ISSN: 2377-4630

Monici et al. Int J Anesthetic Anesthesiol 2024, 11:180
DOI: 10.23937/2377-4630/1410180
Volume 11 | Issue 2
Open Access

International Journal of
Anesthetics and Anesthesiology

SYSTEMATIC REVIEW AND META-ANALYSIS

The Efficacy and Safety of Remimazolam versus Propofol in Patients Undergoing Colonoscopy: A Systematic Review and Meta-Analysis

Vitor Cavalcante Monici[1], Alessandra Rocha Ribeiro Souto[1], Henrique de La Rocque Vieira de Mello dos Reis[1], Augusto Silva Alves[1], Ângelo Antônio Silva Lima[1], José Riccardo Ferrette Barreto[2], Igor Mourão Almeida[3], Henrique Augusto Guaresqui[3] and Flavia Farah Sabe[4]*

[1]*Universidade de Brasília - UnB, Brazil*

[2]*Universidade Estadual de Ciências da Saúde de Alagoas, Brazil*

[3]*Escola Superior de Ciências da Santa Casa de Misericórdia de Vitória - EMESCAM, Brazil*

[4]*Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo FMRP - USP, Brazil*

***Corresponding author:** *José Riccardo Ferrette Barreto, Universidade Estadual de Ciências da Saúde de Alagoas, Brazil*

Abstract

Background: Anesthesia with Propofol is common in patients undergoing colonoscopy, however, Remimazolam, a ultra-short-acting benzodiazepine, emerges as an alternative for this procedure. There are no clear protocols to guide choice between them. This study aims to explore the use of Remimazolam compared to propofol in patients undergoing colonoscopy.

Methods: Searches were conducted in the PubMed, Embase, and Cochrane Central in October 2023. Inclusion criterion: Randomized clinical trials (RCT) comparing Remimazolam and Propofol; Exclusion criterion: Case reports and case series, divergent intervention or population. Primary outcomes were discharge time and adverse events, secondary outcomes included injection pain, time to fully alertness, induction time, and hypotension. A meta-analysis was performed according to Cochrane recommendations.

Results: Five RCTs involving 1505 patients were included, 633 (42.05%) underwent sedation with Propofol. Discharge time favors Remimazolam (MD = -0.09, 95% CI -1.11 to 0.93, p = 0.86); as well as Adverse events (n = 1125 patients, OR = 0.53, 95% CI, 0.34 to 0.83, p = 0.006). Due to high heterogeneity and a possible outlier, a sensitivity analysis was performed detailing discharge time (MD = -0.62; 95% CI -1.12 to -0.12, p = 0.02). Both analyses showed statistical significance.

Conclusion: Remimazolam use in patients undergoing colonoscopy proved safer and more effective compared to Propofol regarding discharge time and adverse events such hypotension. However, due to the short number of available studies and heterogeneity in some secondary outcomes, further studies are necessary to confirm this superiority.

Keywords

Remimazolam, Propofol, Colonoscopy, Meta-analysis, Patient discharge, Safety

Introduction

In order to improve patient satisfaction and safety, Colonoscopy is usually performed under anesthesia in developed countries [1]. Due to its fast induction and recovery time [2], Propofol is currently the main drug used for this procedure and the most used anesthetic globally [3]. However, adverse events, such as cardiorespiratory depression and hypotension, in addition to nonlinear pharmacokinetics [4,5], limits the safety of Propofol use and suggest that safer medication should be sought after. An possible alternative is Remimazolam, a novel ultra-short-acting benzodiazepine [6], with similar onset and offset times to Propofol, but with the advantage of having first-order pharmacokinetics [4] and not being associated with significant cardiorespiratory depression

Citation: Monici VC, Souto ARR, Reis HLRVM, Alves AS, Lima AAS, et al. (2024) The Efficacy and Safety of Remimazolam versus Propofol in Patients Undergoing Colonoscopy: A Systematic Review and Meta-Analysis. Int J Anesthetic Anesthesiol 11:180. doi.org/10.23937/2377-4630/1410180

Accepted: August 05, 2024: **Published:** August 07, 2024

[3]. Therefore, we hypothesized that the use of Remimazolam in colonoscopy would have non-inferior efficacy compared to the use of Propofol, while having a better safety profile, with a smaller chance of adverse events during and after the procedure.

