# Comparison of the recovery quality between remimazolam and propofol after general anesthesia: systematic review and a meta-analysis of randomized controlled trials (#100073)



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# Comparison of the recovery quality between remimazolam and propofol after general anesthesia: systematic review and a meta-analysis of randomized controlled trials

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Introduction: To evaluate the recovery quality between remimazolam and propofol after general anesthesia surgery. Methods: Eligible Randomized controlled trials (RCTs) in PubMed, Cochrane Central, Scopus, and Web of Science up to January 15, 2024 for comparison the recovery quality of remimazolam and propofol after general anaesthesia. The primary outcomes were the total QoR-15 and five dimensions of QoR-15 on postoperative day 1 (POD1). Results: Seven RCTs with a total of 817 patients were included in this meta-analysis. Our statistical analysis showed that remimazolam group had higher QoR-15 score. In the five dimensions of QoR-15, remimazolam group was superior to propofol group in terms of physical independence, and there were no significant difference in terms of emotional status, psychological support, physical comfort and pain. The intraoperative and postoperative time characteristics were similar in the two groups. Remimazolam group was lower than propofol group in incidence of hypotension, bradycardia and injection pain. Conclusions: Our analysis showed that the recovery quality of the remimazolam group after general anaesthesia was more superior. The incidence of adverse events was low in remimazolam group. As a potential anesthetic, we need a larger sample RCTs to verify the benefits of recovery quality in patients treated with remimazolam.

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**Keywords: general anaesthesia, meta-analysis, propofol, quality of recovery, QoR, remimazolam, systematic review**

## 1 Introduction

In recent years, surgical technology has unique advantages in clinic treatment and anesthetic plays an important role in surgical techniques. Doctors and patients are increasingly concerned about the quality of recovery (QoR) after general anesthesia, not just the success or failure of surgery [1]. Choosing the right drug among the various anesthetics can be a challenge. Propofol has long been considered a more comfortable administration of general anesthesia than inhalation anesthesia because of its low incidence of nausea and vomiting. However, it also has limitations, such as low blood pressure and a high incidence of injection pain [2]. Remimazolam is a benzodiazepine sedative/anesthesia that can be administered intravenous [3]. Due to rapid metabolism by tissue esterases into inactive metabolites [4], it has the characteristics of rapid onset and offset in vivo, and can be antagonized by flumazenil [5]. Clinical trials have demonstrated the safety and efficacy of general anesthesia [6]. Remimazolam has a similar sedative effect to propofol and is superior to propofol in terms of injection pain and the risk of hypotension. Acturally, propofol may be superior to remimazolam in terms of depth of anesthesia [7].

Quality of recovery is a broad concept that assesses recovery from multiple perspectives of the patient[8], at present, QoR-15 is the most widely used to evaluate the quality of postoperative recovery. The QoR-15 was evolved from the larger QoR-40, and they were just equally effective in measuring quality of

postoperative recovery [9]. A meta-analysis of the hemodynamic effects by Peng et al. [10] only included two RCTs that showed no significant difference between remimazolam and propofol in total QoR-15 scores on POD1. We systematically updated this study by collecting 7 RCTs and conducted a comprehensive meta-analysis about quality of recovery after general anaesthesia between remimazolam and propofol.

## 2 Methods

We conducted and reported analyses in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020. The protocol has been listed in PROSPERO International Prospective Register of Systematic Reviews (CRD42024497497). From January 15, 2024 to January 22, 2024, we screened the articles. Then we took a week to extract the data until January 30, 2024. Finally we spent a month analyzing the data until February 29, 2024.

### 2.1 Search strategy

We searched PubMed, Scopus, Cochrane Central, and Web of Science databases for eligible studies up to January 15, 2024, in unrestricted languages. Checking the registration number at Clinical Trials and the database to make sure no data was missing. The search strategy is as follows: Title /Abstract “remimazolam” and Title/Abstract “propofol” and All Fields “quality of recovery”, and we did not search grey literature. CZ and FQ independently performed the search strategy and resolved their disagreements through discussion.

## 2.2 Eligibility criteria and study selection

The two authors completed the selection of articles independently. If there was different point of view, they resolved it through discussion. There are no language restrictions for articles in this search. We included all RCTs that met the following PICO study question criteria. 1) Population: patients requiring surgery under general anesthesia, no surgical type is considered; 2) Intervention: the study experimental group used remimazolam to induce and maintain anesthesia; 3) Comparator: the study control group used propofol to induce and maintain anesthesia; 4) Outcomes: quality of recovery index, intraoperative and postoperative time characteristic indexs and adverse events. We excluded studies with the following criteria: duplicate literature, review or meta-analysis artiles, studies without using propofol as a control group, data unavailable for analysis, and no project data reported.

## 2.3 Outcome measures

The primary outcome was the recovery quality of total QoR-15 and five dimensions of QoR-15 on POD1 (physical comfort, physical independence, emotional state, psychological support, and pain) between remimazolam and propofol group. Secondary outcomes were duration of PACU stay (min), time to extubation (min), duration of anesthesia (min), duration of operation (min), duration of postoperative hospital stay (day), the QoR-40 and adverse events. The QoR-15 consists of 15 items, including physical comfort (5 items), emotional state

(4 items), psychological support (2 items), physical independence (2 items) and pain (2 items), each item is scored on an 11-point scale according to the frequency on the scale, the total score range from 0 to 150, the higher the score, the better the quality of recovery. The QoR-40 scale ranges from 40 to 200 and the higher the score, the better the quality of recovery.

**2.4 Data extraction**

The extracted data includes first author, year of publication, registration number, country, sample size, American Society of Anesthesiologists (ASA) physical status, body mass index (BMI), gender ratio, type of surgery, specific interventions and comparisons methods, scale design and predetermined outcomes. Two independent authors used standard tables for data extraction and resolved their disagreements through discussion.

**2.5 Risk of bias assessment**

Our two authors independently assessed the risk of bias domains using the Cochrane risk of bias assessment tool. The Cochrane risk of bias tool detects the following types of bias: random sequence generation, allocation concealment, binding of participants and personnel, blinding of outcome assessment, incomplete outcome date and selective reporting. Each bias domain was judged as having a high, unclear, or low risk of bias.

