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RESEARCH ARTICLE

Meta-Analysis of Remimazolam and Midazolam for Sedation in Outpatient Oral and Maxillofacial Surgery: Implications for Safety and Recovery

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ABSTRACT

Aim: This investigation aims to assess the efficacy and safety profiles of remimazolam and midazolam in patients undergoing ambulatory oral and maxillofacial surgery.

Material and Methods: This is a systematic review and meta-analysis of randomized controlled trials. We searched three databases (PUBMED, EMBASE, and Cochrane Library) for the relevant literature. We applied STATA 18.0 software to analyze data.

Results: This meta-analysis investigated two studies involving 123 patients. Operation times for remimazolam and midazolam were 31.8±7.1 min vs. 30.0±8.8 min (*MD* = 1.97; 95% CI [-5.21, 9.15]; *p* = 0.59). Percentage of successful sedations between the research groups were 95.0% vs. 70.0% (*MD* = 8.14%; 95% CI [0.88, 75.48]; *p* = 0.06). Time in recovery room was respectively 13.9 ± 13.4 vs. 23.9 ± 9.3 minutes (*MD* = -8.44; 95% CI [-21.28, 4.40]; *p* = 0.20).

Discussion and Conclusion: Remimazolam offers clear advantages over midazolam in terms of sedation, faster recovery, and fewer side effects for patients undergoing ambulatory oral and maxillofacial surgery. Its benefits make it a suitable option for outpatient settings where rapid recovery and patient comfort are critical. While midazolam remains a valid option, particularly for the benefits of its longer-lasting effects, remimazolam's properties suggest it may become the preferred choice for shorter procedures requiring quick recovery.

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Oral and maxillofacial surgery is a crucial field of medicine where the accurate application of anesthetics is essential for ensuring the safety and comfort of patients undergoing different surgical procedures (Greenidge et al., 2020; Lee et al., 2020; Reddy et al., 2020). These procedures, particularly when conducted in an ambulatory setting, necessitate careful administration of sedation and maintenance of hemodynamic stability to reduce perioperative hazards. The fact that a significant number of patients can experience perioperative problems such as hypertension, hypotension, bradycardia, and postoperative nausea and vomiting (PONV) underscores the necessity for efficient sedation during these surgeries. Research has indicated approximately 20-30% of patients to encounter postoperative nausea and vomiting (PONV), a troubling complication that can have a substantial effect on the duration of recovery, patient comfort, and the overall result of the surgical procedure (Kim et al., 2023).

The advent of novel anesthetic drugs has sparked ongoing debates regarding the optimal approaches to sedation and anesthesia management in this particular surgical procedure. Midazolam, a commonly prescribed benzodiazepine, has historically been the preferred sedative due to its well-established efficacy in alleviating anxiety and inducing sleep prior to surgical interventions. This treatment's widespread use in medical settings demonstrates its effectiveness for managing perioperative symptoms. However, some outpatient environments may face challenges due to the pharmacokinetic characteristics of midazolam, such as its extended half-life and reduced metabolism rate, which strongly favor quick recuperation and minimal adverse reactions. Extended sedation or delayed awakening from anesthesia may complicate patient management after surgery and lengthen recovery time (Kim et al., 2023).

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Remimazolam, a benzodiazepine with ultra-short-acting properties, has recently gained attention as a potential substitute for anesthesia in oral and maxillofacial surgery. This novel sedative has a distinctive metabolic pathway, undergoing rapid degradation by tissue esterases instead of the commonly observed cytochrome P450 mechanism numerous other medications employ. The variation in metabolism leads to a considerably reduced context-sensitive half-life, enabling more accurate regulation of the level and duration of sedation (Hayakawa et al., 2023). Remimazolam's rapid start and recovery characteristics make it highly suitable for outpatient treatments where prompt patient turnover and low postoperative problems are crucial. Moreover, the pharmacological characteristics of remimazolam, such as its capacity to sustain steady hemodynamics, render it a desirable option for those with cardiovascular sensitivities (Hayakawa et al., 2023).