Methods

Background

The guidelines set by the Preferred Reported Items for Systematic Reviews and Meta-Analyses 2020 (PRISMA) were employed to conduct a systematic review followed by a meta-analysis, along with adherence to Cochrane Handbook for Systematic Reviews [7,8]. The protocols for this study was registered in PROSPERO (CRD42023469113) prior searches were initiated. Additionally, Population, Intervention, Control, and Outcomes (PICO) framework were used to define the research strategy.

Eligibility

Randomized and observational (prospective or retrospective) studies were Included for patients undergoing colonoscopy who received either Propofol or Remimazolam and directly compared them on the same outcomes. Conversely, case reports or case series and studies where the intervention wasn't the aforementioned (not comparing both drugs) or that encompassed a population younger than 18 years were excluded.

Information sources

This systematic review, followed by a meta-analysis, utilized data from five scientific publication platforms: Cochrane, EMBASE, SCOPUS, Pubmed, and Web of Science. The search strategy was defined as: (colonoscopy AND Remimazolam AND Propofol), followed by the exclusion of studies based on duplication, abstract coherence to the subject, and finally full text analysis, in that order. When evaluating based on abstract content, two authors made independent articles selection and reached consensus on divergent selected ones. The latest search was conducted on October 6, 2023, with no language restrictions. Four different individuals participated in gathering information from articles, independently analyzing the five selected papers and compiling data into tables. Data presented as median and interquartile range were transformed to mean and standard deviation for purposes of data aggregation [9].

Endpoints

For analysis purposes, the following outcomes were considered: Discharge time after colonoscopy, which includes time from end of last administration to discharge and time to discharge from recovery room (1); Injection pain, which includes administration site pain and injection site pain (2); Induction time, which includes induction time onset, time at MOAA/S (Modified Observer's Assessment of Alertness/Sedation Scale, a scale used to measure the level of sedation in patients during procedures requiring anesthesia)(3); Time to fully alert, representing mean duration measured from the initiation of three consecutive MOAA/S scores following the conclusion of the procedure (4); Hypotension (5); and adverse events as per the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0 (6).

Quality assessment

As only randomized and observational studies were included, the Cochrane Risk of Bias assessment tool version 2 (Rob-2) and the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) guidelines were employed - the former for bias calculation and latter for level of evidence. In this phase, an author classified the data as high (⊕⊕⊕⊕), moderate (⊕⊕⊕⊖), low (⊕⊕⊖⊖), or very low (⊕⊖⊖⊖), as suggested by guidelines [10].

Statistical analysis

This study used Review Manager software (version 5.4) for statistical meta-analysis. Moreover, for dichotomous and the latter for continuous Odds Ratio (OR) and Mean Difference (MD) were used for parameters respectively, adhering to a 95% confidence interval. All p-values < 0.05 were deemed significant, while the I-s (NCI-CTCAE) square test was applied for statistical heterogeneity, with distribution across three groups: < 40% categorized as low, 40-60% as moderate, and > 60% as high. Given low heterogeneity identified, a random-effects model was applied for all outcomes considered.

Results

Search results

The search yielded a total of 153 articles, 16 were deemed eligible for full-text analysis (Figure 1). Eleven studies were excluded after applying inclusion and exclusion criteria, as detailed in Table 1. A total of 5 studies (encompassing 1505 patients) were included in this review. Search in clinical trial registries identified ongoing studies comparing Remimazolam and Propofol in patients undergoing colonoscopy; however, initial results are yet to be made available.