**2.6 Statistical analysis**

Review Manager (Rev Man 5.4.1; The Cochrane Collaboration, 2020) was used in this meta-analysis, we pooled continuous outcomes as mean differences (MDs) with 95% CI under the fixed-effect model. Inverse Variance method was utilized to calculate the MDs value. If the results were represented in quartiles, we contact the article author by email or phone to get the original data, and if there was no response, we convert the data to mean and standard deviation when it meets the conversion criteria. Moreover, Mantel-Haenszel odds ratio (OR) and 95% CI were used for the number of events and samples of dichotomous data. We adopted a 2-tailed test and $P < 0.05$ for the overall effect observed was indicated significant differences. Statistical heterogeneity was assessed with the Q test and I-square ($I^2$) statistic test. The random effects model was used to evaluate the stability of the combined results of the fixed effects model. If a strong heterogeneity ($I^2 \geq 50\%$) was found, a leave-one-out sensitivity analysis was employed to evaluate the single comparison-driven conclusion, and if no source of heterogeneity was found, a random effects model was put to use.

## 3 Results

### 3.1 Study results

A total of 193 relevant literatures were searched in PubMed, Scopus, Cochrane Central, and Web of Science databases（FIGURE 1）. 129 articles were removed using the tool, 51 were removed by reading the title and abstract, and 6 were removed after reading the full text. We also checked ClinicaTrials. gov to make

sure there are no missing articles. Finally, we received 7 unique literatures were retrieved for this systematic review and meta-analysis [11-17].

### 3.2 Demographics and characteristics

Our analysis included seven studies with a total of 817 patients, of which four were conducted in China and three were conducted in Korea. Patients aged from18 to 86 years were divided into remimazolam group and propofol group, respectively. The doses in the remimazolam group were not exactly the same, induction dose of remimazolam: four RCTs used the dosage recommended by the instructions (6 mg/kg/h), one RCT used larger dose (12 mg/kg/h) and two RCTs used a bolus dose (0.2-0.3 mg/kg and 0.3 mg/kg, respectively); maintenance dose of remimazolam: six RCTs used the dosage recommended by the instructions, only one RCT used a lesser dose (0.3 mg/kg/h). Table 1 shows the baseline summary of the included RCTs.

### 3.3 Quality assessment of included studies

According to the Cochrane Risk of Bias Assessment Tool, the quality of the included randomized controlled trials was estimated to be medium to high. The summary and risk of bias for the included studies are shown in FIGURE 2.

### 3.4 Comparison of remimazolam with propofol in the term of total QoR-15 on the POD1

The primary outcome was the change in QoR-15 on the POD1. Three studies [11, 14, 17] with 304 patients examined QoR-15 on the pre-operation. Our statistical

152 analysis showed there was no significant difference between the two groups (MD =
153 -0.09; 95% CI, -1.41 to 1.23; $I^2$ = 39%; P = 0.89) (FIGURE 3A). Four studies [11,
154 14, 15, 17] involving 418 patients investigated QoR-15 on the POD1. Our
155 statistical analysis showed that the score of QoR-15 in remimazolam group was
156 higher than that in propofol group (MD = 3.68; 95% CI, 2.21 to 5.15; $I^2$ = 67%; P
157 ＜0.00001), which indicated that remimazolam group had better quality of
158 recovery on the POD1 (FIGURE 3B). Due to the high heterogeneity, we adopted
159 the leave-one-out method to eliminate the study of Zhao et al., and the analysis still
160 reached the same conclusion, supporting the superiority of remimazolam group
161 (MD = 2.44; 95% CI, 0.74 to 4.13; $I^2$ = 0%; P=0.005) (FIGURE 3C).

162 **3.5 Comparison of remimazolam with propofol in the term of five dimensions**
163 **of QoR-15**

164 We analyzed five dimensions of QoR-15 scores, emotional status, physical comfort,
165 psychological support, physical independence, pain. Three studies [11, 15, 17]
166 involving 361 patients have reported these five dimensions. In term of physical
167 independence, remimazolam group was better than propofol group, with significant
168 difference and low heterogeneity (MD = 0.79; 95% CI, 0.31 to 1.27; $I^2$ = 0%;
169 P=0.001) (FIGURE 4D). There was no significant difference in emotional status,
170 physical comfort, psychological support and pain between remimazolam group and
171 propofol group (p＞0.05) (FIGURE 4A, 4B, 4C, 4E).

172 **3.6 Comparison of remimazolam with propofol in the term of intraoperative**

**and postoperative time characteristics and QoR-40 on POD1**

We also analyzed other factors related to the quality of postoperative recovery. 4 [11, 15-17], 5 [11, 13, 15-17], 5 [13-17], 5 [11, 14-17], 4 [11, 14, 16, 17], 2 [12, 13] studies were involved in time to extubation, duration of anesthesia, duration of surgery, duration of PACU, duration of postoperative hospital stay and QoR-40 on the POD1, respectively. However, no significant differences were observed in these respects ($p > 0.05$), and the heterogeneity was low to high (FIGURE 5A, 5B, 5C, 5D, 5E, 5F).

### 3.7 Incidence of adverse events

Table 2 show adverse events reported by two or more RCTs. The incidence of postoperative nausea/vomiting (PONV) in remimazolam group was higher than that in propofol group, but there was no significant difference between the two groups after statistical analysis (RR = 1.66; 95% CI, 0.98 to 2.79; $I^2 = 0\%$; P=0.06)(Supplementary Figure S1). Remimazolam group was lower than propofol group in incidence of hypotension, bradycardia and injection pain.

## 4 Discussion

In this meta-analysis study, we reviewed seven RCTs analyzing remimazolam for the quality of recovery after general anaesthesia. A total of 817 patients in remimazolam group and propofol group were included in our report. Our aim was to evaluate the recovery quality between remimazolam and propofol after general anesthesia surgery.

Remimazolam, used for general anesthesia in surgery, is a benzodiazepine with the basic sedative structure of midazolam and the ester structure of remifentanil. After entering the body, it directly binds to $GABA_A$ receptors producing anesthetic effect [18], with an onset time of 1-3 min. Tissue esterases in vivo can break the ester bond and metabolize it into inactive CNS7054 with lose efficacy time of 6.8-9.9 min [3]. These pharmacokinetics characteristics enable the remifentanil to reach the operable state quickly, and patient can recover quickly after the surgery with few adverse reactions. Among the RCTs included in our analysis, 4 RCTs used 6 mg/kg/h for anesthesia induction and 3 RCTs used 12 mg/kg/h or a bolus dosage. The use of large doses was based on the effectiveness and safety of previous studies[19, 20].

According to our findings, the quality of recovery of remimazolam group was better than that of propofol group, and that incidence of adverse effects, such as hypotension, bradycardia and injection pain, remimazolam group was lower than propofol group. In terms of time to extubation, duration of anesthesia, duration of surgery, duration of PACU and duration of postoperative hospital stay, remimazolam group was similar to propofol group.