The choice of an anesthetic agent in outpatient settings, especially for short surgeries, can greatly influence both the experience during the operation and the post-surgery recovery period. As an agent known for its ultra-short duration of action and few adverse effects, remimazolam presents a possible benefit compared to conventional sedatives such as midazolam. Although midazolam is effective, it can lead to prolonged recovery periods and an increased likelihood of side effects, such as delayed awakening or lingering sleepiness. Furthermore, the prompt reversal of remimazolam's effects through flumazenil injection adds an extra level of control in anesthetic management, making it a remarkably adaptable choice (Kim et al., 2023).

Postoperative nausea and vomiting (PONV) is a common and troublesome consequence that often occurs after anesthesia, particularly in oral and maxillofacial surgery. In this context, nausea and vomiting can directly affect the surgical site and impede the healing process. Research on remimazolam indicates that its positive impact on cardiovascular function and quick elimination from the body may further decrease the likelihood of experiencing PONV beyond midazolam's relatively low occurrence of PONV (Kim et al., 2023). Ensuring a smooth and rapid recovery is critical in ambulatory procedures where patients are usually discharged on the same day and so minimizing postoperative problems is important.

This investigation aims to assess the efficacy and safety profiles of remimazolam and midazolam in patients undergoing ambulatory oral and maxillofacial surgery. This is in response to the increasing interest in optimizing anesthesia for outpatient surgeries. The study will specifically examine the effects of each medication on sedation quality, recovery duration, and occurrence of perioperative complications such as PONV. The goal is to determine the most suitable sedative for use under these circumstances (Hayakawa et al., 2023; Kim et al., 2023). By understanding the distinct advantages and constraints of each medication, medical professionals can make more knowledgeable choices regarding how to customize anesthetics to suit the specific requirements of their patients, thereby enhancing results and augmenting the overall surgical encounter.

Methods

We conduct a systematic review and meta-analysis in accordance with the standards provided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Page et al., 2020). Ethical committee approval is not required for this meta-analysis.

We carry out a systematic search using computerized databases such as PUBMED, Excerpta Medica dataBASE (EMBASE), and Cochrane Library in order to identify the relevant papers published up until August 2024. The following keywords were used in the search strategy: "oral surgery" OR "maxillofacial surgery" AND "remimazolam" AND "midazolam". We also review the reference lists of the relevant articles for any additional studies.

We categorized strategic search terms for the Patient-Intervention-Comparison-Outcome (PICO) model as follows. The patients are adults (≥ 18 years old) undergoing ambulatory oral and maxillofacial surgery. The intervention is treatment with remimazolam. The comparison is treatment with midazolam. The outcomes involve the successful number of sedations, operating time, the Modified Observer's Alertness/Sedation (MOAA/S) scale, the Bi-Spectral Index (BIS) scale, and adverse events (i.e., apnea, cardiac arrhythmias, headache, dizziness). The study design involves randomized controlled trials.

The exclusion criteria are (1) studies published as case reports, reviews, or conference abstracts; (2) studies with potentially duplicated data; (3) studies published in a language other than English; and (4) studies not available in full-text format.

We examined the complete texts of the remaining articles. In addition, we examined the bibliographies of these articles to identify any supplementary articles that were pertinent to our research. Figure 1 displays the PRISMA flowchart and depicts the screening findings.