Study characteristics

Clinical features of the included studies are detailed in Table 1. All 5 studies were randomized (2 multi-center [11,12], 3 single-center [13-15]). The Clinical trials were conducted involving patient allocation into two groups, one receiving remimazolam treatment and other receiving propofol treatment. Among them, only one used etomidate along with Propofol [13]. Sample sizes ranged from 132 to 480 patients in included studies. Average age and Body Mass Index (BMI) of patients

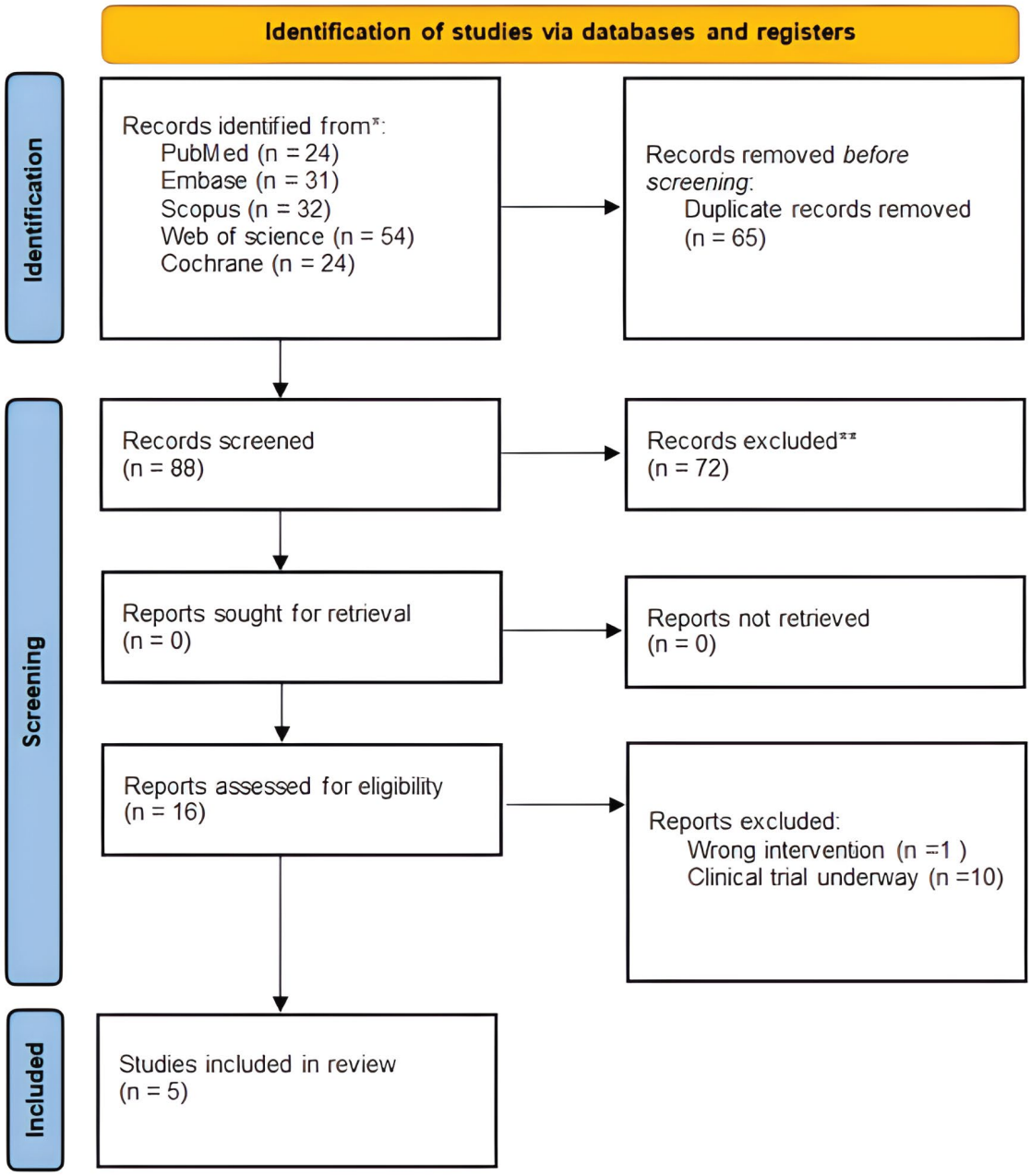

Figure 1: PRISMA flow diagram.

ranged from 44.3 to 69.12 years and 22 to 24.75 $kg.m^{-2}$, respectively. In terms of readiness for discharge, times varied among included studies, ranging from 13.92 to 50.9 minutes. Injection pain, full alertness, induction time, hypotension, and adverse events tracked during the anesthetic procedure also varied among comprising studies. The average follow-up period ranged from 1 to 5 days among studies.

