD = 0.23, 95% CI: – 0.25 to 0.71, $P = 0.34$). Zhang's trial proved this ($Tau^2 = 0.05$, $\chi^2 = 1.75$, df = 1, $I^2 = 43\%$, $P = 0.19$; Fig. 10E)[31].

Sensitivity analysis and publication bias: Sensitivity analysis by omitting one study at a time showed that after the deletion of Liu's study, the correlation between remimazolam and propofol in causing respiratory depression became significant (RR = 0.19,

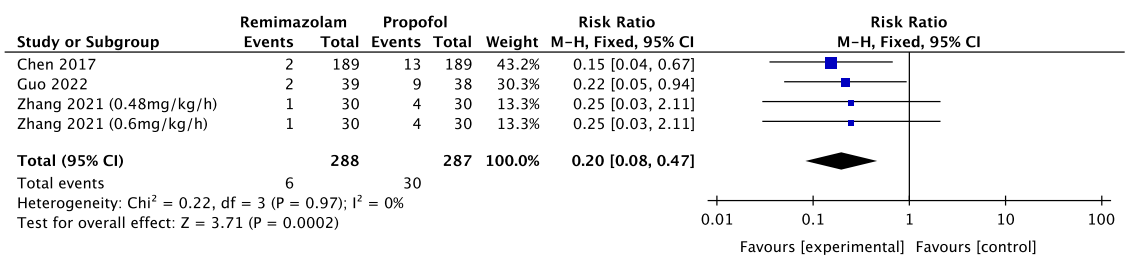

Figure 5. A forest plot of the respiratory depression after administration of remimazolam or propofol.

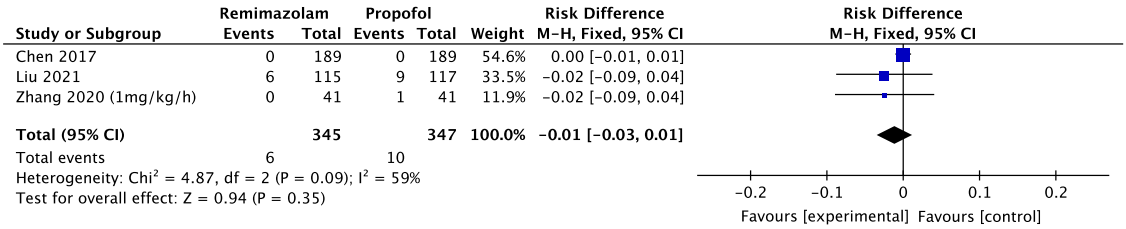

Figure 6. A forest plot of the bradycardia after administration of remimazolam or propofol.

95% CI: 0.07–0.55). In the sensitivity analysis, other results remained unchanged.

Publication bias was assessed using funnel plots (Fig. 11). A visual inspection was performed to determine whether there was any asymmetry in the funnel plot. Funnel plot symmetry of patients with injection pain (A), hypotension (B), respiratory depression (C), bradycardia (D), patients who reached the primary treatment endpoint (E), and time for full alertness after surgery (F) indicated that the risk of publication bias was low. The funnel plot describing the time for discharge (G) was asymmetric, and there may have been publication bias. It is possible that some studies with small sample sizes and no statistically significant effects were not published. The effect of the time after surgery, when the patient leaves the hospital, should be carefully explained.

Discussion

A meta-analysis of seven studies showed that remimazolam is superior to propofol in terms of adverse reactions such as injection pain, hypotension, respiratory depression, and bradycardia after anesthesia (Table 4). In addition, although there was no significant difference in the endpoint of the operation between remimazolam and propofol, remimazolam had a longer metabolic time in terms of time to full alertness and time to discharge after the operation.

