

Efficacy and safety of remimazolam vs. propofol for general anesthesia with tracheal intubation: Systematic review and meta-analysis

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Abstract. Remimazolam is an ultra-short-acting intravenous benzodiazepine derivative approved for sedation during gastroscopy and colonoscopy. The present study aimed to compare the safety and efficacy of remimazolam and propofol for general anesthesia with tracheal intubation by meta-analysis. A comprehensive search was conducted in databases, including PubMed, Embase, Cochrane Library and Web of Science, to identify relevant randomized controlled trials (RCTs). The search period was from the inception of these databases until February 2024. All eligible randomized controlled trials that report at least one outcome of interest were subjected to quality assessment and data extraction by two researchers independently using Review Manager 5.4 software. Data analysis was conducted using R software. A total of 14 RCTs with 1,275 patients were included for meta-analysis. Compared with propofol, remimazolam significantly reduced incidence of hypotension [odds ratio (OR)=0.31, 95% confidence interval (CI; 0.23, 0.43), $P<0.0001$], bradycardia [OR=0.06, 95% CI (0.00, 1.20), $P=0.06$] and injection pain [OR=0.02, 95% CI (0.01, 0.08), $P<0.0001$] with shorter time to recovery of consciousness (ROC) [mean difference (MD)=5.47 min, 95% CI (-10.70, -0.24 min), $P=0.04$] but longer time to loss of consciousness [MD=37.01 sec, 95% CI (24.42, 49.60 sec), $P<0.0001$]. Remimazolam was a safer and more effective alternative to propofol for general anesthesia with tracheal intubation and demonstrated a lower risk of adverse events with shorter time to ROC.

Introduction

General anesthesia with tracheal intubation is a key procedure in surgical settings that necessitate effective sedation and muscle relaxation (1). General anesthesia, which induces a reversible state of unconsciousness, analgesia and muscle relaxation, has a rich history dating back to the 19th century when ether and chloroform were first used. Since then, numerous advancements have been made, with propofol emerging as a widely used intravenous anesthetic agent for induction and maintenance of anesthesia (2,3). Despite its widespread use, propofol is associated with certain limitations, including injection pain and dose-dependent cardiorespiratory depression (4,5). Other commonly used sedatives, such as midazolam (6), etomidate (7) and dexmedetomidine (8), also demonstrate similar drawbacks.

Remimazolam is an ultra-short-acting intravenous benzodiazepine derivative and has been approved for sedation during gastroscopy and colonoscopy (9-11). It acts on γ -aminobutyric acid type A receptors and is rapidly metabolized by tissue esterase enzymes into an inactive form (12). Due to its rapid onset and offset of action, short recovery time, rare accumulation following long-term infusion and fewer serious side effects, remimazolam has been approved by regulatory authorities for general anesthesia as an alternative to other currently commonly used sedatives (first approved in January 2020 in Japan and the European Commission in April 2023) (13,14). Despite these promising attributes, to the best of our knowledge, there is a lack of comprehensive evidence comparing remimazolam directly with propofol for general anesthesia with tracheal intubation. The present meta-analysis aimed to pool data from eligible studies to provide a comprehensive evaluation of the comparative efficacy and safety profiles of remimazolam and propofol for general anesthesia with tracheal intubation.

Materials and methods

Literature search. A comprehensive search was conducted in databases, including PubMed ([ncbi.nlm.nih.gov/pubmed/](https://pubmed.ncbi.nlm.nih.gov/)), Embase (Embase.com), Cochrane Library (<https://www.cochranelibrary.com/>), and Web of Science (<https://www.woas.com/>).

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Key words: general anesthesia, meta-analysis, propofol, remimazolam, tracheal intubation

Table I. Literature search strategy.

A, PubMed	
Search number	Query
#1	Search 'tracheal intubation' [Mesh]
#2	Search ((tracheal intubation [Title/Abstract]) OR endotracheal intubation [Title/Abstract])
#3	#1 OR #2
#4	Search (((remimazolam [Title/Abstract]) AND propofol [Title/Abstract]) AND control [Title/Abstract])
#5	Search ((anesthesia [Title/Abstract]) OR general anesthesia [Title/Abstract])
#6	#3 AND #4 AND #5
B, Cochrane	
# 1	MeSH descriptor: (tracheal intubation) explode all trees
# 2	((tracheal intubation*) OR (endotracheal intubation*)): ti, ab, kw
# 3	#1 OR #2
# 4	MeSH descriptor: (remimazolam) explode all trees
# 5	MeSH descriptor: (propofol) explode all trees
# 6	MeSH descriptor: (control) explode all trees
# 7	MeSH descriptor: (anesthesia) explode all trees
# 8	((anesthesia*) OR (general anesthesia*)): ti, ab, kw
# 9	#7 OR #8
#10	#3 AND #4 AND #5 AND #6 AND #9
C, Embase	
#1	'tracheal intubation'/exp OR 'endotracheal intubation': ti, ab
#2	'remimazolam': ti, ab AND 'propofol': ti,ab AND 'control': ti, ab
#3	'anesthesia': ti, ab OR 'general anesthesia': ti,ab
#4	#1 AND #2 AND #3
D, Web of science	
#1	TS=(tracheal intubation OR endotracheal intubation)
#2	TI=(remimazolam AND propofol AND control AND anesthesia)
#3	#1 AND #2

webofscience.com/wos/), to identify relevant studies. The search period was from the inception of these databases until February 2024. The search strategy employed specific keywords such as 'remimazolam', 'propofol', 'general anesthesia', 'tracheal intubation', 'endotracheal intubation' and 'control' (Table I).