Risk of bias assessment

Risk of bias assessment for all included studies and PRISMA checklist are summarized in Table 2 and Table 3, respectively. All of the included studies were deemed to have a low risk of bias, as determined by the RoB 2 software, yielding a Low risk result. The summary of findings for all measured outcomes and evidence certainty are detailed in Table 2 and Table 3, respectively.

Pooled analysis of outcomes

Five studies (n = 1505 patients) investigated readiness time for discharge after colonoscopy [11-15]. Patients undergoing colonoscopy with Remimazolam did not show a statistically significant average difference compared to Propofol group (MD = -0.09, 95% CI -1.11 to 0.93, p = 0.86; Figure 2). However, statistical heterogeneity observed was substantial (i^2 = 82%). Evidence certainty was graded as moderate due to inconsistency and heterogeneity.

Data pooling from five studies (n = 1505 patients) showed that those anesthetized with Remimazolam were associated with less injection pain (OR = 0.11, 95% CI, 0.05 to 0.22, p < 0.00001; i^2 = 63%; evidence certainty: moderate, Figure 1) [11-15].

Four of the included studies (n = 1257 patients)

DOI: 10.23937/2377-4630/1410180

Table 1: Include studies.

Study	Title	Design	Sample size	Country	Age	BMI	Intervention	Control
XIMEI WANG 2022	Safety and efficacy of Remimazolam besylate in patients undergoing colonoscopy: A multicentre, single-blind, randomized, controlled, phase trial	Multicentre, single-blind, randomized, controlled, phase III trial	477	China	Remimazolam: 44.3 (33.0-54.0); Propofol: 46.4 (37.5-56.0); (p = 0.095)	Remimazolam besylate: 22.82 (20.70-24.90) ; Propofol: 22.87 (21.10-24.60) (p = 0.843)	Remimazolam besylate	Propofol injection
SHAOHUI 2020	Effect of Remimazolam versus Propofol sedation on the quality of recovery after colonoscopy A randomised, controlled, noninferiority trial	Multicentered, randomized, positive-controlled, phase III clinical trial	388	China	Remimazolam: 44.47 ± 11.67; Propofol: 44.43 ± 11.37; (p = 0.975)	Remimazolam: 23.19 ± 2.92; Propofol: 23.21 ± 2.84 (p = 0.953)	Remimazolam tosylate	Propofol
XIANWEN LIU 2023	The Efficacy and Safety of Remimazolam Tosilate versus Etomidate-Propofol in Elderly Outpatients Undergoing Colonoscopy: A Prospective, Randomized, Single-Blind, Non-Inferiority Trial	Single-center, prospective, randomized, single blind, non-inferiority trial	260	China	Remimazolam: 68.87 ± 2.58; Propofol: 69.12 ± 2.75; (p = 0.476)	Remimazolam: 25.35 ± 2.07; Propofol: 24.75 ± 2.16; (p = 0.073)	Remimazolam tosylate	Etomidade-propofol
YUSHEN YAO 2022	Discharge readiness after Remimazolam versus Propofol for colonoscopy A randomised, double-blind trial	Prospective, single-centre, randomised, double-blind, parallel-group, noninferiority clinical trial.	132	China	Remimazolam: 49 [41 to 56]; Propofol: 48 [39 to 56]; (p = 0.776)	Remimazolam: 22.4 [19.8 to 24.6]; Propofol: 22.0 [20.1 to 25.3]; (p = 0.562)	Remimazolam	Propofol
LULU GUO 2022	The efficacy and safety of Remimazolam tosylate versus Propofol in patients undergoing colonoscopy: A multicentered, randomized, positive-controlled, phase III clinical trial	Randomised, controlled, noninferiority trial	248	China	Remimazolam 48 [40 to 52] and Propofol 49 [41 to 55]; (p = 0.25)	Remimazolam 24.1 ± 2.5 (p = 0.48)	Remimazolam tosylate 5 mg	Propofol 1.5 mg kg1

BMI: Body Mass Index; ±: Standard deviation; p: p-value

ISSN: 2377-4630

Table 2: Summary of findings for primary and secondary outcomes.