In this study, we found that the remimazolam group experienced fewer postoperative adverse reactions than the propofol group. This was reflected in most of the included studies[26–32]. A prospective study was conducted by Zhang *et al.*[32], which compared adverse reactions between the remimazolam and propofol groups. Of the 41 patients in the propofol group, 33 (80.4%) experienced injection pain. However, only one person in the remimazolam group reported injection pain (2.4%) ($P < 0.001$). Similarly, in a prospective randomized trial by Chen *et al.*[26], 31 of 189 people in the propofol group felt pain at the injection site after the operation (16.4%), while no patient in the remimazolam group felt injection pain ($P < 0.0001$). One of the most common disadvantages of propofol is injection pain, but it can be improved to some extent by avoiding small veins and using various drugs (such as lidocaine) for pretreatment[33]. Our results suggest that this may be due to the short metabolic half-life of remimazolam, reduced local and in-vivo accumulation, and reduced release of active metabolites[34]. This also highlights the advantage of remimazolam over propofol in that it reduces injection pain symptoms in patients after endoscopic surgery.

Benzodiazepines have the least significant effects on the cardiovascular system. When sedation is obvious, peripheral blood vessels dilate, and cardiac output and peripheral resistance decrease slightly[35]. In addition, in Chen's trial[26], only 24 of 189 patients in the remimazolam group had hypotension (13.04%), which was much lower than 81 patients in the propofol group (42.86%) ($P < 0.0001$). The same phenomenon also appeared in a prospective trial by Dai *et al.*[27]. Among the 46 patients in the remimazolam (0.2 mg/kg) group, only six (13.0%) had postoperative hypotension. However, among the 48 patients in the propofol group, 21 cases (43.8%) of postoperative hypotension occurred ($P < 0.01$). On the contrary, in a prospective randomized trial by Liu *et al.*[29], 15 of 115 patients (13.0%) in the remimazolam group had hypotension. Only 12 of 117 patients (10.2%) in the propofol group had hypotension symptoms. In the six trials with hypotension selected by us, remimazolam caused fewer side effects of postoperative hypotension than propofol. Studies have shown that longer propofol sedation and larger propofol dose are associated with a longer duration and more severe

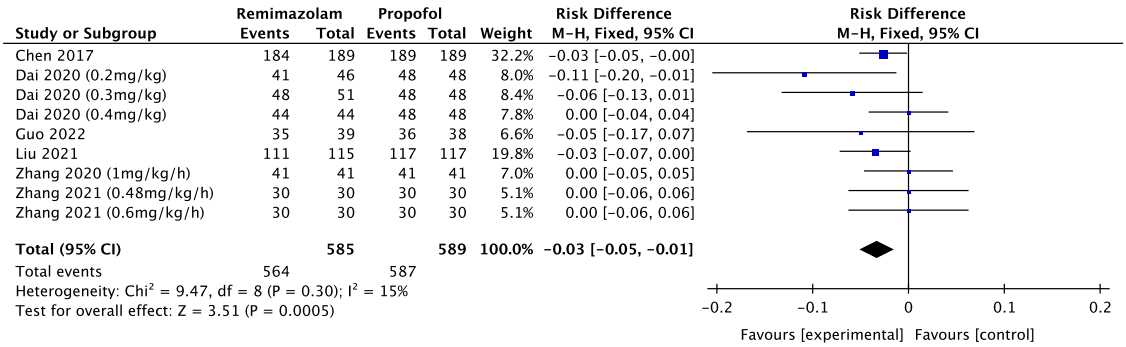

Figure 7. A forest plot of the operation completion rate sedated by remimazolam or propofol.

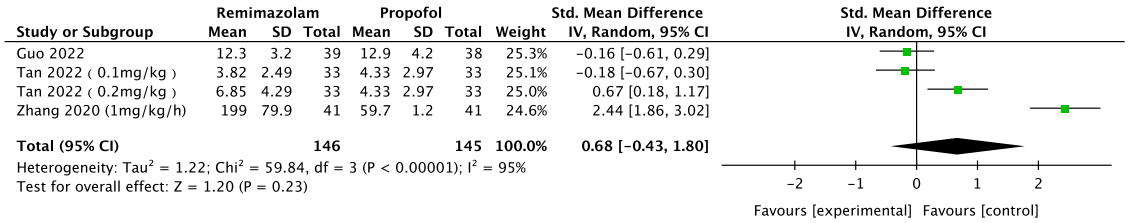

Figure 8. A forest plot of the time for fully alert after the operation.

hypotension[36], which may explain the above results. There is evidence that in healthy subjects, single sedation with propofol less than 200 mg rarely causes clinically significant hypotension[37]. In another prospective trial, Zhang *et al.*[31] administered fewer doses to patients in the propofol group; however, there are no records of postoperative hypotension complications. We consider this to be an important publication bias.