Inclusion criteria. Only randomized controlled trials (RCTs) were considered for inclusion, regardless of whether they implemented allocation concealment or blinding methods. The intervention group received remimazolam (group R) as an intravenous anesthetic, either alone or in combination with analgesics such as sufentanil and rocuronium, as well as muscle relaxants. The comparison group received propofol (group P) as intravenous anesthetic and the same combination of drugs as the remimazolam group. The selected literature needed to report ≥ 1 of the following outcome measures: Time to loss of consciousness (LOC), time to recovery of consciousness

(ROC), time to extubation and occurrence of adverse reactions such as hypotension, injection pain, bradycardia, nausea or vomiting and hypoxemia.

Exclusion criteria. Patients who did not undergo endotracheal intubation were excluded from the study. Additionally, studies without control groups, literature types such as reviews, case reports or abstracts, those without full-text availability, lacking relevant outcome measures or written in languages other than English were also excluded.

Data extraction and quality assessment. Two independent investigators performed the literature screening based on the aforementioned inclusion and exclusion criteria. Once the eligible studies were identified, data extraction was conducted using a standardized form. The extracted information included the first author, publication year, age and sex distribution of the study population, sample size and details regarding the

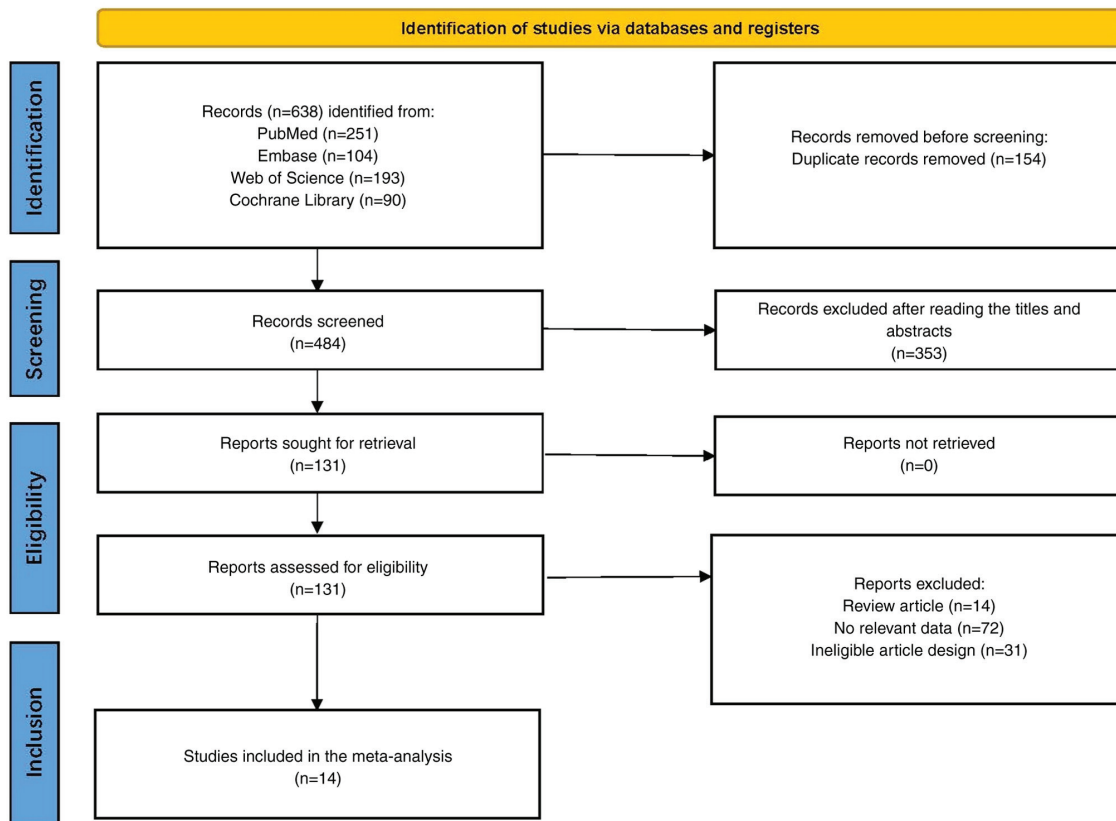


Figure 1. Flowchart of literature selection.