At present, the scales commonly used to evaluate the quality of postoperative recovery include QoR-15, QoR-40 and the post-operative quality of recovery scale (PostopQRS).

QoR-15 was developed from QoR-40, and both were evaluated in five dimensions, including physical comfort, physical independence, emotional state, psychological support, and pain, with the highest scores were 150 and 200, respectively [21, 22]. The higher score indicates a better recovery quality of rehabilitation [23]. The RCT of Mao, et al. [24] evaluated QoR-15 after general anesthesia with remimazolam in urological surgery, showing that remimazolam was significantly lower than propofol. The meta-analysis by Peng et al. [10] found no significant difference between remimazolam and propofol including Mao, et al. and an RCT. Our pooled analysis of four RCTs showed the superiority of remimazolam but with high heterogeneity. The high heterogeneity might be due to the inclusion of patients aged 60 to 80 years in Zhao's RCT, remimazolam has a significantly higher superiority in postoperative recovery quality on the POD1, and the advantages of remimazolam in anesthesia in the elderly might be the direction of future research. Excluding the RCT of Zhao et al., the superiority of remimazolam were the same and the heterogeneity was low.

We further wanted to validate previous results with QoR-40 on POD1.

The RCT of li et al. [16] used QoR-40 to evaluate the recovery quality elderly patients 3 days after surgery, and found that remimazolam was significantly better than propofol. Two RCTs used PostopQRS scale [25, 26] enrolled colonoscopy patients aged 18 to 75 years. One research showed that remimazolam was superior to propofol in the rate of cognitive recovery on POD1 and POD7 and the overall

recovery rate on POD7, while the other research showed that there was no significant difference between remimazolam and propofol in recovery quality on POD1. Due to the lack of original data of PostopQRS scale in literature, we included only two RCTs and reached a simple conclusion that there was no significant difference between remimazolam and propofol in QoR-40 on POD1. We also analyzed other measures related to QoR, which showed no significant differences in PACU residence time, extubation time, anesthesia time, surgical time and postoperative hospital stay between remimazolam and propofol.

The adverse reactions of anesthetics should also be paid attention to. According to our statistical results, the incidence of injection pain, hypotension and bradycardia in the remimazolam group was lower than those in the propofol group, which was consistent with the precious literature results [6, 7]. It seems to indicate that remimazolam could be used as anesthesia in clinical surgery to better improve patient comfort.

This paper presents the first comprehensive systematic review and meta-analysis of the recovery quality after general anesthesia surgery with remimazolam. There are some limitations to our study. The races included in our analysis were all Asian, so our results may only apply to Asians. The age range of patients included in each RCT is different. It is not possible to determine whether there is a difference in the quality of postoperative recovery between elderly and non-elderly people. In the future, we will need larger sample sizes for subgroup analysis.

## 5 Conclusions

Our systematic review and meta-analysis showed that in patients with general anaesthesia surgery, remimazolam treatment was superior to propofol group in terms of the total QoR-15 scores, and comparable to propofol group in terms of time to extubation, duration of anesthesia, duration of surgery, duration of PACU stay, duration of postoperative hospital stay and QoR-40 on the POD1. Additional RCTs with larger sample sizes and longer follow-up periods are needed to consolidate the benefits of recovery quality in patients treated with remimazolam.

## References


1. Wessels, E., et al., *Quality of recovery in the perioperative setting: A narrative review.* Journal of Clinical Anesthesia, 2022. **78**.
2. Keam, S.J., *Remimazolam: First Approval.* Drugs, 2020. **80**(6): p. 625-633.
3. Kilpatrick, G.J., *Remimazolam: Non-Clinical and Clinical Profile of a New Sedative/Anesthetic Agent.* Frontiers in Pharmacology, 2021. **12**.
4. Lee, A. and M. Shirley, *Remimazolam: A Review in Procedural Sedation.* Drugs, 2021. **81**(10): p. 1193-1201.
5. Ustundag, Y., Z. Karasu, and Y. Yilmaz Urun, *Standardized versus nonstandardized pharmacologic treatment for hepatorenal syndrome.* European Journal of Gastroenterology & Hepatology, 2021. **33**(10): p. 1334-1335.
6. Ko, C.-C., et al., *The use of remimazolam versus propofol for induction and maintenance of general anesthesia: A systematic review and meta-analysis.* Frontiers in Pharmacology, 2023. **14**.
7. Zhang, J., et al., *Remimazolam versus propofol for procedural sedation and anesthesia: a systemic review and meta-analysis.* Minerva Anestesiologica, 2022. **88**(12).
8. Royse C, C.S., *Satisfaction is not substantially affected by quality of recovery: different constructs or are we lost in statistics?* Anaesthesia, 2017. **72**.
9. Myles, P.S., et al., *Measurement of quality of recovery after surgery using the 15-item quality of recovery scale: a systematic review and meta-analysis.* British Journal of Anaesthesia, 2022. **128**(6): p. 1029-1039.
10. Xilin Peng, M., et al., *Hemodynamic Influences of Remimazolam Versus Propofol During the Induction Period of General Anesthesia: A Systematic Review and Meta-analysis of Randomized Controlled Trials.* Pain Physician, 2023. **26**.