N	Outcomes	Trials	n	I^2 (%)	Effect model	MD/OR (95% CI)	p-value
1	Discharge	5	1505	82	REM	-0.09 [-1.11, 0.93]	0.86
2	Injection pain	5	1505	63	REM	0.11 [0.05, 0.22]	< 0.00001
3	Fully alert	4	1293	83	REM	-3.09 [-38.16, 31.98]	0.86
4	Induction time	5	1505	96	REM	21.31 [9.95, 32.67]	0.0002
5	Hypotension	5	1505	67	REM	0.40 [0.26, 0.63]	<0.0001
6	Adverse events	3	1125	56	REM	0.53 [0.34, 0.83]	0.006

I^2: Heterogeneity; MD: Mean Difference; OR: Odds Ratio; REM: Random Effect Model; CI: Confidence Interval

Table 3: GRADE of primary and secondary outcomes.

N	Outcomes	Design	D1	D2	D3	D4	D5	Certainty
1	Discharge	RCT	Not serious	Not serious	Not serious	Serious	None	⊕⊕⊕◯ Moderate
2	Injection pain	RCT	Not serious	Serious	Not serious	Not serious	None	⊕⊕⊕◯ Moderate
3	Hypotension	RCT	Not serious	Serious	Not serious	Not serious	None	⊕⊕⊕◯ Moderate
4	Adverse events	RCT	Not serious	Not serious	Serious	Serious	None	⊕⊕⊕◯ Moderate
5	Time to fully alert	RCT	Not serious	Serious	Not serious	Not serious	None	⊕⊕◯◯ Low
6	Induction time	RCT	Not serious	Serious	Not serious	serious	None	⊕⊕◯◯ Low

RCT: Randomized Controlled Trial; D1, Risk of bias; D2, Inconsistency; D3, Indirectness; D4, Imprecision; D5 Other considerations

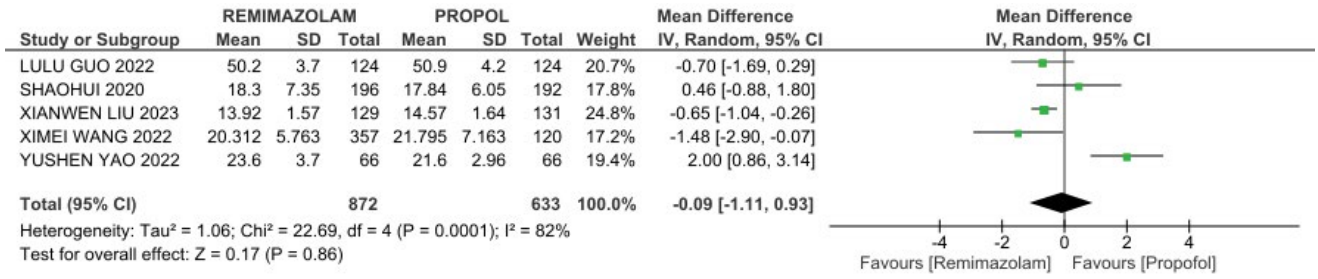

Figure 2: Discharge: Forest plot.