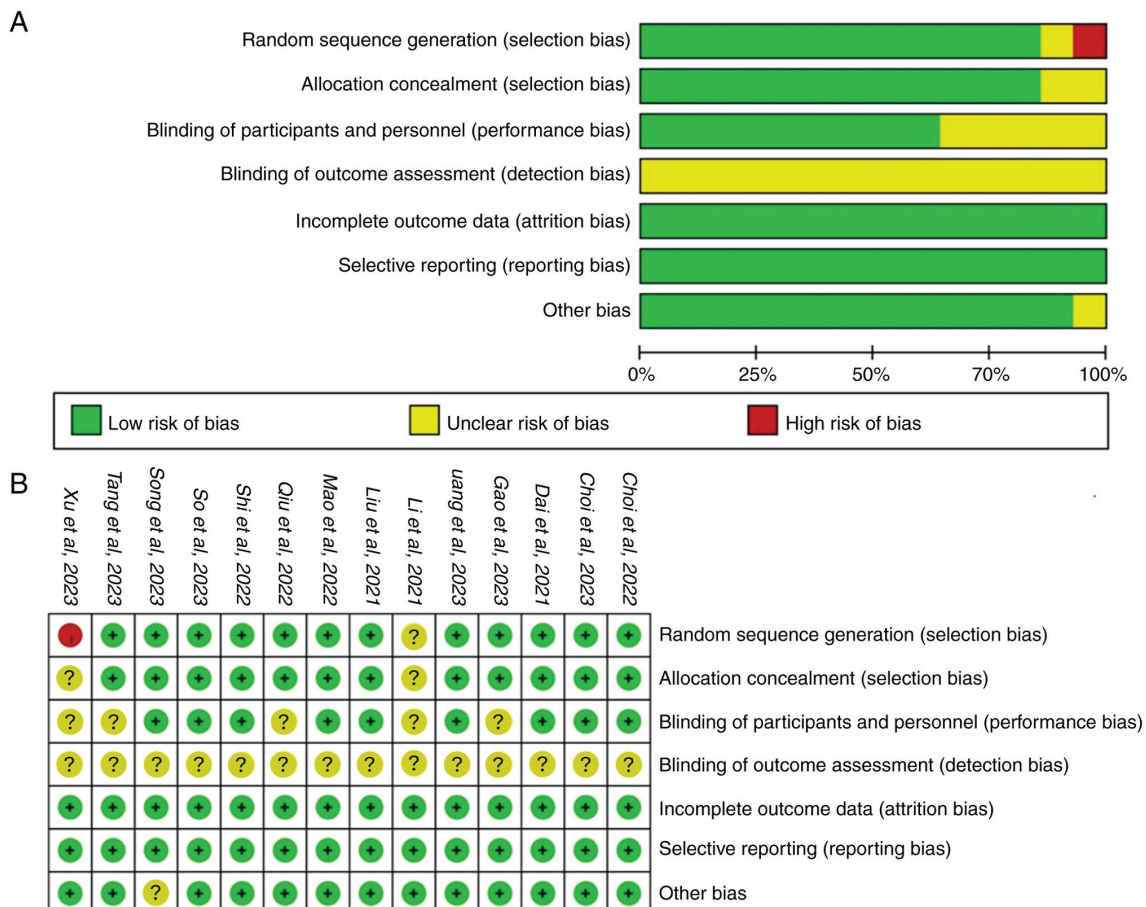


Figure 2. Cochrane bias risk assessment of included studies. (A) Summary of bias risk. (B) Bias risk of each study.

Table II. General characteristics of studies.

First author, year	Country	Sample size		Age, years		Sex, M/F		Surgery	Induction dosage		Maintenance dosage		(Refs.)
		R	P	R	P	R	P		R	P	R	P	
Li <i>et al</i> , 2021	China	52	52	48.6±13.8 ^a	46.8±11.3 ^a	24/28	25/27	Elective endotracheal intubation	0.2 mg/ kg	2.5 mg/ kg	0.2-0.6 mg/ kg/h	4.0-10.0 mg/ kg/h	(19)
Xu <i>et al</i> , 2023	China	30	30	69.9±4.3 ^a	68.6±3.3 ^a	14/16	13/17	Orthopedic	0.2 mg kg	1.5 mg/ kg	Remifentanyl 10.0-15.0 μ g/ kg/h/ 1.02.0% sevoflurane	Remifentanyl 10.0-15.0 μ g/ kg/h & 1.0%- 2.0% sevoflurane	(20)
Gao <i>et al</i> , 2023	China	20	20	67.22±4.4 ^a	67.2±4.4 ^a	16/4	15/5	Carotid artery stenosis	0.3 mg /kg	1.5-2.0 mg/ kg	Sevoflurane at adjusted concentration	Sevoflurane at adjusted concentration	(21)
Qiu <i>et al</i> , 2022	China	28	28	62.8±7.1 ^a	64.7±8.9 ^a	21/7	19/9	Endoscopic submucosal dissection	0.3 mg/ kg	2.0 mg/ kg	NR	NR	(22)
Tang <i>et al</i> , 2021	China	40	40	54.9±8.5 ^a	52.7±7.0 ^a	25/15	20/20	Cardiac	0.3 mg/ kg	1.5 mg/ kg	NR	NR	(23)
Song <i>et al</i> , 2023	South Korea	40	41	58.6±6.4 ^a	60.1±5.2 ^a	25/15	28/13	NR	6.0 mg/ kg/h	2.0 mg/ kg	1.0 mg/ kg/h	1.0 mg/ kg/h	(24)
Choi <i>et al</i> , 2022	South Korea	70	69	39.5 (33.0-48.0) ^b	41.0 (37.0-47.0) ^b	0/70	0/69	Open thyroidectomy	6.0 mg/ kg/h	5.0 μ g/ ml	1.0-2.0 mg/ kg/h	2.0-6.0 μ g/ ml	(25)
Shi <i>et al</i> , 2022	China	38	38	52.7±4.9 ^a	51.6±5.55 ^a	16/22	18/20	Endoscopic variceal ligation	0.2 mg/ kg	2.0 mg/ kg	1.0-2.0 mg/ kg/h	NR	(26)
So <i>et al</i> , 2023	South Korea	42	39	74.5 (70.0-78.3) ^b	76.0 (70.0-81.0) ^b	22/20	20/19	Elective laparoscopic cholecystectomy	6.0 mg/ kg/h	1.5-2.0 mg/ kg	1.0-2.0 mg/ kg/h	100.0 μ g/ kg/min	(27)
Choi <i>et al</i> , 2023	South Korea	48	48	52.3±9.1 ^a	52.8±8.2 ^a	26/22	22/26	NR	6.0 mg/ kg/h	1.5-2.0 mg/ kg	1.0 mg/ kg/h	3.0-6.0 mg/ kg/h	(28)
Dai <i>et al</i> , 2021	China	142	48	47.9±13.6 ^a	52.0±13.7 ^a	86/56	26/22	Elective	0.2-0.4 mg/ kg	2.0 mg/ kg	Sufentanyl/ remifentanyl 6.0-8.0 mg/kg	Sufentanyl/ remifentanyl 6.0-8.0 mg/kg	(29)

Table II. Continued.