Propofol may have variable respiratory effects at typical doses[38]. In a study by Chen *et al.*[26], while the number of patients in both groups was 189, only 2 patients in the remimazolam group had respiratory depression, which was much lower than 13 patients in the propofol group ($P = 0.0064$). Only two trials have recorded the phenomenon of respiratory depression in patients after anesthesia[26,31]. Therefore, we concluded that propofol is associated with a higher risk of respiratory depression than remimazolam. We concluded that there was no significant difference in bradycardia between the remimazolam and propofol groups[26,29,32]. This was also because the sample size was too small to draw definitive conclusions. These observations may be due to cardiopulmonary inhibition caused by the effect of propofol on the sensitivity of central chemical receptors[39].

As sedatives, remimazolam and propofol provide a foundation for the completion of endoscopic surgery. Although both sedatives completed their task in most of the trials we included, in Chen's trial[26], remimazolam did not effectively support the completion of the operation in 5 patients (2.65%) ($P = 0.061$). Similarly, in Liu's trial[29], the operation could not be completed in 4 patients with remimazolam (3.47%) ($P = 0.059$). Dai's prospective trial also showed that remimazolam at a low dose did not fully support the completion of the operation[27], but in 0.2 and 0.3 mg/kg remimazolam groups, 5 (10.9%) and 3 (5.88%) patients failed to complete the operation, respectively ($P < 0.05$ and no data). This can be attributed to the difference in the average end-elimination half-life of remimazolam and other sedatives, resulting in a shorter time required for patients to regain full alertness after the use of remimazolam[40]. Some studies have shown that remimazolam has a faster onset of action, shorter duration of action, and a shorter and more consistent recovery time from sedation than midazolam[41]. According to Guo's prospective study[28], 4 of 39 patients in the remimazolam group did not complete the operation, whereas 2 of 38 patients in the propofol group did not complete the operation ($P = 0.350$). This may be because Guo *et al.* selected patients who were older and were taking personalized administration.

For the postoperative monitoring of endoscopic surgery, outpatient surgery has a relatively strict postoperative safety procedure, which is due to the risk of traffic accidents for patients after outpatient surgery. Patients are advised to avoid driving and using public transport without an escort within 24 h of sedation in outpatient surgery[42,43]. Similarly, most international recommendations for patients undergoing sedative endoscopy prohibit them from actively using public transport within 24 h[44]. Therefore, monitoring after endoscopic surgery has become increasingly important. In a prospective randomized trial conducted by Tan *et al.*[30], we found that the postoperative awakening time in the propofol group (4.33 ± 2.97 min) was longer than that in the 0.1 mg/kg remimazolam group (3.82 ± 2.49 min), but shorter than that in the 0.2 mg/kg remimazolam group (6.85 ± 4.29 min) ($P = 0.001$ and $P < 0.01$, respectively). However, the experiment by Zhang *et al.* also revealed a relatively obvious single phenomenon: the postoperative awakening time of patients in the remimazolam group was 199 ± 79.9 s, which was more than 139.3 s greater than 59.7 ± 1.2 s in the propofol group ($P < 0.05$). Although remimazolam required a longer time for patients to wake up after surgery, the overall time did not reach an unacceptable level.

The discharge time is usually defined subjectively and reported in different ways. Therefore, SMD is a more appropriate measurement method for determining the discharge time difference[45]. In the trial of Liu *et al.*[29], the discharge time of patients in the propofol group was 14.57 ± 1.67 min, and the average value was 0.65 min longer than that of 13.92 ± 1.57 min in the remimazolam group

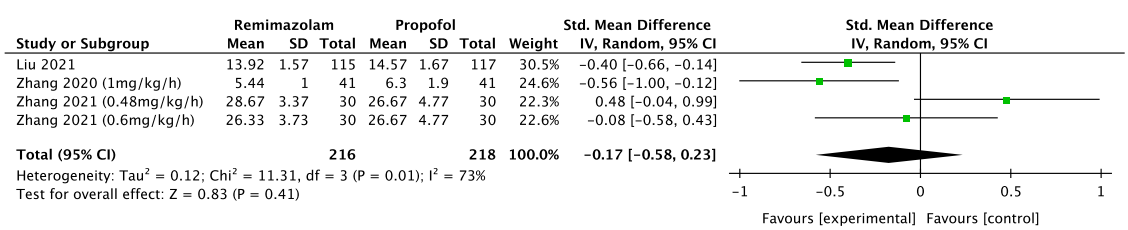

Figure 9. A forest plot of the time for discharge of operation.