11. Choi, J.Y., et al., *Comparison of remimazolam-based and propofol-based total intravenous anesthesia on postoperative quality of recovery: A randomized non-inferiority trial.* Journal of Clinical Anesthesia, 2022. **82**.
12. Huang, Y., et al., *Efficacy and safety of remimazolam compared with propofol in hypertensive patients undergoing breast cancer surgery: a single-center, randomized, controlled study.* BMC Anesthesiology, 2023. **23**(1).
13. Kim, E.-J., et al., *Comparison of postoperative nausea and vomiting between Remimazolam and Propofol in Patients undergoing oral and maxillofacial surgery: a prospective Randomized Controlled Trial.* BMC Anesthesiology, 2023. **23**(1).
14. Lee, H.-J., et al., *Comparison of the recovery profile of remimazolam with flumazenil and propofol anesthesia for open thyroidectomy.* BMC Anesthesiology, 2023. **23**(1).
15. Tang, L., et al., *Effect of general anaesthesia with remimazolam versus propofol on postoperative quality of recovery in patients undergoing ambulatory arthroscopic meniscus repair: a randomised clinical trial.* BJA Open, 2023. **8**.
16. Li Huixin, X.F., Zhang Wei,Yang jianjun,Wang Zhongyu,Yuan Jingjing, *Comparison of effects of remimazolam and propofol on quality of postoperative recovery in aged patients with goal-directed hemodynamic management strategies.* Chin J Aneathesiol, 2021. **41**.
17. Zhao Songya, L.X., Lyu Shuaiguo,Shan Yingying,Miao Changhong, *Effects of remimazolam versus propofol on postoperative recovery quality in elderly patients undergoing thoracoscopic laparoscopic radical esophagectomy.* Natl Med J China, 2023. **103**.
18. Brohan, J. and B.G. Goudra, *The Role of GABA Receptor Agonists in Anesthesia and Sedation.* CNS Drugs, 2017. **31**(10): p. 845-856.
19. Doi, M., et al., *Efficacy and safety of remimazolam versus propofol for general anesthesia: a multicenter, single-blind, randomized, parallel-group, phase IIb/III trial.* Journal of Anesthesia, 2020. **34**(4): p. 543-553.
20. Chen Yu, C.S., Zhu Xiaogang, Ji Fuhai, *Sedative effect of remimazolam for induction of general anesthesia in elderly patients.* Chin J Aneathesiol, 2020. **8**.
21. Gornall, B.F., et al., *Measurement of quality of recovery using the QoR-40: a quantitative systematic review.* British Journal of Anaesthesia, 2013. **111**(2): p. 161-169.
22. PA. Stark, B.M.S., * Paul S. Myles, M.B., B.S., M.P.H., M.D., F.C.A.R.C.S.I., F.A.N.Z.C.A., F.R.C.A.,† Justin A. Burke, M.B., B.S., F.A.N.Z.C.A.‡, *Development and Psychometric Evaluation of a Postoperative Quality of Recovery Score.* Anesthesiology, 2013. **118**.
23. Myles, P.S., *Measuring quality of recovery in perioperative clinical trials.* Current Opinion in Anaesthesiology, 2018. **31**(4): p. 396-401.
24. Mao, Y., et al., *Quality of Recovery After General Anesthesia with Remimazolam in Patients' Undergoing Urologic Surgery: A Randomized Controlled Trial Comparing Remimazolam with Propofol.* Drug Design, Development and Therapy, 2022. **Volume 16**: p. 1199-1209.
25. Guo, L., et al., *Effect of remimazolam versus propofol sedation on the quality of recovery after colonoscopy.* European Journal of Anaesthesiology, 2022. **39**(12): p. 953-955.
26. Luo, W., et al., *Efficacy and safety of remimazolam tosilate versus propofol in patients undergoing day surgery: a prospective randomized controlled trial.* BMC Anesthesiology, 2023. **23**(1).

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## Table 1(on next page)

Baseline summary of the included RCTs

RCT: randomized controlled trials; ASA: American Society of anesthesiologists; BMI: body mass index; IV: intravenous; TCI: target-controlled infusion.

| Rank | Trails | Country | Study design | Sample size | ASA | Surgery type | Participant characteristics | | Remimazolam | Propofol | Scale design |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Remimazolam group | Propofol group | | | |
| 1 | Choi 2022 (NCT05016518) | Korea | RCT | 139 | I,II | Open thyroidectomy | Age (39.5 (33-48)) F/M (70/0) | Age (41.0 (37-47)) F/M (69/0) | (IV) Induction: 6 mg/kg/h Maintenance: 1-2 mg/kg/h | (TCI) Induction: 5 μg/mL Maintenance: 2-6 μg/mL | QoR-15 |
| 2 | Lee 2023 (NCT05047939) | Korea | RCT | 57 | I,II | Open thyroidectomy | Age (45±13.4) F/M (21/7) BMI (24.3 (22.8–26.0)) | Age (51±12.1) F/M (19/10) BMI (22.6 (20.9–25.3)) | (IV) Induction: 6 mg/kg/h Maintenance: 1-2 mg/kg/h | (TCI) Induction: 3 ng/ml Maintenance: 2 ng/ml | QoR-15 |
| 3 | Tang 2023 (ChiCTR2100053014) | China | RCT | 114 | I,II | Meniscus repair | Age (48.5 (19-62)) F/M (29/27) BMI (24.73±2.93) | Age (50 (19-64)) F/M (31/27) BMI (23.95±2.85) | (IV) Induction: 6 mg/kg/h Maintenance: 0.4-2 mg/kg/h | (TCI) Induction: 2 μg/mL 3.5 μg/mL after 20 s Maintenance: 1-3 μg/ml | QoR-15 |
| 4 | Zhao 2023 | China | RCT | 108 | I,II | Esophagectomy | Age (65.4±3.1) F/M (19/35) BMI (21.2±0.8) | Age (64.5±3) F/M (21/33) BMI (21.5±0.8) | (IV) Induction: 0.2-0.3 mg/kg Maintenance: 0.4-1 mg/kg/h | (IV) Induction: 1-2 mg/kg Maintenance: 4-10 mg/kg/h | QoR-15 |
| 5 | Kim 2023 (KCT0006965) | Korea | RCT | 189 | I,II | Oral and maxillofacial surgery | Age (41.7±12.2) F/M (33/61) BMI (23.8±3.3) | Age (43.3±13.2) F/M (36/59) BMI (23.7±2.9) | (IV) Induction: 12 mg/kg/h Maintenance: 1-2 mg/kg/h | (TCI) Induction: 3-5 μg/mL Maintenance: 3-5 μg/mL | QoR-40 |
| 6 | Li 2021 (ChiCTR2100044570) | China | RCT | 90 | II,III | Laparoscopic surgery | Age (74±3) F/M (23/22) BMI (22.4±2.8) | Age (71±4) F/M (26/19) BMI (23.4±3.4) | (IV) Induction: 6 mg/kg/h Maintenance: 0.5-1 mg/kg/h | (IV) Induction: 2 mg/kg Maintenance: 4-12 mg/kg/h | QoR-40 |
| 7 | Huang 2023 (ChiCTR2000040579) | China | RCT | 120 | II,III | Breast cancer surgery | Age (62.6±8.9) BMI (24.3±2.6) | Age (63.8±11) BMI (24.8±2.7) | (IV) Induction: 0.3 mg/kg Maintenance: 0.3 mg/kg/h | (IV) Induction: 2 mg/kg Maintenance: 2 mg/kg/h | QoR-40 |