First author, year	Country	Sample size		Age, years		Sex, M/F		Surgery	Induction dosage		Maintenance dosage		(Refs.)
		R	P	R	P	R	P		R	P	R	P	
Kuang <i>et al</i> , 2023	China	42	42	65.4±3.9 ^a	65.2±4.4 ^a	19/23	20/22	Lobectomy	0.3 mg/ kg	2.0 mg/ kg	0.6-1.2 mg/ kg/h	2.0-10.0 mg/ kg/h	(30)
Liu <i>et al</i> , 2021	China	30	30	54.9±11.3 ^a	50.6±10.5 ^a	14/16	17/13	Valve replacement	1.8 mg/kg/h	2.5 µg/ml	Sufentanil 0.2 µg/kg/h/ dexmedeto- midine 0.5 µg/ kg/h	Sufentanil 0.2 µg/kg/h / dexmedeto- midine 0.5 µg/ kg/h	(31)
Mao <i>et al</i> , 2022	China	64	64	52.5±17.5 ^a	50.0±25.8 ^a	41/23	45/19	Urological	0.2-0.3 mg/ kg	2.0-3.0 mg/ kg	1.0-2.0 mg/ kg/h	4.0-10.0 mg/ kg/h	(32)

Data are presented as ^amean and SD or ^bmedian and range. R, remimazolam; P, propofol; M, male; F, female; NR, not reported.

anesthesia induction and maintenance protocols in the experimental and control groups. Any discrepancies were resolved through discussion.

In accordance with the Cochrane Handbook for Systematic Reviews of Interventions (Version 5), the Cochrane Risk of Bias Tool was employed to assess the methodological quality of the included studies (15). The risk of bias assessment encompassed random sequence generation, allocation concealment, blinding, intention-to-treat analysis, completeness of data, selecting outcome reporting and other potential biases associated with baseline comparability. The evaluation was performed independently by two researchers using Review Manager (Version 5.4; Cochrane Collaboration, 2020).

The present systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (16) and the protocol was registered in the PROSPERO database (ID no. CRD42024520840; crd.york.ac.uk/prospero/#myprospero).

Statistical analysis. Data analysis was conducted using R software (4.1.2) (17). Categorical variables were assessed using odds ratio (OR) and their corresponding 95% confidence interval (CI), while continuous variables were analyzed using mean difference (MD) and their corresponding 95% CI. The included studies were considered heterogenous based on the guidance of Cochrane Handbook and a random effect model was used for the meta-analysis. Publication bias among the included studies was assessed using funnel plots and Egger's test (18). P<0.05 was considered to indicate a statistically significant difference.

Results

Literature search. A comprehensive search yielded 638 relevant articles. After eliminating duplicates, 484 unique articles remained. Assessment of titles and abstracts led to the exclusion of 353 studies that were irrelevant to the research question. Following this initial screening, the full texts of the remaining 131 articles were obtained and subjected to evaluation based on the predetermined inclusion and exclusion criteria. Consequently, 117 studies were excluded from the final analysis due to reasons such as being review articles, not adhering to the specified study design or lacking the requisite outcome variables. Ultimately, 14 articles fulfilled the inclusion criteria and were included in the present study (Fig. 1).

General characteristics of included studies. Included studies were published from 2021 to 2023. The sample sizes of the studies ranged between 40 and 190 participants, aggregating to a total of 1,275 individuals. Among the included articles, group R comprised 686 cases, while group P encompassed 598 cases. A comprehensive summary of included studies is shown in Table II.

Quality assessment of included studies. All 14 included articles were RCTs (Fig. 2). However, there were instances of unclear and high risk of bias. One study had unclear randomization (19) and another used admission order for random allocation (20), posing a high risk of bias. Two studies had unclear allocation concealment (19,20), while five did not

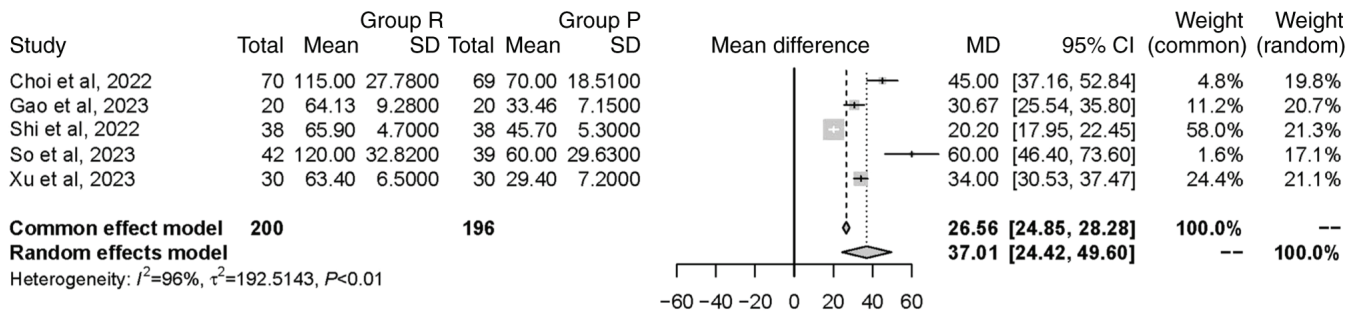


Figure 3. Meta-analysis of time to loss of consciousness. R, remimazolam; P, propofol.