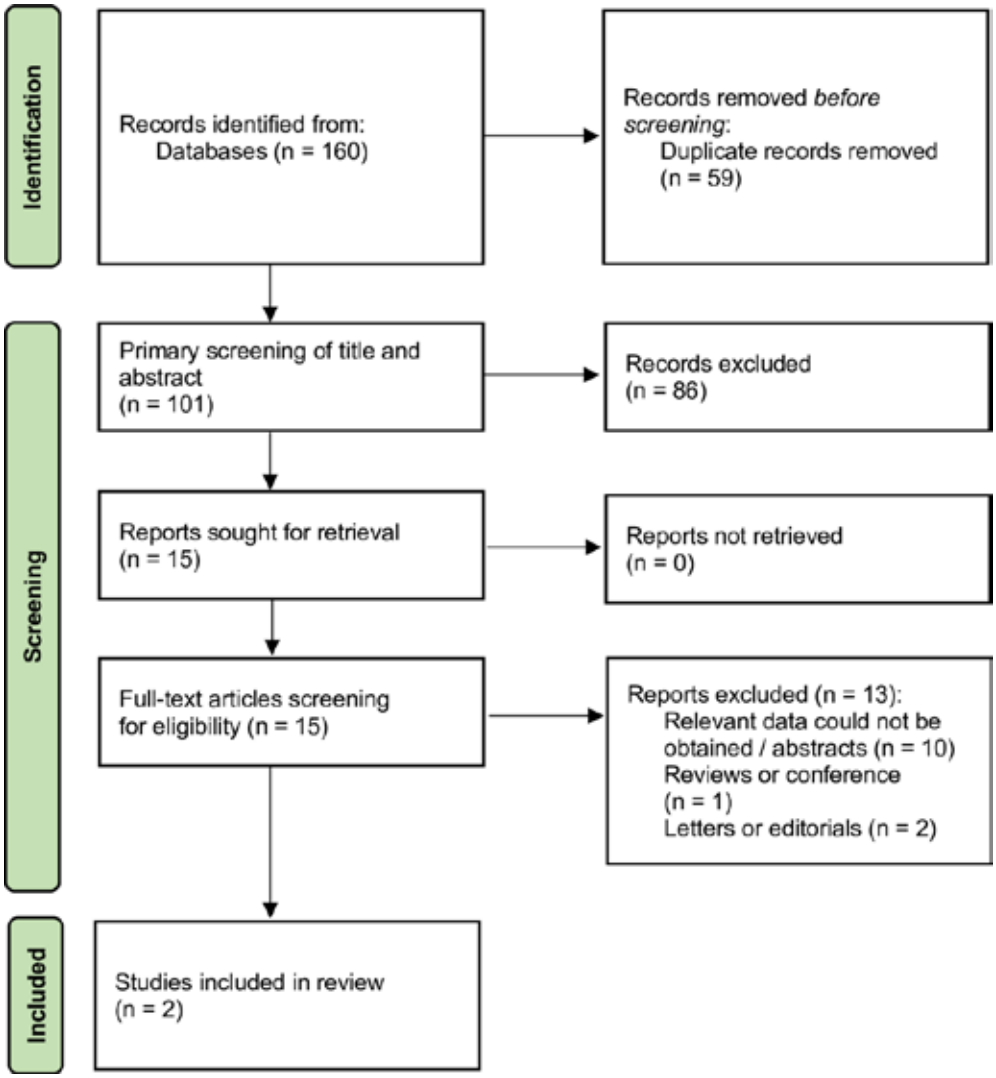

Figure 1. PRISMA flowchart and screening findings.

Data extraction was performed by two authors (M.H.S. and S.B.) who were masked to the journal, the article titles, and the study authors. Any disagreement in opinion was resolved by consensus with all investigators. The following data were extracted from the trials: publication year, study design, patient population, number of patients, intervention, and outcomes.

The quality of the published articles was reviewed based on the Cochrane risk of bias. The randomized trials are assessed using the Revised Tool to Assess Risk of Bias in Randomized Trials (RoB 2) (Sterne et al., 2019. We used the RobVis application to visualize the risk of bias assessments (McGuinness et al., 2021).

Data management and statistical analyses were done with STATA (Ver. 18.0; StataCorp, College Station, TX), with $p < 0.05$ being considered significant in this meta-analysis.