Table 3

Dose of sedatives at corresponding stages in each study.

Groups	Number of patients	Initial doses	Supplemental doses[a]	Maintenance doses[a]
Chen *et al.*,[26]				
Remimazolam	189	5 mg[b]	2.5 mg[b]	–
Propofol	189	1.5 mg/kg	0.5 mg/kg	–
Dai *et al.*,[27]				
Remimazolam (0.2 mg/kg)	46	0.2 mg/kg	NM	NM
Remimazolam (0.3 mg/kg)	51	0.3 mg/kg	NM	NM
Remimazolam (0.4 mg/kg)	44	0.4 mg/kg	NM	NM
Propofol	48	2.0 mg/kg	NM	NM
Liu *et al.*,[29]				
Remimazolam	111	0.15 mg/kg	0.075 mg/kg	–
Propofol	117	0.1 mg/kg	0.05 mg/kg	–
Tan *et al.*,[30]				
Remimazolam (0.1 mg/kg)	33	0.1 mg/kg	0.05 mg/kg	–
Remimazolam (0.2 mg/kg)	33	0.2 mg/kg	0.05 mg/kg	–
Propofol	33	1–1.5 mg/kg	0.5 mg/kg	–
Xiaoqiang Zhang *et al.*,[32]				
Remimazolam	41	0.2 mg/kg	–	1.0 mg/kg/h
Propofol	41	2.5 mg/kg	–	3.0 mg/kg/h
Shuoya Zhang *et al.*,[31]				
Remimazolam (0.48 mg/kg/h)	30	0.25 mg/kg	–	0.48 mg/kg/h
Remimazolam (0.6 mg/kg/h)	30	0.25 mg/kg	–	0.6 mg/kg/h
Propofol	30	2.5 mg/kg	–	5.0 mg/kg/h
Guo *et al.*,[28]				
Remimazolam	39	0.15 mg/kg	0.05 mg/kg	–
Propofol	38	1.5 mg/kg	0.5 mg/kg	–

NM, not mentioned.

[a]The method of administering sedatives during each study surgery varies, including supplementing sedatives or continuously pumping sedatives.

[b]No mention of weight in the study.

($P = 0.002$). However, in the trial of Zhang *et al.*[32], the discharge time of patients in the propofol group was 26.67 ± 4.77 min, while the time in the two doses of remimazolam group was 28.67 ± 3.37 min and 26.33 ± 3.73 min: the average discharge time in the propofol group was 2.00 min shorter than that in the 0.48 mg/kg/h remimazolam group ($P < 0.05$), but 20 s longer than that in the 0.6 mg/kg/h remimazolam group ($P < 0.05$). Therefore, in our meta-analysis, there is no definite conclusion to prove the difference between propofol and remimazolam in the impact on the discharge time of patients undergoing endoscopic surgery. In another meta-analysis of propofol and midazolam, a benzodiazepine sedative, for selective endoscopy in patients with liver disease, midazolam had a longer recovery time and discharge time after surgery than propofol[46].