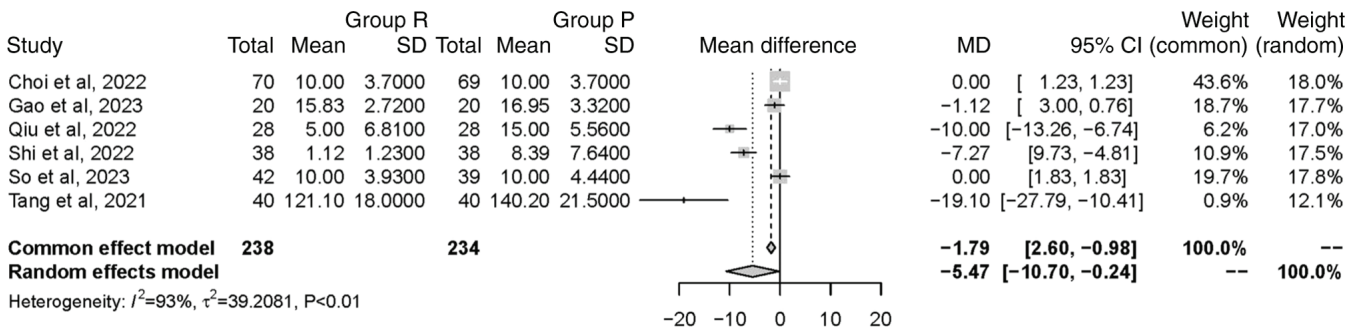


Figure 4. Meta-analysis of time to recovery of consciousness. R, remimazolam; P, propofol.

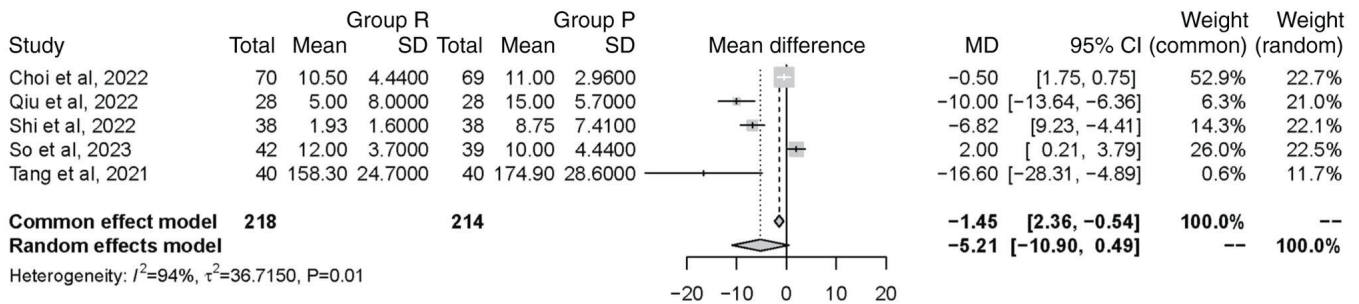


Figure 5. Meta-analysis of time to extubation. R, remimazolam; P, propofol.

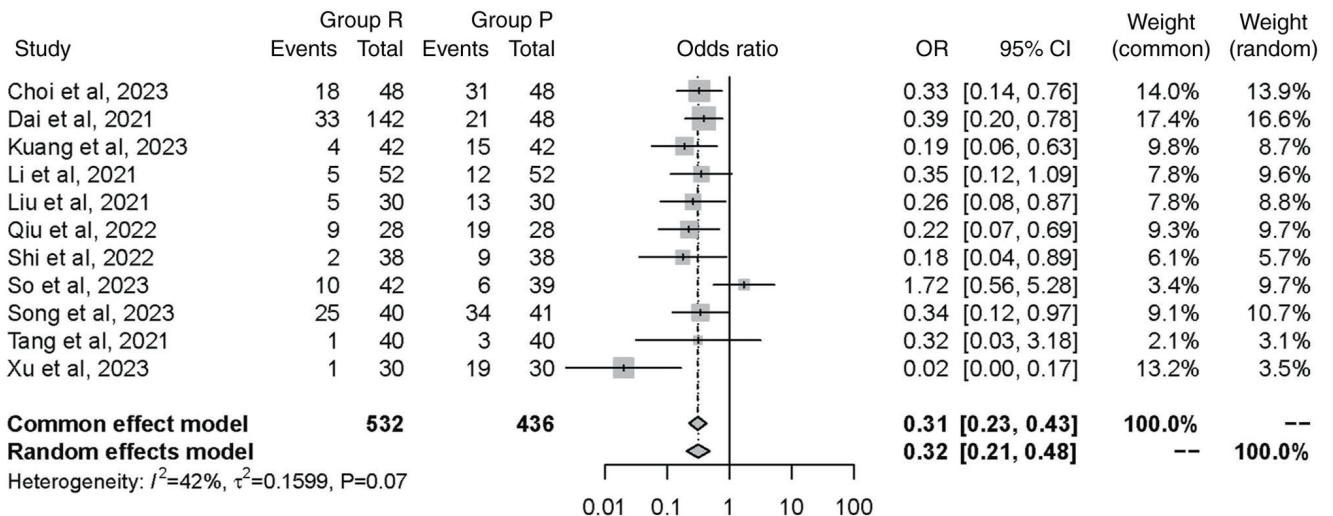


Figure 6. Meta-analysis of hypotension. R, remimazolam; P, propofol.