1

## Table 2(on next page)

Adverse events

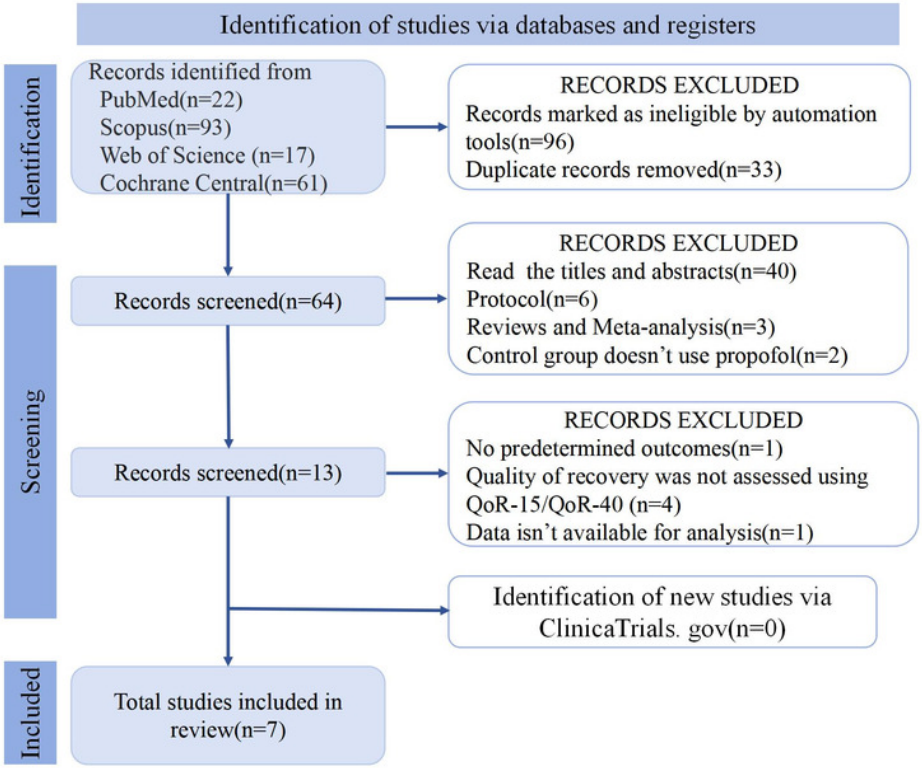
R: remimazolam group; P: propofol group; PONV: postoperative nausea/vomiting

| References | Sample size | | PONV, n | | Injection pain, n | | Hypotension, n | | Bradycardia, n | |
|---|---|---|---|---|---|---|---|---|---|---|
| | R | P | R | P | R | P | R | P | R | P |
| Choi 2022 | 70 | 69 | NA | NA | 0 | 2 | 1 | 7 | NA | NA |
| Lee 2023 | 28 | 29 | 3 | 0 | NA | NA | NA | NA | NA | NA |
| Tang 2023 | 56 | 58 | 6 | 5 | 0 | 3 | 18 | 34 | 3 | 10 |
| Zhao 2023 | 54 | 54 | NA | NA | NA | NA | 19 | 34 | 3 | 18 |
| Kim 2023 | 94 | 95 | 11 | 10 | NA | NA | NA | NA | NA | NA |
| Li 2021 | 45 | 45 | 11 | 4 | NA | NA | 42 | 67 | 4 | 36 |
| Huang 2023 | 60 | 60 | 2 | 1 | NA | NA | 22 | 35 | NA | NA |
| Total incidence (%) | | | 11.7 | 7 | 0 | 3.9 | 35.8 | 61.9 | 6.5 | 40.8 |

1

# Figure 1

PRISMA2020 flow diagram of articles.



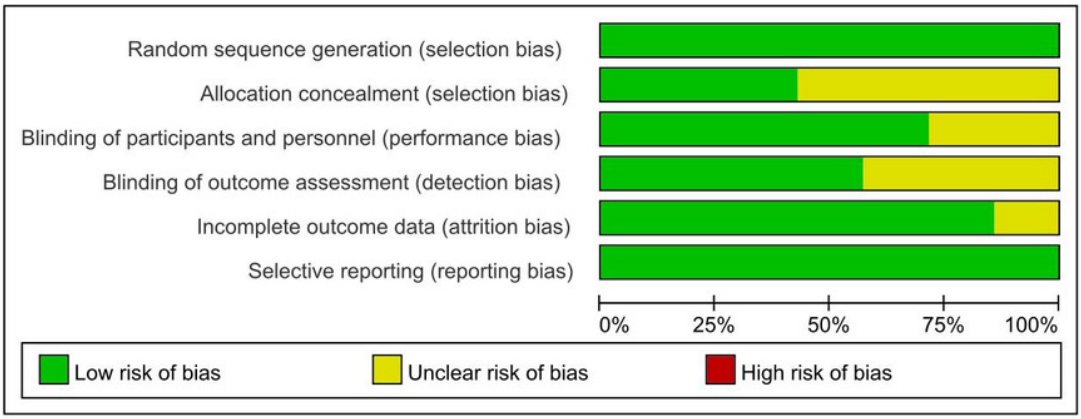
# Figure 2

Risk of bias Assessment

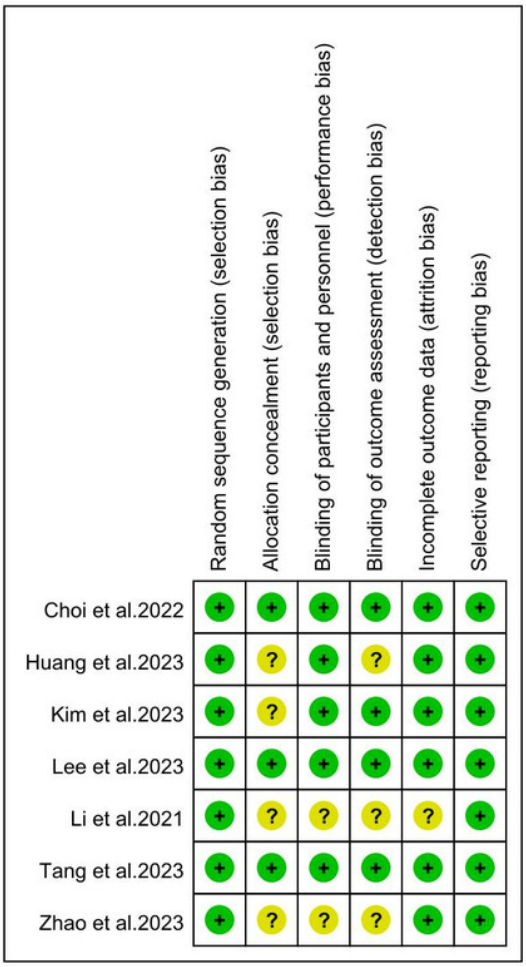
(A) Risk of bias evaluated by the Cocharne Collaboration Risk of Bias Assessment Instrument

(B) Risk of bias assessment for included articles

A


Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
0%
25%
50%
75%
100%
Low risk of bias
Unclear risk of bias
High risk of bias