The dose of remimazolam used in many studies is a guide dose, but it is usually required to exceed the specification dose in practical application[47]. Therefore, we performed a subgroup analysis of the dose of remimazolam in each eligible outcome and grouped it according to whether the initial dose of remimazolam at the time of induction exceeded 0.2 mg/kg. After subgroup analysis, the initial dose of remimazolam was not significantly related to the occurrence of adverse reactions. Since the definition of discharge time is too subjective, it did not reflect how much it was related to the dose. Only 228 of 242 patients in the subgroup with initial doses of remimazolam not exceeding 0.2 mg/kg completed surgery ($P = 0.007$), but 152 of 156 patients in the

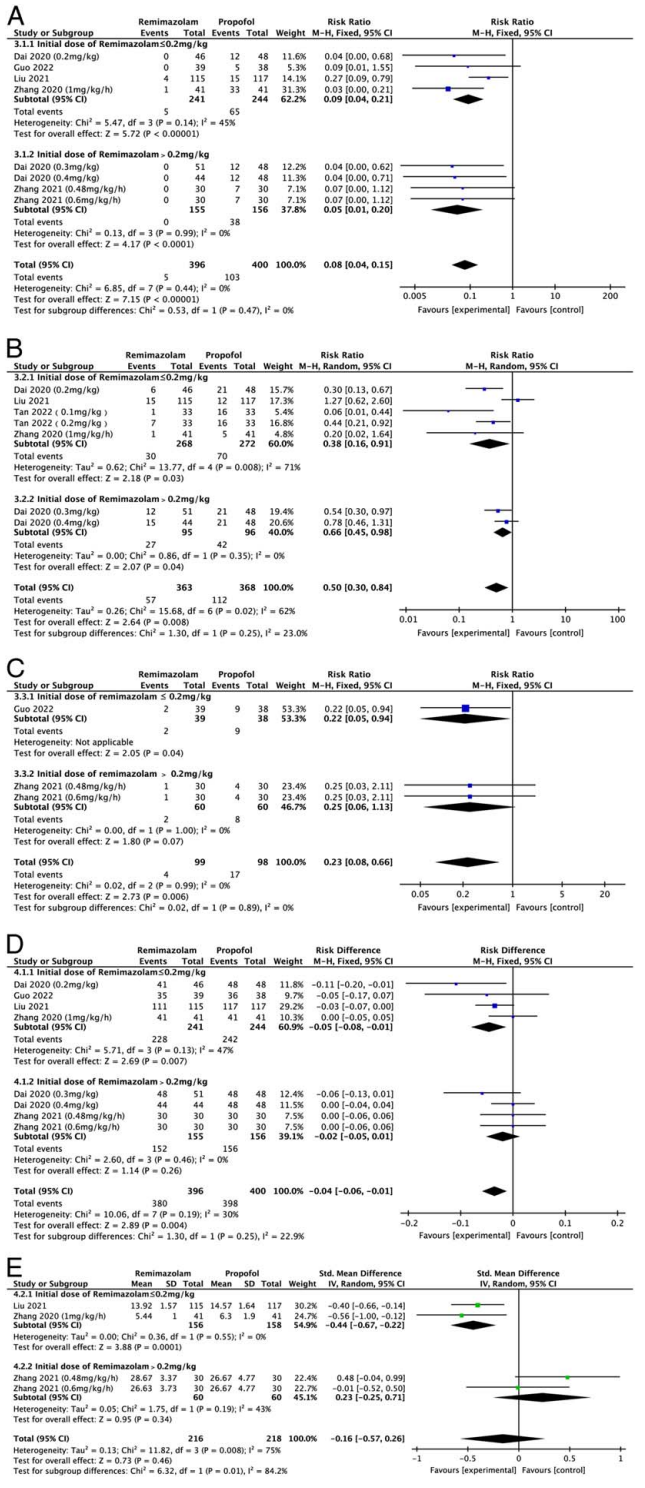

Figure 10. Forest plots of subgroup analysis for remimazolam dose. (A) Injection pain; (B) hypotension; (C) respiratory depression; (D) operation completion rate; (E) time for discharge.