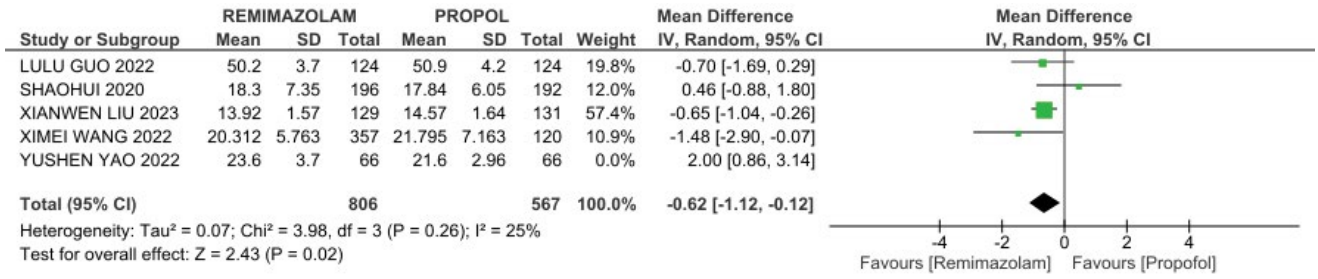

Figure 3: Discharge: Sensitivity analysis.

recorded time to full alertness after colonoscopy procedure [11-14]. In that subgroup, our pooled data showed no significant difference between Remimazolam and Propofol groups (MD = -3.09, 95% CI, -38.16 to 31.98, p = 0.86, i^2 = 83%, evidence certainty: low, Figure 2).

All included studies analyzed induction time between Remimazolam and Propofol groups [11-15]. A significant difference was reported in outcome (n = 1505 patients, MD = 21.31, 95% CI 9.95 to 32.67, p = 0.0002; evidence certainty = low, Figure 3) favoring Propofol group.

Other important outcomes are hypotension and total adverse events, both of which showed significant differences (n = 1505 patients, OR = 0.4, 95% CI, 0.26 to 0.63, p < 0.0001; evidence certainty: moderate [11-15] and (n = 1125 patients, OR = 0.53, 95% CI, 0.34 to 0.83, p = 0.006; evidence certainty: moderate) [11-13]. Both favoring Remimazolam group.

Sensitivity analysis

Due to high heterogeneity (> 60%), and a possible outlier affecting the outcome results, it was necessary to conduct a sensitivity analysis to evaluate outcome behavior. When excluding 2022 study by Yao [14], effect estimates revealed a clear superiority of Remimazolam group over Propofol approach in terms of readiness for discharge (MD = -0.62; 95% CI -1.12 to -0.12) (Figure 3).

Sensitivity analysis also revealed heterogeneity substantially decreased to (i^2 = 25%), demonstrating Yao study differs from others with the same approach.

Lastly, excluding one study, analysis showed notable differences compared to main analysis regarding discharge (p = 0.02) favoring Remimazolam group (Figure 3). This presented less heterogeneity and statistical significance, being graded as moderate.

Discussion

This study utilized a stringent methodological approach combining systematic review with meta-analysis to assess the efficacy and safety of Remimazolam compared to Propofol in sedating patients undergoing colonoscopy.

In total, research encountered 153 articles, of which 16 met the criteria for detailed analysis. Ultimately, this review incorporated an in-depth investigation pooling data from five randomized clinical trials, encompassing a total of 1505 patients.

The primary emphasis of this meta-analysis is a specific consideration on time to discharge. The delay in patient discharge and the increased utilization of recovery room resources may arise from an extended drug elimination half-life and the presence of active metabolites, notably observed in patients with renal or hepatic dysfunction. Therefore, a reduction in discharge time would yield significant resource savings. This highlights the importance of discerning the most efficacious and economically prudent options to enhance patient care and optimize resource allocation. This distinctive focus sets the present study apart from previous ones.

Both sedative agents analyzed appeared to exhibit comparable efficacy in context of patient readiness for discharge post-colonoscopy. Post-procedure hospital discharge, statistically analyzed in terms of group comparison through the p-value, revealed no significant differences between the use of Propofol and Remimazolam, although the studies showed a relevant heterogeneity with an 82% variability, indicating considerable diversity between studies. However, a sensitivity analysis pinpointed the study by Yao [14] as a probable outlier. This observation aligns with prior research underscoring Remimazolam's efficacy when juxtaposed with conventional sedatives. Thus, the findings suggest Remimazolam might offer recovery advantages post-procedure compared to Propofol. This is particularly evident in its high procedural success rate, more expedited recovery post-procedure, and facilitation of early patient discharge [16].