We determined the effectiveness of each trial by computing the average difference and its 95% confidence interval (CI). We computed the mean difference (MD) and its 95% confidence interval (CI) using the inverse variance approach with a random-effects model. We used the chi-square and I^2 tests to analyze the heterogeneity of the study. I^2 statistics that fall between 75–100% indicate the heterogeneity to be statistically significant (Higgins et al., 2011). The sensitivity analysis was performed using R package meta (ver. 3.6.1). The trial sequential analysis (TSA) was conducted using the program TSA (version 0.9.5.10 Beta). Publication bias was assessed by funnel plot using hypotension as an end point. Begg's tests were also performed, with $p < 0.05$ being regarded as indicating potential publication bias.

Results

Identifying Eligible Studies

This meta-analysis included a total of two studies involving 123 patients, with 62 patients in the remimazolam group and 61 patients in the midazolam group (Guo et al., 2023; Li et al., 2023). The clinical baseline characteristics of the patients are presented in Table 1. The mean age of patients treated with remimazolam is 23.8 ± 5.1 years, compared to 24.1 ± 4.7 years for the midazolam group (*MD* = -0.16; 95% CI [-2.68, 2.36]; $p = 0.90$). Men accounted for 45.2% and 50.8% of the population in the respective studies (MD = 0.79; 95% CI [0.38, 1.64]; $p = 0.53$). All included trials had a low risk of bias. The quality of included trials is outlined in Figure 2.