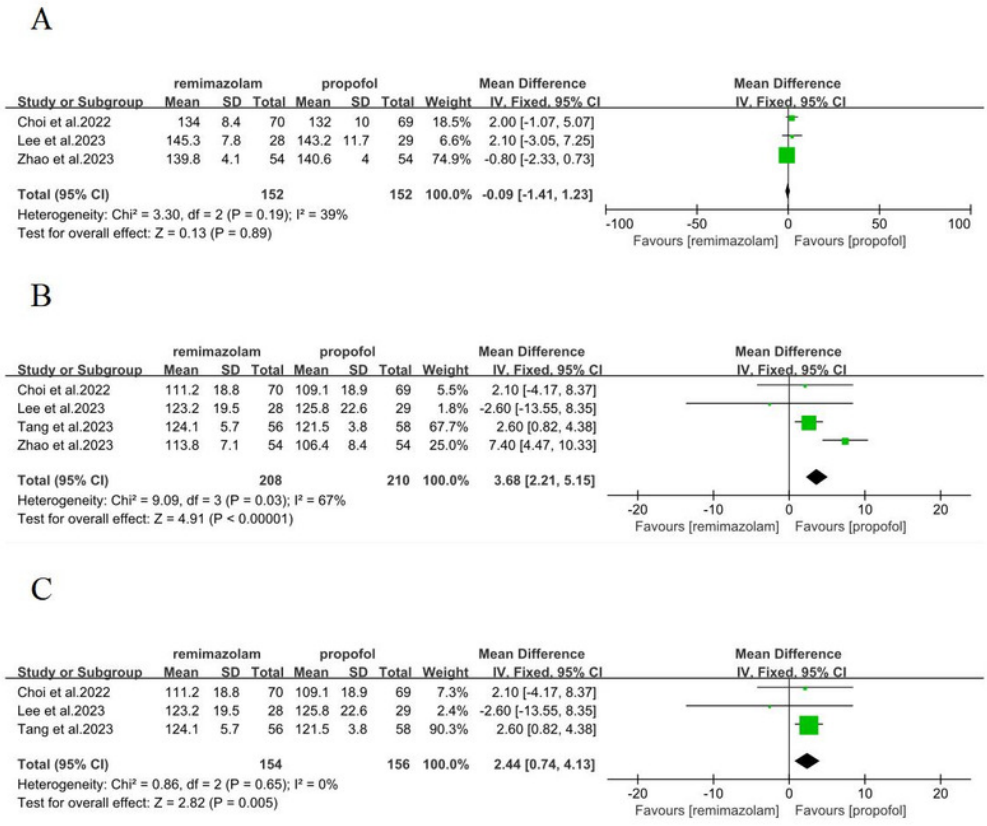
B


Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Choi et al.2022
Huang et al.2023
Kim et al.2023
Lee et al.2023
Li et al.2021
Tang et al.2023
Zhao et al.2023

# Figure 3

Forest plot comparing between remimazolam group and propofol group.

(A) QoR-15 on the pre-operation; (B) QoR-15 on the POD1; (C) QoR-15 after leave-one-out on the POD1 (CI, confidence interval; IV, inverse variance)

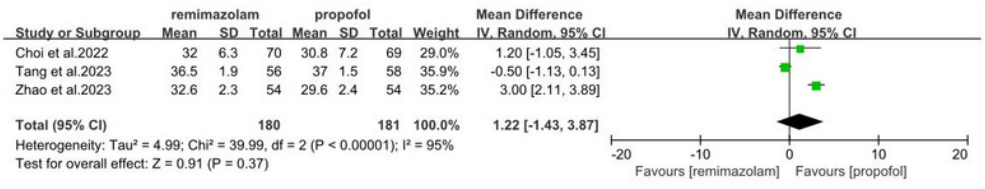


# Figure 4

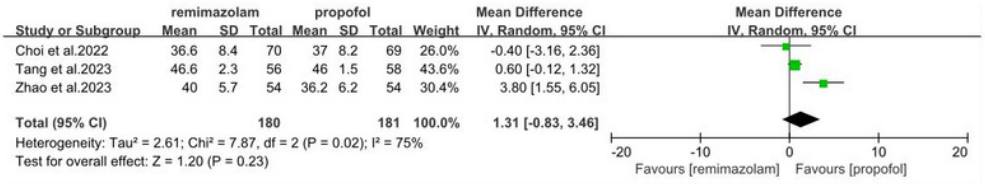
Forest plot comparing between remimazolam group and propofol group.

(A) Emotional status (B) physical comfort (C) psychological support (D) physical independence (E) pain (CI, confidence interval; IV, inverse variance)

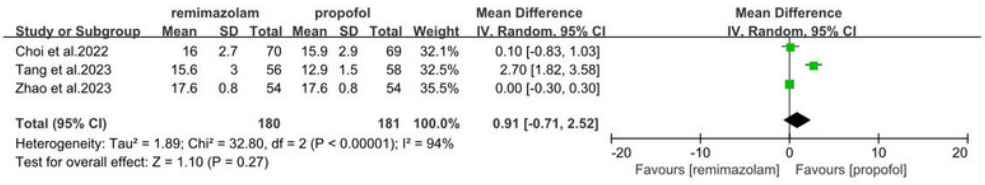
A


remimazolam propofol Mean Difference Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI IV, Random, 95% CI
Choi et al.2022 32 6.3 70 30.8 7.2 69 29.0% 1.20 [-1.05, 3.45]
Tang et al.2023 36.5 1.9 56 37 1.5 58 35.9% -0.50 [-1.13, 0.13]
Zhao et al.2023 32.6 2.3 54 29.6 2.4 54 35.2% 3.00 [2.11, 3.89]
Total (95% CI) 180 181 100.0% 1.22 [-1.43, 3.87]
Heterogeneity: Tau² = 4.99; Chi² = 39.99, df = 2 (P < 0.00001); I² = 95%
Test for overall effect: Z = 0.91 (P = 0.37)
-20 -10 0 10 20
Favours [remimazolam] Favours [propofol]