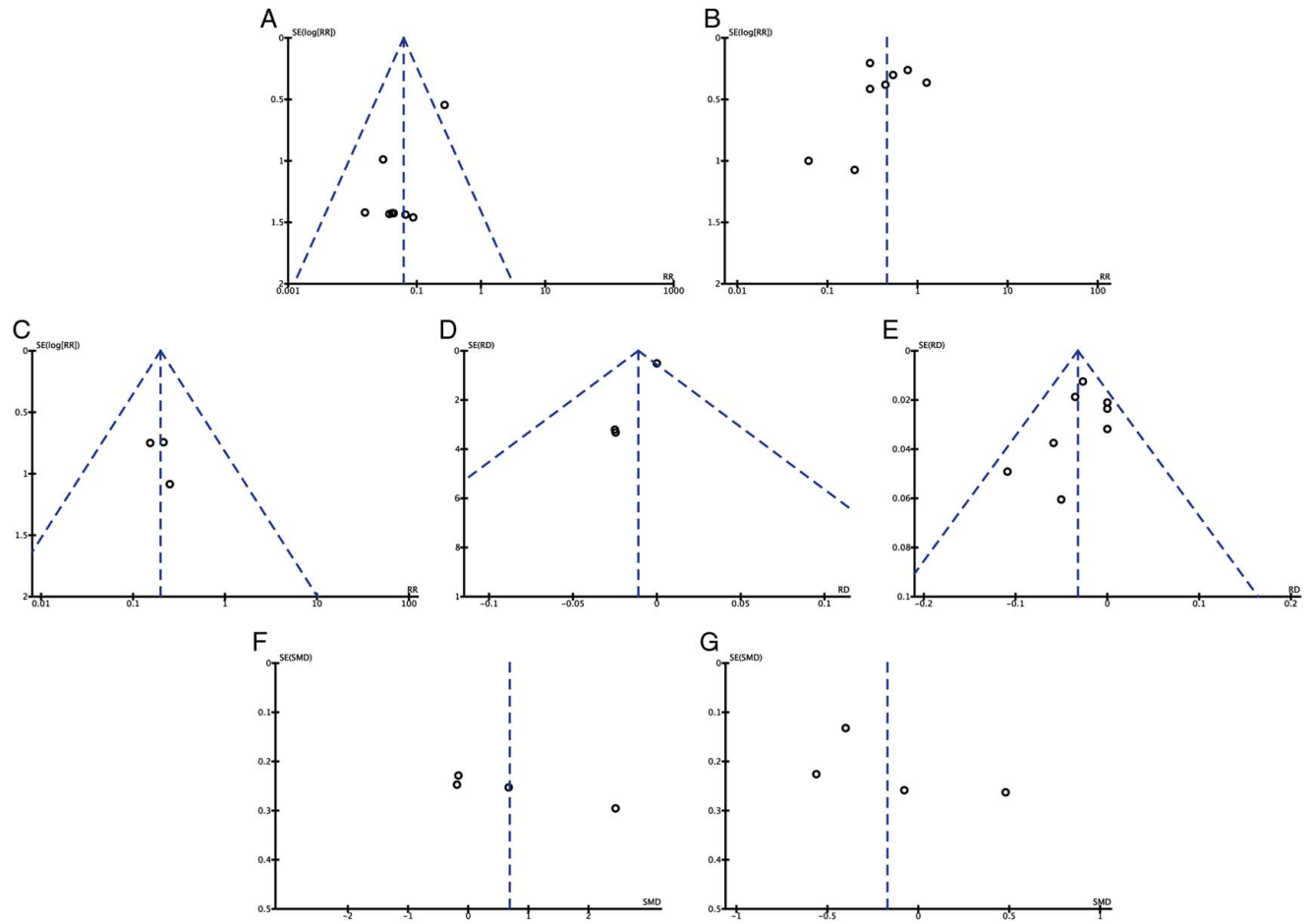

Figure 11. The results of funnel plot. (A) Injection pain; (B) hypotension; (C) respiratory depression; (D) bradycardia; (E) operation completion rate; (F) time for fully alert; (G) time for discharge.

subgroup with doses exceeding 0.2 mg/kg completed surgery ($P = 0.26$). This means that in terms of the ability to complete the operation, the high initial dose of remimazolam may be more advantageous. A recent study simulating population pharmacodynamics with the Markov mixed-effects model showed that high-dose remimazolam combined with fentanyl could provide a better sedative effect[48]. The relevant clinical trials also mentioned that the dose of remimazolam had little effect on the adverse reactions of anesthesia[47]. This was consistent with our analysis.