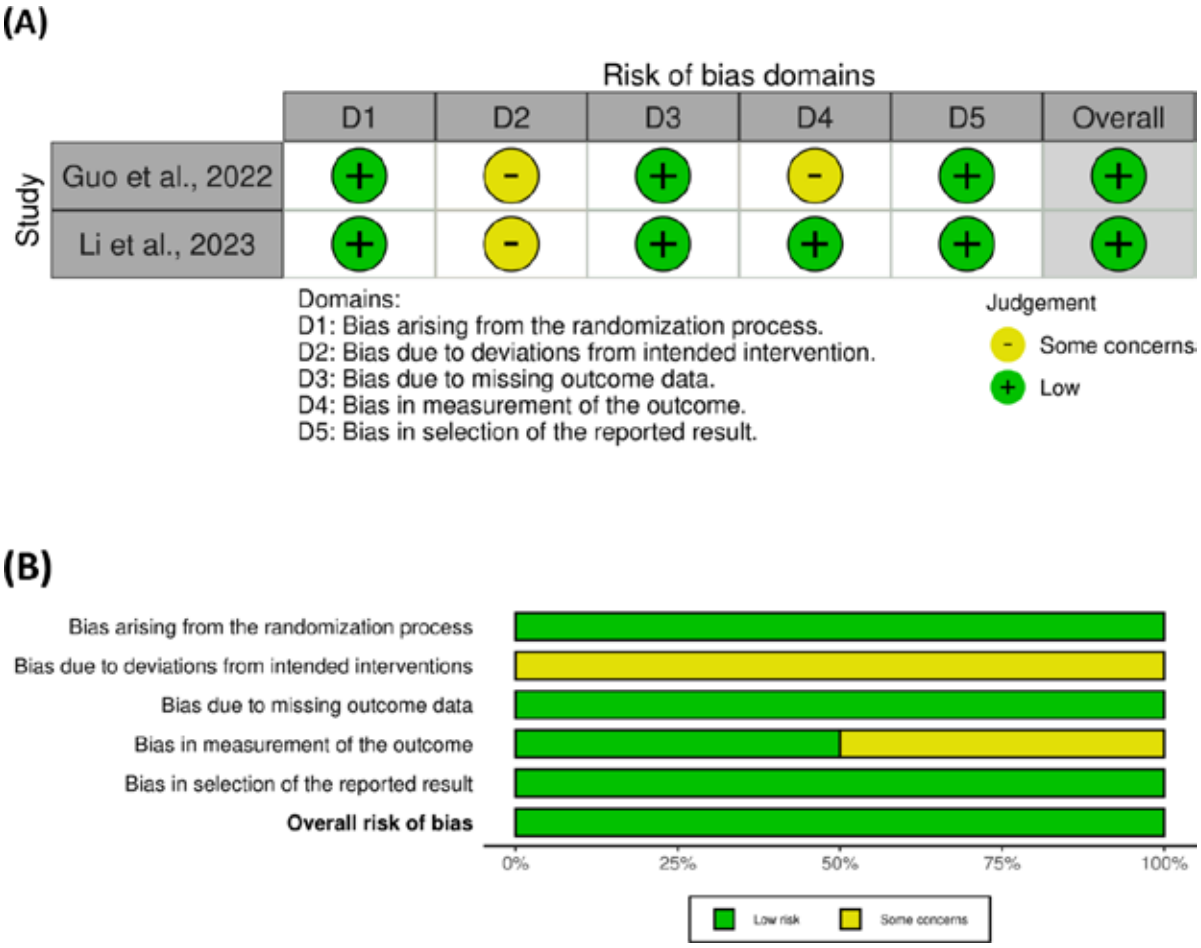

Figure 2. Quality of the included trials.

Table 1

Baseline Characteristics of the Included Trials

Study	Country	Remimazolam group			Midazolam group		
		Population	Age	# of males (percentage of total pop.)	Population	Age	# of males, (percentage of total pop.)
Guo et al., 2022	China	20	29.8 ± 4.3	13 (65.0%)	20	28.2 ± 5.5	12 (60.0%)
Li et al., 2023	China	42	21 ± 2.0	16 (38.1%)	41	22.1 ± 2.4	18 (43.9%)

Meta-analysis

Operation times for remimazolam and midazolam were 31.8 ± 7.1 min vs. 30.0 ± 8.8 min (*MD* = 1.97; 95% CI [-5.21, 9.15]; $p = 0.59$). Percentage of successful sedations among the research groups was 95.0% vs. 70.0%, respectively (*MD* = 8.14; 95% CI [0.88, 75.48]; $p = 0.06$). Time in recovery room was respectively 13.9 ± 13.4 vs. 23.9 ± 9.3 minutes (*MD* = -8.44; 95% CI [-21.28, 4.40]; $p = 0.20$).

Thes statistical analyses show no statistically significant differences between patients treated with remimazolam and midazolam in terms of the analyzed adverse events: hypotension (5.0% vs. 0%; $p = 0.28$), bradycardia (0% vs. 5%; $p = 0.49$), tachycardia (20.0% vs. 15.0%; $p = 0.68$), dizziness (7.1% vs. 9.8%; $p = 0.67$), nausea (0% vs. 7.3%; $p = 0.18$), vomiting (0% vs. 4.9%; $p = 0.28$), and feeling hungover (0% vs. 4.9%; $p = 0.28$).

Discussion

The comparative analysis of remimazolam and midazolam in ambulatory oral and maxillofacial surgery reveals notable distinctions in their effectiveness, time required for recovery, and profiles for adverse effects. These differences hold considerable clinical significance when selecting a sedative for outpatient settings. Benzodiazepines frequently utilize both agents (i.e., remimazolam and midazolam). Being a more recent medication, however, remimazolam has garnered interest due to its ability to induce drowsiness more rapidly, to facilitate a speedier recovery, and to offer a more advantageous safety profile compared to midazolam.