From a safety standpoint, research has revealed that sedation with Remimazolam is associated with decreased hypotension. It is noteworthy to highlight that this is an important outcome to analyze when assessing safety, as inadequate blood flow to vital organs can lead to diminished oxygen supply, potentially resulting in complications such as dizziness, fainting, or, in severe cases, organ damage. The compelling findings in research suggest that Remimazolam operates through a distinctive mechanism, orchestrating the modulation of the bradykinin B1 receptor and autophagy to mitigate pain, as elucidated by relevant studies [17]. This unique mechanism not only demonstrates potential in pain relief but also holds promise in enhancing circulatory stability.

Remimazolam is noted to have a lower likelihood of injection-associated pain compared to Propofol. This is attributed to the water solubility of Remimazolam, which leads to reduced tissue stimulation. In contrast, there is a suggested potential association between injection-related discomfort and the activation of lipid components in the vascular compatibility of Propofol, resulting in pain at the injection site [18]. This aspect is crucial, as patients who receive Remimazolam are less likely to experience discomfort, leading to decreased anxiety. Consequently, these patients are also less prone to feeling disoriented or uncooperative during the medical procedure.

On the other hand, despite the heterogeneity, time to fully alert does not show a significant difference, Possessing distinctive properties, Remimazolam emerges as a fast-acting benzodiazepine, serving as an agonist for the γ-aminobutyric acid subtype A (GABA-A) receptor. Its rapid onset, and complete recovery are noteworthy features. Importantly, its metabolic pathway sets it apart, operating independently of hepatic and renal function, with swift metabolism into inactive compounds facilitated by tissue esterases [6]. In contrast, Propofol has a brief half-life primarily due

to rapid liver metabolism, high lipid solubility facilitating quick tissue distribution, strong protein binding (mainly to albumin), and renal clearance. These factors contribute to the fast onset and offset of its anesthetic effects [19]. These insights resonate with existing literature [20].

Conversely, Propofol demonstrated an edge regarding induction time, achieving faster MOAA/S score 3, this suggests a potential benefit in scenarios where swift sedation induction is advantageous Such situations include emergency surgical procedures, diagnostic interventions requiring patient comfort, control of acute seizures, management of acute trauma or injuries, emergency mechanical ventilation, dealing with highly agitated or anxious patients, and certain outpatient procedures where efficient sedation is essential for procedure effectiveness and reduced recovery time.

This study encountered several limitations, notably a restricted quantity of available studies and significant heterogeneity among the selected ones. To address this heterogeneity, a sensitivity analysis was conducted to identify contributing factors and enhance the robustness of the findings. The variability in the design of included studies and the administered doses of both Remimazolam and Propofol contribute to the complexity of the analysis. This introduces potential limitations in drawing definitive conclusions from the existing body of evidence.

Nevertheless, it is paramount to emphasize the pronounced statistical heterogeneity detected across studies. This variability could be attributed to factors such as mismatched research protocols or unique characteristics of the studied populations. Given inconsistencies observed in literature, confidence intervals were categorized as moderate, demanding judicious interpretation of conclusions.

Conclusion

In essence, Remimazolam emerges as a viable alternative to Propofol, especially concerning readiness for discharge post-colonoscopy, and presents a potentially favorable safety profile. However, marked heterogeneity among some secondary outcomes underscores imperative for caution in interpreting some findings. Consequently, it is advocated that additional research should be performed to appraise these sedative agents across varied patient demographics and to mitigate observed discrepancies in the current body of literature.

Conflicts of Interest

The authors declare no conflicts of interest.

Acknowledgments

The authors would like to thank Flavia Farah Sabe, for their review of the manuscript.