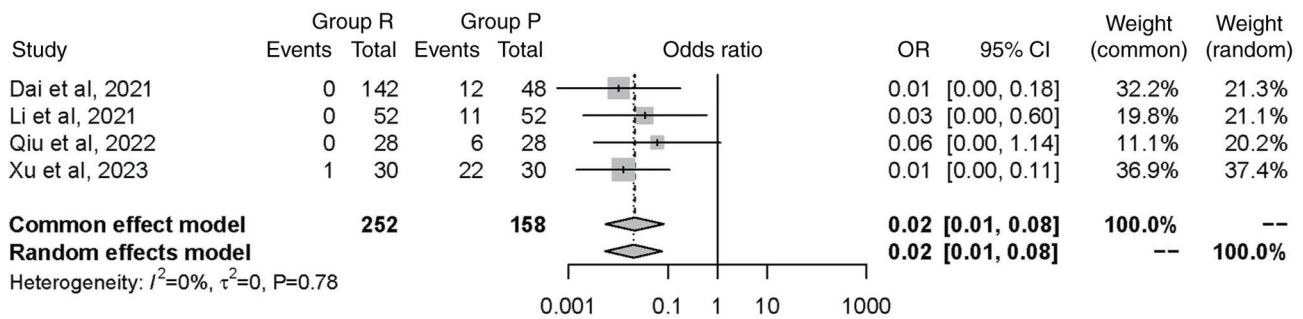


Figure 7. Meta-analysis of injection pain. R, remimazolam; P, propofol.

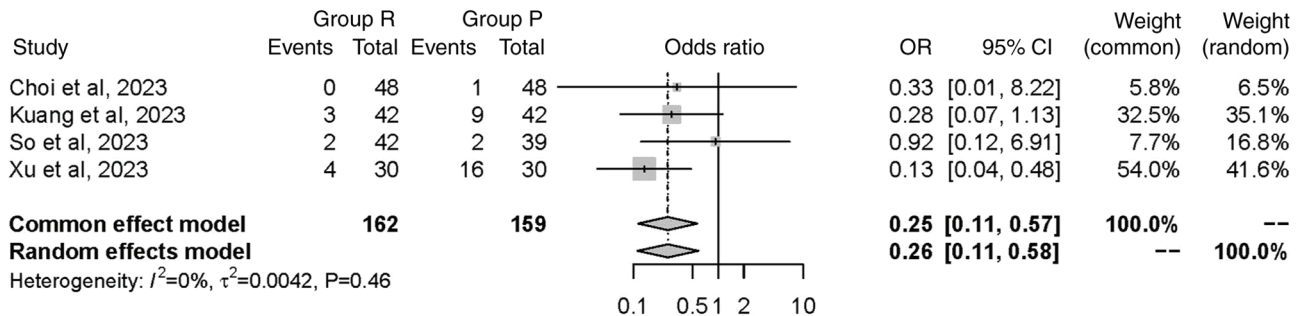


Figure 8. Meta-analysis of bradycardia. R, remimazolam; P, propofol.

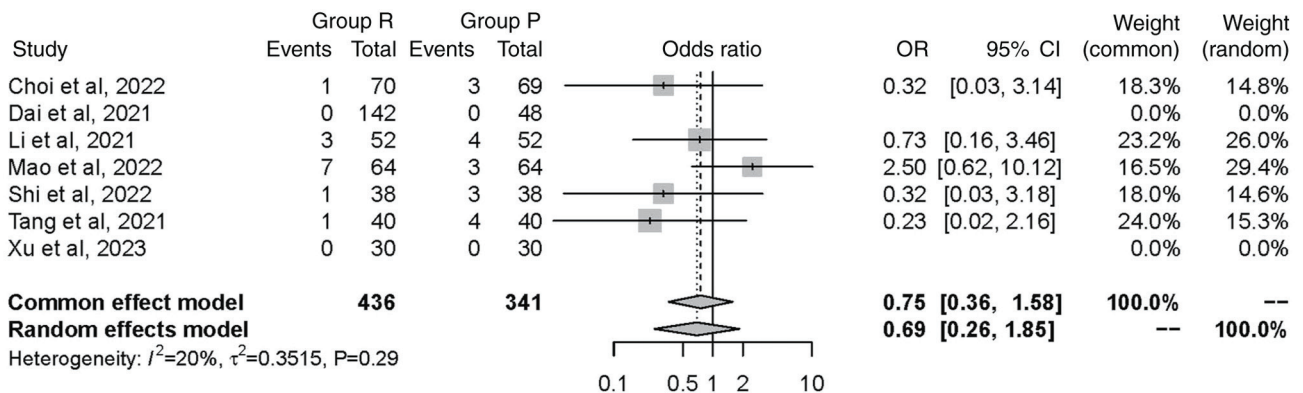


Figure 9. Meta-analysis of nausea or vomiting. R, remimazolam; P, propofol.

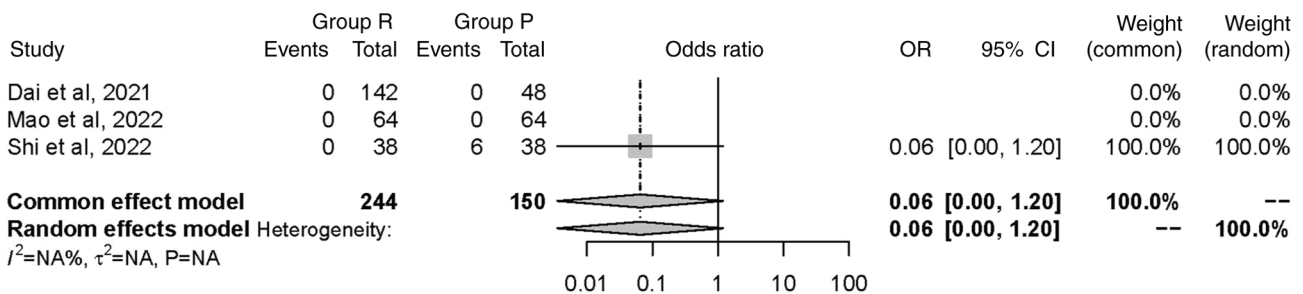


Figure 10. Meta-analysis of hypoxemia. R, remimazolam; P, propofol.

report blinding, resulting in an unclear risk (19-23). None of the studies mentioned intention-to-treat analysis and one study did not address baseline comparability (24), both of which

were categorized as unclear risk. Overall, all included studies had some degree of bias, with uncertain impact on the reliability and stability of the combined results.