The analyzed studies consistently show remimazolam to have a higher successful sedation rate compared to midazolam in outpatient oral and maxillofacial surgery. Guo et al. (2023) discovered their remimazolam group to have a considerably higher success rate for sedation (95%) compared to the midazolam group (70%). The increased effectiveness of remimazolam can be attributed to its quicker onset of activity and superior ability at maintaining sedation levels, as evidenced by the higher bi-spectral index (BIS) and modified observer's assessment of alertness/sedation (MOAA/S) ratings at various stages during and post-surgery. These findings align with the results of Li et al. (2023), who observed remimazolam to result in a quicker onset of sedation and more efficient maintenance compared to midazolam. Despite its widespread use and reliability, midazolam has slower onset times for sedation and requires more frequent administration to maintain sedation. This increases the likelihood of administering sedative drugs during procedures, potentially complicating the anesthesia process and reducing overall efficiency.

An important advantage of remimazolam compared to midazolam is its effect on recovery duration. Multiple studies have consistently demonstrated remimazolam to facilitate expedited recovery and to accelerate discharge from the clinic. According to Guo et al. (2023), patients in the remimazolam group have a shorter stay in the recovery room compared to those in the midazolam group. However, the difference in time (35.5 minutes vs. 33.6 minutes) was not statistically significant. Nevertheless, remimazolam evidently is generally inclined toward faster recuperation, as patients attained higher Aldrete ratings more quickly, indicating a swifter restoration of consciousness and orientation.

Li et al. (2023) corroborated these findings by demonstrating how patients who'd been administered remimazolam experienced considerably reduced recovery times, including accelerated emergence from anesthesia and expedited resumption of regular activities compared to those who'd received midazolam. Remimazolam's ultra-short duration of action and rapid metabolism contribute to quicker recuperation, resulting in reduced post-surgery sedation.

Compared to midazolam, remimazolam shows a higher occurrence of postoperative adverse effects. Both Guo et al. (2023) and Li et al. (2023) discovered their patients in the remimazolam group to have lower incidences of adverse effects such as nausea, dizziness, and hangover-like symptoms compared to those in the midazolam group. The active metabolites of midazolam are believed to cause negative effects, potentially leading to longer recovery times and lower patient satisfaction.

Furthermore, remimazolam's superior hemodynamic profile also renders it a safer option for individuals with cardiovascular vulnerabilities, as this induces fewer variations in heart rate and blood pressure compared to midazolam. This characteristic is crucial in ambulatory surgery settings where patient turnover and safety are of utmost importance.

Remimazolam's enhanced sedation efficacy, expedited recuperation, and reduced occurrence of adverse reactions also resulted in elevated satisfaction ratings among both patients and physicians. Li et al. (2023) found the use of remimazolam to result in significantly greater satisfaction among both patients and practitioners compared to midazolam. The streamlined sedation procedure and accelerated recovery durations contribute to the enhanced satisfaction, leading to an improved overall patient experience and procedural efficiency.

Despite the promising results of the examined studies, certain limitations need to be acknowledged. The investigations conducted by Guo et al. (2023) had relatively small sample sizes, which could restrict the applicability of the findings. Furthermore, the diversity of surgical techniques used in their study was not completely consistent, which may have had an impact on the required sedation levels and recovery duration. Subsequent studies should strive to incorporate broader and more varied groups of patients and explore the application of remimazolam under a more extensive array of surgical interventions.

To summarize, remimazolam exhibits distinct benefits compared to midazolam in terms of successful sedation, quicker recovery, and diminished adverse effects for patients undergoing ambulatory oral and maxillofacial surgery. Remimazolam has several advantages that make it an attractive choice for use in outpatient environments, where rapid recuperation and patient well-being are of utmost importance. Although midazolam is still a viable choice, especially in situations where its extended duration of effects can be advantageous, the characteristics of remimazolam indicate that it may become the preferred drug in many instances, especially for brief procedures requiring quick recovery. Additional research is required to validate these findings over larger and more diverse groups of patients.