In the 21st century, endoscopic physicians must have expertise in sedation, analgesia, patient monitoring, and an understanding of the potential complications. The purpose of sedation and analgesia is to relieve patients' anxiety and discomfort, improve examination results, and reduce patients' memory of events. Ideally, sedative and analgesic drugs should take effect quickly and produce predictable effects. This should not lead to compensation for cardiopulmonary damage[49]. Another guideline states that the use of sedatives should minimize the risk of medication while maximizing patient comfort[50]. Based on this concept, our research focuses on the advantages and disadvantages of the combination of remimazolam with opioids, which are increasingly popular among endoscopic surgeons compared to the traditional sedative propofol. Admittedly, as a traditional sedative, propofol is generally preferred in terms of

Table 4

Results of meta-analysis on the safety of remimazolam and propofol.

		Overall effect			Heterogeneity		Safety	
Adverse events	**Study**	**Effect estimate**	**95% CI**	***P***	I^2 **(%)**	***P***	**Remimazolam**	**Propofol**
Injection pain	9	0.06	0.03–0.12	< 0.00001	11	0.34	Advantaged	Disadvantaged
Hypotension	8	0.45	0.28–0.73	0.001	69	0.002	Advantaged	Disadvantaged
Respiratory depression	4	0.2	0.08–0.47	0.0002	0	0.97	Advantaged	Disadvantaged
Bradycardia	3	− 0.01	− 0.03–0.01	0.35	59	0.09	–	–

the success rate of surgery or the time of recovery or discharge. However, the satisfaction of patients after surgery is affected by the side effects of the drugs; in this respect, remimazolam has a strong advantage. Therefore, less wound pain after injection, less hypotension, and fewer cardiopulmonary events may make remimazolam a better choice for more patients undergoing endoscopy or surgery.

Although we selected only RCTs and conducted a strict meta-analysis, our study still has limitations. The quality of our systematic reviews and meta-analyses was inevitably limited by the quality of the included studies. Most of the selected RCTs were single-blind, and a few trials did not mention the blind settings. Moreover, all seven RCTs were single-center studies, and the representativeness and consistency of the results could not be guaranteed. In addition, the remimazolam dosage was slightly different in the included studies. All studies used intermittent additional doses according to the sedative effect, and the patients were divided into groups according to the initial induction dose. Therefore, our results cannot provide valuable suggestions for the selection of remimazolam dosage for endoscopic sedation. The doses of adjuvant opioid analgesics may not have been consistent in all the studies, and the units of measurement for their doses may have been different, which may have affected our results. Moreover, the operation sites in each study, including hysteroscopy, gastrointestinal endoscopy, and other different endoscopic procedures, were different. The included studies were primarily conducted in China, and the patient population may have limitations. We will continue to track and search for studies on the clinical use of remimazolam and more accurate data to enrich and update our research.

Conclusion

Through a systematic review and meta-analysis of RCTs, we clarified the effect of remimazolam on endoscopic surgery and compared it with that of propofol. The summary data shows that compared to propofol, remimazolam is safer to use during endoscopic surgery and has fewer overall adverse events. And it has little to do with the initial dose of remimazolam. However, the present meta-analysis did not guarantee the surgical success rate of remimazolam. Although there was no significant difference in the recovery and discharge times between the remimazolam and propofol groups, based on safety, we believe that the length of postoperative observation is less important. In conclusion, our study employed small-sample RCTs to compare the use of remimazolam and propofol in endoscopic surgery. Statistically significant endpoints still provide priority consideration for the clinical selection of remimazolam for endoscopic surgery.

Ethical approval

None.

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Author contribution

M.-j.Z.: study design, data collection, data analysis, and writing; H.-f.H.: data collection and data analysis; X.-l.L.: data collection and writing; X.-m.L.: study design; D.-c.W.: final approval of the version to be submitted; M.-j.K.: study design and final approval of the version to be submitted.

Conflicts of interest disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Research registration unique identifying number (UIN)

1. Name of the registry: PROSPERO.
2. Unique identifying number or registration ID: CRD420223 67470.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=367470.

Guarantor

Ming-jie Kuang.

Data availability statement

The original contributions proposed in the study are included in these papers/supplementary materials. Please contact the corresponding author directly for further inquiries.

Data statement

The data that support the findings of this study are openly available in [Medline] at [PubMed (nih.gov)].

Provenance and peer review

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