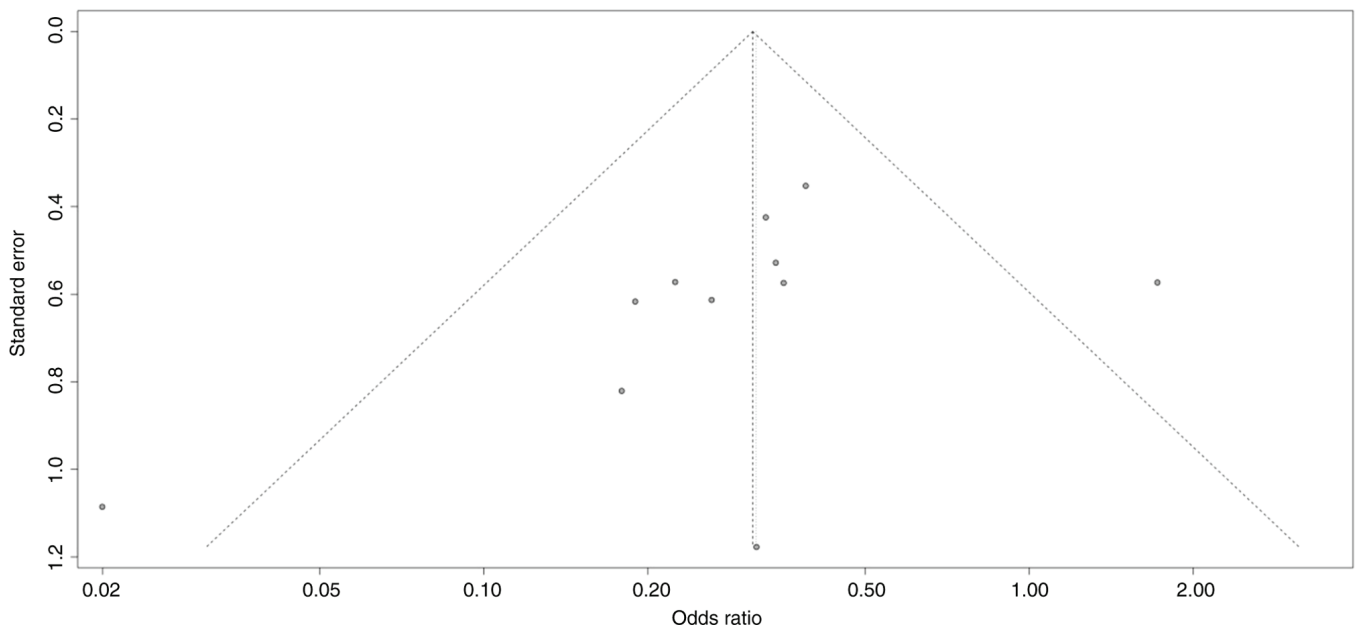


Figure 11. Funnel plot of hypotension.

Meta-analysis

Time to LOC. A total of five studies (20,21,25-27), involving a total of 396 patients, investigated the time to LOC. Significant heterogeneity was observed between the included studies ($P < 0.01$; $I^2 = 96\%$). The random effects model revealed that group R had a significantly longer time to LOC compared with group P [MD=37.01 sec, 95% CI (24.42, 49.60 sec), $P < 0.0001$]. This indicated that the intervention in group R led to delayed onset of unconsciousness (Fig. 3).

Time to ROC. A total of six studies (21-23,25-27), involving a total of 472 patients, examined the time to ROC. Significant heterogeneity was found between the included studies ($P < 0.01$; $I^2 = 93\%$). The random effects model revealed that group R had a significantly shorter time to ROC compared with group P [MD=-5.47 min, 95% CI (-10.70, -0.24 min), $P = 0.04$]. This indicated that the intervention in group R led to a faster ROC (Fig. 4).

Time to extubation. A total of five studies (22,23,25-27), comprising a total of 432 patients, examined the time to extubation. Significant heterogeneity was found between the included studies ($P < 0.01$; $I^2 = 94\%$). The random effects model indicated no significant difference in time to extubation between groups [MD=-5.21 min, 95% CI (-10.90, 0.49 min), $P = 0.07$]. This finding suggested that the intervention in group R did not have a significant impact on the duration of extubation (Fig. 5).

Hypotension. A total of 11 studies (19,20,22-24,27-32), comprising a total of 968 patients, investigated the incidence of hypotension. Although the studies showed relatively low heterogeneity ($P = 0.07$; $I^2 = 42\%$), a random effects model was used and found a significant reduction in the incidence of hypotension in group R compared with group P [OR=0.32, 95% CI (0.21, 0.48), $P < 0.0001$; Fig. 6].