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References

Greenidge, E., Krieves, M., & Solorzano, R. (2020). Global anesthesia in oral and maxillofacial surgery. *Oral and Maxillofacial Surgery Clinics of North America, 32*(3), 427–436. https://doi.org/10.1016/j.coms.2020.04.004

Guo, Z., Wang, X., Wang, L., Liu, Y., & Yang, X. (2023). Can remimazolam be a new sedative option for outpatients undergoing ambulatory oral and maxillofacial surgery? *Journal of Oral and Maxillofacial Surgery, 81*(1), 8–16. https://doi.org/10.1016/j.joms.2022.09.008

Hayakawa, Y., Fujii-Abe, K., Akitomi, S., Niwa, S., Abe, M., Otsuka, M., Ikeda, M., Ishikawa, T., Yajima, M., & Kawahara, H. (2023). Comparison of remimazolam and propofol for intubated general anesthesia for oral and maxillofacial surgery. *Anesthesia Progress, 70*(4), 159–167. https://doi.org/10.2344/523398

Higgins, J. P. T., Altman, D. G., Gøtzsche, P. C., Jüni, P., Moher, D., Oxman, A. D., Savović, J., Schulz, K. F., Weeks, L., & Sterne, J. A. C. (2011). The Cochrane collaboration's tool for assessing risk of bias in randomised trials. *BMJ*, *343*, d5928.

Kim, E. J., Kim, C. H., Yoon, J. Y., Byeon, G. J., Kim, H. Y., & Choi, E. J. (2023). Comparison of postoperative nausea and vomiting between remimazolam and propofol in patients undergoing oral and maxillofacial surgery: A prospective randomized controlled trial. *BMC Anesthesiol*, *23*(1), 132. https://doi.org/ 10.1186/s12871-023-02091-3

Lee, J. S., Roser, S. M., & Aziz, S. R. (2020). Oral and maxillofacial surgery in low-income and middle-income countries. *Oral and Maxillofacial Surgery Clinics of North America, 32*(3), 355–365. https://doi.org/10.1016/j.coms.2020.04.001

Li, X., Tian, M., Deng, Y., She, T., & Li, K. (2023). Advantages of sedation with remimazolam compared to midazolam for the removal of impacted tooth in patients with dental anxiety. *Journal of Oral and Maxillofacial Surgery, 81*(5), 536–545. https://doi.org/10.1016/j.joms.2023.02.001

McGuinness, L. A., & Higgins, J. P. T. (2021). Risk-of-bias VISualization (robvis): An R package and shiny web app for visualizing risk-of-bias assessments. *Research Synthesis Methods, 12*, 55–61.

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Akl, E. A., Brennan, S. E., Chou, R., Glanville, J., Grimshaw, J. M., Hróbjartsson, A., Lalu, M. M., Li, T., Loder, E. W., Mayo-Wilson, E., McDonald, S., McGuinness, L. A., Stewart, L. A., Thomas, J., Tricco, A. C., Welch, V. A., Whiting, P., & Moher, D. (2020). The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ*, *372*, n71. https://doi.org/10.1136/bmj.n71

Reddy, C. L., Patterson, R. H., Wasserman, I., Meara, J. G., & Afshar, S. (2020). Oral and maxillofacial surgery: An opportunity to improve surgical care and advance sustainable development globally. *Oral and Maxillofacial Surgery Clinics of North America, 32*(3), 339–354. https://doi.org/10.1016/j.coms.2020.03.001

Sterne, J. A. C., Savovic, J., Page, M. J., Elbers, R. G., Blencowe, N. S., Boutron, I., Cates, C. J., Cheng H. -Y., Corbett, M. S., Eldridge, S. M., Emberson, J. R., Hernán, M. A., Hopewell, S., Hróbjartsson, A., Junqueira, D. R., Jüni, P., Kirkham, J. J., Lasserson, T., Li, T., McAleenan, A., Reeves, B. C., Shepperd, S., Shrier, I.,… Higgins, J. P. T.. (2019). RoB 2: A revised tool for assessing risk of bias in randomised trials. *BMJ*, *366*, l4898. https://doi.org/10.1136/bmj.l4898