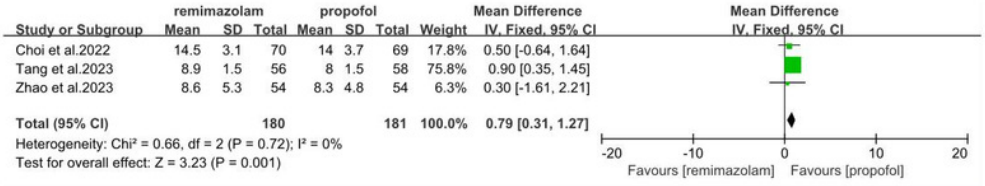
B


remimazolam propofol Mean Difference Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI IV, Random, 95% CI
Choi et al.2022 36.6 8.4 70 37 8.2 69 26.0% -0.40 [-3.16, 2.36]
Tang et al.2023 46.6 2.3 56 46 1.5 58 43.6% 0.60 [-0.12, 1.32]
Zhao et al.2023 40 5.7 54 36.2 6.2 54 30.4% 3.80 [1.55, 6.05]
Total (95% CI) 180 181 100.0% 1.31 [-0.83, 3.46]
Heterogeneity: Tau² = 2.61; Chi² = 7.87, df = 2 (P = 0.02); I² = 75%
Test for overall effect: Z = 1.20 (P = 0.23)
-20 -10 0 10 20
Favours [remimazolam] Favours [propofol]

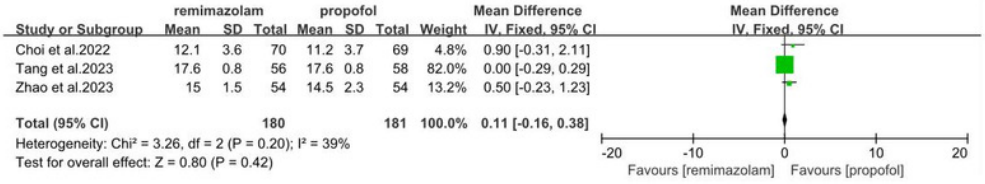
C


remimazolam propofol Mean Difference Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI IV, Random, 95% CI
Choi et al.2022 16 2.7 70 15.9 2.9 69 32.1% 0.10 [-0.83, 1.03]
Tang et al.2023 15.6 3 56 12.9 1.5 58 32.5% 2.70 [1.82, 3.58]
Zhao et al.2023 17.6 0.8 54 17.6 0.8 54 35.5% 0.00 [-0.30, 0.30]
Total (95% CI) 180 181 100.0% 0.91 [-0.71, 2.52]
Heterogeneity: Tau² = 1.89; Chi² = 32.80, df = 2 (P < 0.00001); I² = 94%
Test for overall effect: Z = 1.10 (P = 0.27)
-20 -10 0 10 20
Favours [remimazolam] Favours [propofol]

D


remimazolam propofol Mean Difference Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Fixed, 95% CI IV, Fixed, 95% CI
Choi et al.2022 14.5 3.1 70 14 3.7 69 17.8% 0.50 [-0.64, 1.64]
Tang et al.2023 8.9 1.5 56 8 1.5 58 75.8% 0.90 [0.35, 1.45]
Zhao et al.2023 8.6 5.3 54 8.3 4.8 54 6.3% 0.30 [-1.61, 2.21]
Total (95% CI) 180 181 100.0% 0.79 [0.31, 1.27]
Heterogeneity: Chi² = 0.66, df = 2 (P = 0.72); I² = 0%
Test for overall effect: Z = 3.23 (P = 0.001)
-20 -10 0 10 20
Favours [remimazolam] Favours [propofol]

E

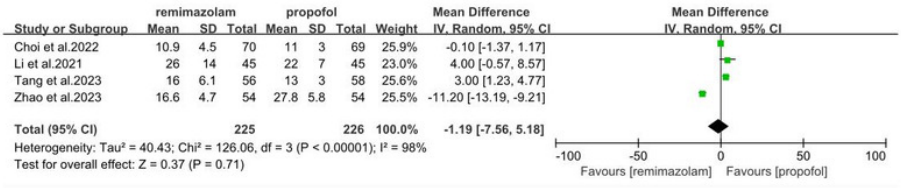

remimazolam propofol Mean Difference Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Fixed, 95% CI IV, Fixed, 95% CI
Choi et al.2022 12.1 3.6 70 11.2 3.7 69 4.8% 0.90 [-0.31, 2.11]
Tang et al.2023 17.6 0.8 56 17.6 0.8 58 82.0% 0.00 [-0.29, 0.29]
Zhao et al.2023 15 1.5 54 14.5 2.3 54 13.2% 0.50 [-0.23, 1.23]
Total (95% CI) 180 181 100.0% 0.11 [-0.16, 0.38]
Heterogeneity: Chi² = 3.26, df = 2 (P = 0.20); I² = 39%
Test for overall effect: Z = 0.80 (P = 0.42)
-20 -10 0 10 20
Favours [remimazolam] Favours [propofol]

# Figure 5

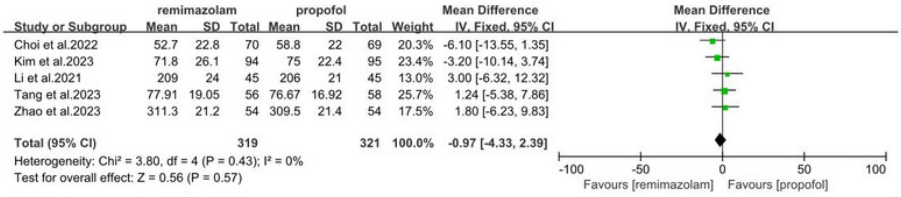
Forest plot comparing between remimazolam group and propofol group.

(A) time to extubation (B) duration of anesthesia (C) duration of surgery (D) duration of PACU (E) duration of postoperative hospital stay (F) QoR-40 on the POD1 (CI, confidence interval; IV, inverse variance)

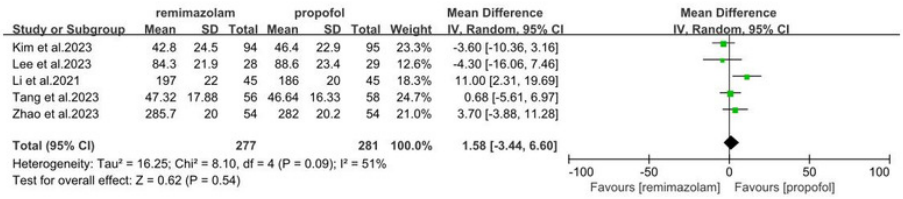
A


remimazolam propofol Mean Difference Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI IV, Random, 95% CI
Choi et al.2022 10.9 4.5 70 11 3 69 25.9% -0.10 [-1.37, 1.17]
Li et al.2021 26 14 45 22 7 45 23.0% 4.00 [-0.57, 8.57]
Tang et al.2023 16 6.1 56 13 3 58 25.6% 3.00 [1.23, 4.77]
Zhao et al.2023 16.6 4.7 54 27.8 5.8 54 25.5% -11.20 [-13.19, -9.21]
Total (95% CI) 225 226 100.0% -1.19 [-7.56, 5.18]
Heterogeneity: Tau² = 40.43; Chi² = 126.06, df = 3 (P < 0.00001); I² = 98%
Test for overall effect: Z = 0.37 (P = 0.71)
-100 -50 0 50 100
Favours [remimazolam] Favours [propofol]