Injection pain. A total of four studies (19,20,22,29), comprising a total of 410 patients, investigated the incidence of

injection pain. Although the studies showed minimal heterogeneity ($P = 0.78$; $I^2 = 0\%$), a random effects model was used in the meta-analysis and found a significant reduction in the incidence of injection pain in group R compared with group P [OR=0.02, 95% CI (0.01, 0.08), $P < 0.0001$; Fig. 7].

Bradycardia. A total of four studies (27,28,30,32), involving a total of 321 patients, examined the incidence of bradycardia. Although the studies showed minimal heterogeneity ($P = 0.46$; $I^2 = 0\%$), a random effects model was used in the meta-analysis. The incidence of bradycardia in group R was significantly lower compared with group P [OR=0.26, 95% CI (0.11, 0.58), $P = 0.001$; Fig. 8].

Nausea or vomiting. A total of seven studies (19,20,23,25,26,29,32), including a total of 777 patients, investigated the incidence of nausea or vomiting. Although the studies demonstrated a low heterogeneity ($P = 0.29$; $I^2 = 20\%$), a random effects model was used. No significant difference in the occurrence of nausea or vomiting was found between groups [OR=0.69, 95% CI (0.26, 1.85), $P = 0.46$]. This suggested intervention in group R did not have a significant effect on the incidence of nausea or vomiting (Fig. 9).

Hypoxemia. A total of three studies (26,29,32), including a total of 394 patients, investigated the incidence of hypoxemia; hypoxemia was reported in one study. The random effects model was used and did not find any significant difference in occurrence of hypoxemia between groups [OR=0.06, 95% CI (0.00, 1.20), $P = 0.07$]. This suggested that the intervention in group R did not have a statistically significant impact on the incidence of hypoxemia (Fig. 10).

Publication bias. Hypotension was reported in 11 studies as the most frequently studied outcome (19,20,22-24,27-32). A funnel plot was used to assess publication bias for hypotension and showed an asymmetrical scatter distribution (Fig. 11). Utilizing Egger's test for quantitative analysis, the

results yielded a non-significant P value of 0.19, indicating no significant publication bias in the studies.

Discussion

The present meta-analysis assessed the efficacy and safety of remimazolam over propofol as an anesthetic agent in general anesthesia with tracheal intubation and supported the superiority of remimazolam. Compared with propofol, general anesthesia with tracheal intubation on remimazolam led to a reduction in time to ROC by 5.47 min and an increase in time to LOC by 37 sec. Although no significant difference was found in time to extubation, remimazolam still demonstrated a trend towards a shorter time to extubation. These outcomes suggested that remimazolam may facilitate a more favorable recovery profile, which is key in clinical settings where rapid patient recovery is essential.

Prior to the emergence of remimazolam, both intravenous and volatile anesthetic agents used in general anesthesia exerted cardiovascular depressant effects, which could result in severe low cardiac output and bradycardia in patients with impaired cardiac function. Here, remimazolam was associated with a significantly lower incidence of hypotension, bradycardia and injection pain. Specifically, the incidence of hypotension was reduced by 69% and bradycardia by 75% in patients administered remimazolam compared with those given propofol. Additionally, the incidence of injection pain was markedly lower in the remimazolam group, indicating an advantage for patients sensitive to injection discomfort.

The present findings align with previous studies that highlighted the stable hemodynamic properties of remimazolam (13,33). For example, Nakayama *et al* (34) emphasized the minimal cardiovascular depression associated with remimazolam, which is particularly beneficial for elderly and critically ill patients. Furthermore, its metabolism independent of organ function renders it suitable for patients with hepatic or renal impairment (12,33). It also decreases surgical stress response and respiratory depression without significant myocardial depression, resulting in fewer anesthesia-associated adverse reactions (23,31,35). However, in patients routinely taking long-term angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, remimazolam has high incidence of hypotensive events (up to 62.5%, compared with 82.9% for propofol) during induction and maintenance of general anesthesia. Therefore, further evaluation of the potential adverse events of remimazolam in specific patient populations is still needed.

Rapid recovery time and superior safety profile of remimazolam could enhance patient throughput and decrease postoperative monitoring requirements, thereby improving surgical workflow and patient outcomes. Unlike propofol which does not have a specific antagonist and may lead to unpredictable delayed recovery following general anesthesia, the effects of remimazolam, as a benzodiazepine, can be completely reversed by flumazenil. The availability of flumazenil as a specific antagonist for remimazolam provides an added safety measure, although its routine use should be approached with caution due to potential re-sedation risks. This is because flumazenil only competitively antagonizes GABA_A receptors, and as the plasma concentration of flumazenil decreases, the sedative effect of remimazolam

may reappear (36,37). It is important to continue monitoring patients for a sufficient duration after administering flumazenil.

The present study has limitations that should be acknowledged. The visible differences in remimazolam and propofol make it challenging to conduct a double-blind clinical trial, which may introduce potential bias. Variability in surgical procedures and dosages between studies may also contribute to heterogeneity. While Egger's test did not indicate significant bias, this does not entirely rule out the possibility of bias affecting the results. The asymmetry in the funnel plot should be interpreted cautiously. Further sensitivity analyses on age, sex and dosage and stricter requirements on study quality can provide additional insights into the robustness of the conclusions drawn from the present meta-analysis. In addition, the studies included in the present meta-analysis were conducted in Asian countries. This may limit the generalizability of the findings to other populations.

In conclusion, remimazolam is a safer and more effective alternative to propofol for general anesthesia with tracheal intubation, with lower risk of adverse events such as hypotension, bradycardia and injection pain and a shorter time to ROC.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

HL and ZT conceived and designed the study, performed the literature review and analyzed and interpreted data. HL wrote the manuscript. HL and ZT confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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