References

1. Trummel JM, Chandrasekhara V, Kochman ML (2017) Anesthesia for colonoscopy and lower endoscopic procedures. Anesthesiology Clin 35: 679-686.
2. Walsh CT (2018) Propofol: Milk of amnesia. Cell 175: 10-13.
3. Kilpatrick GJ (2021) Remimazolam: Non-clinical and clinical profile of a new sedative/anesthetic agent. Front Pharmacol 12: 690875.
4. Wesolowski AM, Zaccagnino MP, Malapero RJ, Kaye AD, Urman RD (2016) Remimazolam: Pharmacologic considerations and clinical role in anesthesiology. Pharmacotherapy 36: 1021-1017.
5. Sneyd JR, Absalom AR, Barends CRM, Jones JB (2021) Hypotension during propofol sedation for colonoscopy: A retrospective exploratory analysis and meta-analysis. British Journal of Anaesthesia 4: 610-622.
6. Kilpatrick GJ, McIntyre MS, Cox RF, Stafford JA, Pacofsky GJ, et al. (2007) CNS 7056: A Novel Ultra-short-acting Benzodiazepine. Anesthesiology 107: 60-66.
7. Higgins J, Thomas J (2023) Cochrane handbook for systematic reviews of interventions. (2nd edn), S.L.: Wiley-Blackwell.
8. Moher D, Liberati A, Tetzlaff J, Altman DG (2009) Preferred reporting items for systematic reviews and meta-analyses: The PRISMA Statement. PLoS Medicine 21: 6.
9. Wan X, Wang W, Liu J, Tong T (2014) Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol 14: 135.
10. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, et al. (2008) GRADE: An emerging consensus on rating quality of evidence and strength of recommendations. BMJ 336: 924-946.
11. Wang X, Hu X, Bai N, Li L, Zhang M, et al. (2022) Safety and efficacy of remimazolam besylate in patients undergoing colonoscopy: A multicentre, single-blind, randomized, controlled, phase □ trial. Front Pharmacol 5: 13.
12. Guo L, Liu T, Zhang Y, Qi D (2022) Effect of remimazolam versus propofol sedation on the quality of recovery after colonoscopy. Eur J Anaesthesiol 39: 953-955.
13. Liu X, Ding B, Shi F, Zhang Y, Liu L, et al. (2021) The efficacy and safety of remimazolam tosilate versus etomidate-propofol in elderly outpatients undergoing colonoscopy: A prospective, randomized, single-blind, non-inferiority trial. Drug Des Devel Ther 15: 4675-4685.
14. Yao Y, Guan J, Liu L, Fu B, Chen L, et al. (2022) Discharge readiness after remimazolam versus propofol for colonoscopy: A randomised, double-blind trial. Eur J Anaesthesiol 39: 911-917.
15. Chen S, Wang J, Xu X, Huang Y, Xue S, et al. (2020) The efficacy and safety of remimazolam tosylate versus propofol in patients undergoing colonoscopy: A multicentered, randomized, positive-controlled, phase III clinical trial. Am J Transl Res 12: 4594-4603.
16. Tang Y, Yang X, Yu Y, Shu H, Xu J, et al. (2022) Remimazolam versus traditional sedatives for procedural sedation: A systematic review and meta-analysis of efficacy and safety outcomes. Minerva Anestesiol 88: 939-949.
17. Xie H, Lu F, Liu W, Wang E, Wang L, et al. (2021) Remimazolam alleviates neuropathic pain via regulating bradykinin receptor B1 and autophagy. J Pharm Pharmacol 73: 1643-1651.

18. Stark RD, Binks SM, Dutka VN, O'Connor KM, Arnstein MJA, et al. (1985) A review of the safety and tolerance of propofol ('Diprivan'). Postgrad Med J 3: 152-156.

19. Sahinovic MM, Struys MMRF, Absalom AR (2018) Clinical pharmacokinetics and pharmacodynamics of propofol. Clin Pharmacokinet 57: 1539-1558.

20. Chang Y, Huang YT, Chi KY, Huang YT (2023) Remimazolam versus propofol for procedural sedation: A meta-analysis of randomized controlled trials. Peer J 11: e15495.