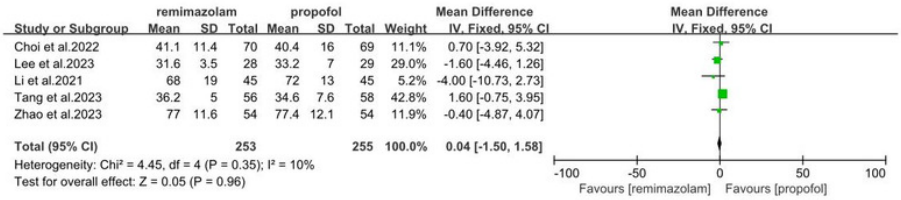
B


remimazolam propofol Mean Difference Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Fixed, 95% CI IV, Fixed, 95% CI
Choi et al.2022 52.7 22.8 70 58.8 22 69 20.3% -6.10 [-13.55, 1.35]
Kim et al.2023 71.8 26.1 94 75 22.4 95 23.4% -3.20 [-10.14, 3.74]
Li et al.2021 209 24 45 206 21 45 13.0% 3.00 [-6.32, 12.32]
Tang et al.2023 77.91 19.05 56 76.67 16.92 58 25.7% 1.24 [-5.38, 7.86]
Zhao et al.2023 311.3 21.2 54 309.5 21.4 54 17.5% 1.80 [-6.23, 9.83]
Total (95% CI) 319 321 100.0% -0.97 [-4.33, 2.39]
Heterogeneity: Chi² = 3.80, df = 4 (P = 0.43); I² = 0%
Test for overall effect: Z = 0.56 (P = 0.57)
-100 -50 0 50 100
Favours [remimazolam] Favours [propofol]

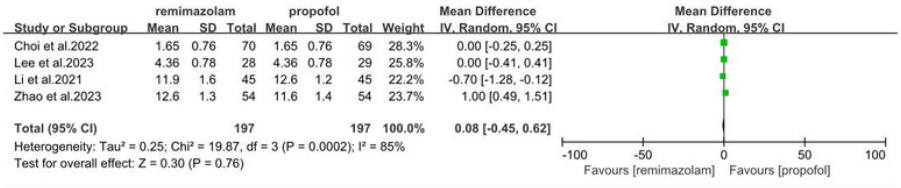
C


remimazolam propofol Mean Difference Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI IV, Random, 95% CI
Kim et al.2023 42.8 24.5 94 46.4 22.9 95 23.3% -3.60 [-10.36, 3.16]
Lee et al.2023 84.3 21.9 28 88.6 23.4 29 12.6% -4.30 [-16.06, 7.46]
Li et al.2021 197 22 45 186 20 45 18.3% 11.00 [2.31, 19.69]
Tang et al.2023 47.32 17.88 56 46.64 16.33 58 24.7% 0.68 [-5.61, 6.97]
Zhao et al.2023 285.7 20 54 282 20.2 54 21.0% 3.70 [-3.88, 11.28]
Total (95% CI) 277 281 100.0% 1.58 [-3.44, 6.60]
Heterogeneity: Tau² = 16.25; Chi² = 8.10, df = 4 (P = 0.09); I² = 51%
Test for overall effect: Z = 0.62 (P = 0.54)
-100 -50 0 50 100
Favours [remimazolam] Favours [propofol]

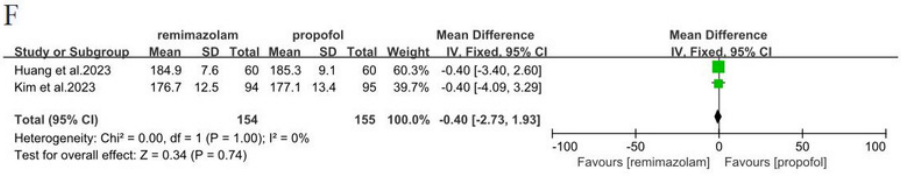
D


remimazolam propofol Mean Difference Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Fixed, 95% CI IV, Fixed, 95% CI
Choi et al.2022 41.1 11.4 70 40.4 16 69 11.1% 0.70 [-3.92, 5.32]
Lee et al.2023 31.6 3.5 28 33.2 7 29 29.0% -1.60 [-4.46, 1.26]
Li et al.2021 68 19 45 72 13 45 5.2% -4.00 [-10.73, 2.73]
Tang et al.2023 36.2 5 56 34.6 7.6 58 42.8% 1.60 [-0.75, 3.95]
Zhao et al.2023 77 11.6 54 77.4 12.1 54 11.9% -0.40 [-4.87, 4.07]
Total (95% CI) 253 255 100.0% 0.04 [-1.50, 1.58]
Heterogeneity: Chi² = 4.45, df = 4 (P = 0.35); I² = 10%
Test for overall effect: Z = 0.05 (P = 0.96)
-100 -50 0 50 100
Favours [remimazolam] Favours [propofol]

E


remimazolam propofol Mean Difference Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI IV, Random, 95% CI
Choi et al.2022 1.65 0.76 70 1.65 0.76 69 28.3% 0.00 [-0.25, 0.25]
Lee et al.2023 4.36 0.78 28 4.36 0.78 29 25.8% 0.00 [-0.41, 0.41]
Li et al.2021 11.9 1.6 45 12.6 1.2 45 22.2% -0.70 [-1.28, -0.12]
Zhao et al.2023 12.6 1.3 54 11.6 1.4 54 23.7% 1.00 [0.49, 1.51]
Total (95% CI) 197 197 100.0% 0.08 [-0.45, 0.62]
Heterogeneity: Tau² = 0.25; Chi² = 19.87, df = 3 (P = 0.0002); I² = 85%
Test for overall effect: Z = 0.30 (P = 0.76)
-100 -50 0 50 100
Favours [remimazolam] Favours [propofol]

F


remimazolam propofol Mean Difference Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Fixed, 95% CI IV, Fixed, 95% CI
Huang et al.2023 184.9 7.6 60 185.3 9.1 60 60.3% -0.40 [-3.40, 2.60]
Kim et al.2023 176.7 12.5 94 177.1 13.4 95 39.7% -0.40 [-4.09, 3.29]
Total (95% CI) 154 155 100.0% -0.40 [-2.73, 1.93]
Heterogeneity: Chi² = 0.00, df = 1 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.34 (P = 0.74)
-100 -50 0 50 100
Favours [remimazolam] Favours [propofol]