Frontiers in Dentistry

A Comparative Evaluation of Midazolam, Ketamine and Their Combination as Sedative Agents in Pediatric Dentistry: A Systematic Review and Meta-analysis

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A B S T R A C T

Objectives: This study reviewed the efficacy of midazolam, ketamine, and their combination for sedation of uncooperative pediatric dental patients.

Materials and Methods: Medline, PubMed, Cochrane Central Register of Controlled Trials, and the World Health Organization International Clinical Trials Registry Platform were searched up to August 31, 2023 for randomized controlled trials (RCTs) comparing midazolam, ketamine, and midazolam-ketamine in pediatric patients. Methodological assessment was conducted using the revised Cochrane ROB-2 tool. A dose-response meta-analysis was performed to analyze the effect of oral midazolam dosage on treatment duration (in minutes).

Results: Initially, 2,345 records were identified through database searching. After removing the duplicates, 1,230 records remained. Of which, 941 were excluded after title and abstract screening. Subsequently, 289 full-text articles were reviewed; of which, 269 were excluded for various reasons. The remaining 20 publications underwent detailed screening for qualitative synthesis. Risk of bias assessment categorized eight studies as low risk, six with some concerns, and six as having high risk of bias. The meta-analysis, involving three RCTs with 215 children, indicated an increasing trend in treatment duration up to 0.8 mg/kg dosage of oral midazolam. The combination of midazolam-ketamine was highly successful in providing rapid and effective pain relief and sedation for challenging pediatric patients, outperforming either drug alone, irrespective of the administration method.

Conclusion: The findings of this systematic review suggest that when it comes to ease of treatment and clinical efficacy, using a combination of midazolam and ketamine is superior to midazolam or ketamine alone.

Keywords: Dental Midazolam; Ketamine; Conscious Sedation; Pediatric Dentistry

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INTRODUCTION

Dental fear can impact preschoolers, dental professionals, and the overall dental care experience [1,2]. Numerous clinical studies have noted a correlation between higher levels of dental anxiety in children and an increased incidence of carious, fractured, and restored tooth surfaces compared to those with lower anxiety levels [3-6]. Consequently, various behavioral management techniques have been

employed to effectively address and mitigate this anxiety. General anesthesia is frequently acknowledged as a costly procedure that requires the expertise of skilled personnel, including anesthesiologists and specialist nurses, and various other services [7-9]. In such situations, mild to moderate sedation can be considered as a method to alleviate discomfort and enhance the convenience of dental care [10-12]. Approximately half of children may be able to receive mild to moderate sedation during the perioperative or procedural periods, potentially benefiting from it [13]. This sedation helps manage or prevent stress and anxiety, which often stem from factors such as being separated from their families, being in an unfamiliar place, or the fear of experiencing pain [14,15].

Midazolam is the most frequently employed medication for induction of mild to moderate sedation during dental surgical procedures, and is known for its high level of safety [16,17]. Several administration routes can be contemplated for induction of mild to moderate sedation with midazolam [18-20]. Among which, the oral route is the most prevalent in children, known for simplicity of administration and lower risk of allergic reactions [21,22]. The transmucosal and intranasal routes of administration are among other effective methods in pediatric patients. Ketamine stands out as one of the most frequently employed anesthetic agents, possessing robust analgesic, hypnotic, and amnesic effects [23,24]. If administered properly, ketamine can be an exceptionally versatile drug, allowing execution of highly painful procedures due to induction of complete analgesia, and aiding in alleviation of postoperative pain and discomfort by induction of amnesia; therefore, it is particularly beneficial in children [25,26]. Ketamine's versatility stems from its water and lipid solubility, allowing administration through various routes such as intravenous, intramuscular, oral, intranasal, rectal, subcutaneous, and epidural methods [27,28]. Ketamine is commonly employed as a sedative in conjunction with midazolam [29-31]. Oral and nasal sedation utilizing a combination of midazolam and ketamine has been proven to be safe and effective in various dental procedures [32-37]. A notable advantage of this pharmaceutical combination is its ability to minimize the necessity for higher drug doses. Given that midazolam is not typically used as the sole sedative for procedural sedation, it is worth exploring the relevant literature and clinical studies comparing midazolam alone to a combination of midazolam and ketamine in reducing dental anxiety in children. To the best of the authors' knowledge, sedation before pediatric dental procedures has not been comprehensively evaluated. Therefore, this study aimed to do a review on the effectiveness of midazolam, ketamine, and their combination for management of young, uncooperative pediatric dental patients with a special focus on ease of treatment and clinical efficacy.

MATERIALS AND METHODS

Protocol registration:

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [9] protocols. The review protocol was registered in PROSPERO, the International Prospective Register for Systematic Reviews (CRD42022359539).

Search strategy:

Medline, PubMed, Cochrane Central Register of Controlled Trials, and the World Health Organization International Clinical Trials Registry Platform databases were searched with search syntaxes designed by a team of dentists and clinical epidemiologists. Methodological Medical Subject Heading (MeSH) terms were generated based on the PICO-formatted question [uncooperative children (P), midazolam (I), midazolam and ketamine (C), ease of treatment and clinical efficiency (O)]. The Cochrane Highly Sensitive Search Technique was employed to identify randomized trials, incorporating controlled vocabulary and free text words (RCTs) into the search strategy.

Inclusion criteria:

This systematic review considered RCTs published in peer-reviewed scientific journals between 1990 and 2023 in English, and studies that investigated the efficacy of a combination of midazolam and ketamine versus midazolam and ketamine alone. The participants were schoolchildren of any age

group with ASA Class I physical health status.

Exclusion criteria:

The exclusion criteria consisted of manuscripts lacking complete data, cross-sectional studies, case reports, case series, animal studies, in vitro studies, abstracts, articles in languages other than English, and cases with clearly positive behavior toward dental treatment.

Study selection and data extraction process:

The literature review was conducted in August 2023. The results were screened by independent authors (MG and KS). Relevant articles were then reviewed based on their abstract and full-text. In case of disagreement between the two reviewers, a third reviewer (HRB) was consulted to resolve any disagreement. An independent investigator (HRB) double-checked every entry before submission in the final data sheet and resolved disagreements through online discussions.

Quality assessment of included studies:

Quality assessment of studies was performed by 2 independent reviewers. Disagreements were discussed to reach a consensus. The risk of bias was assessed using the Cochrane risk of bias tool (RoB2).

Synthesis of results and meta-analysis:

Dose-response meta-analysis was used where applicable using the "Dosresmeta" package in R 4.0.0 (R Foundation for Statistical Computing, Vienna, Austria). The one-stage random effects model was utilized, and the effect size was reported as the standardized mean difference (SMD).

RESULTS

Study selection:

Figure 1 illustrates the process of searching and selecting studies.

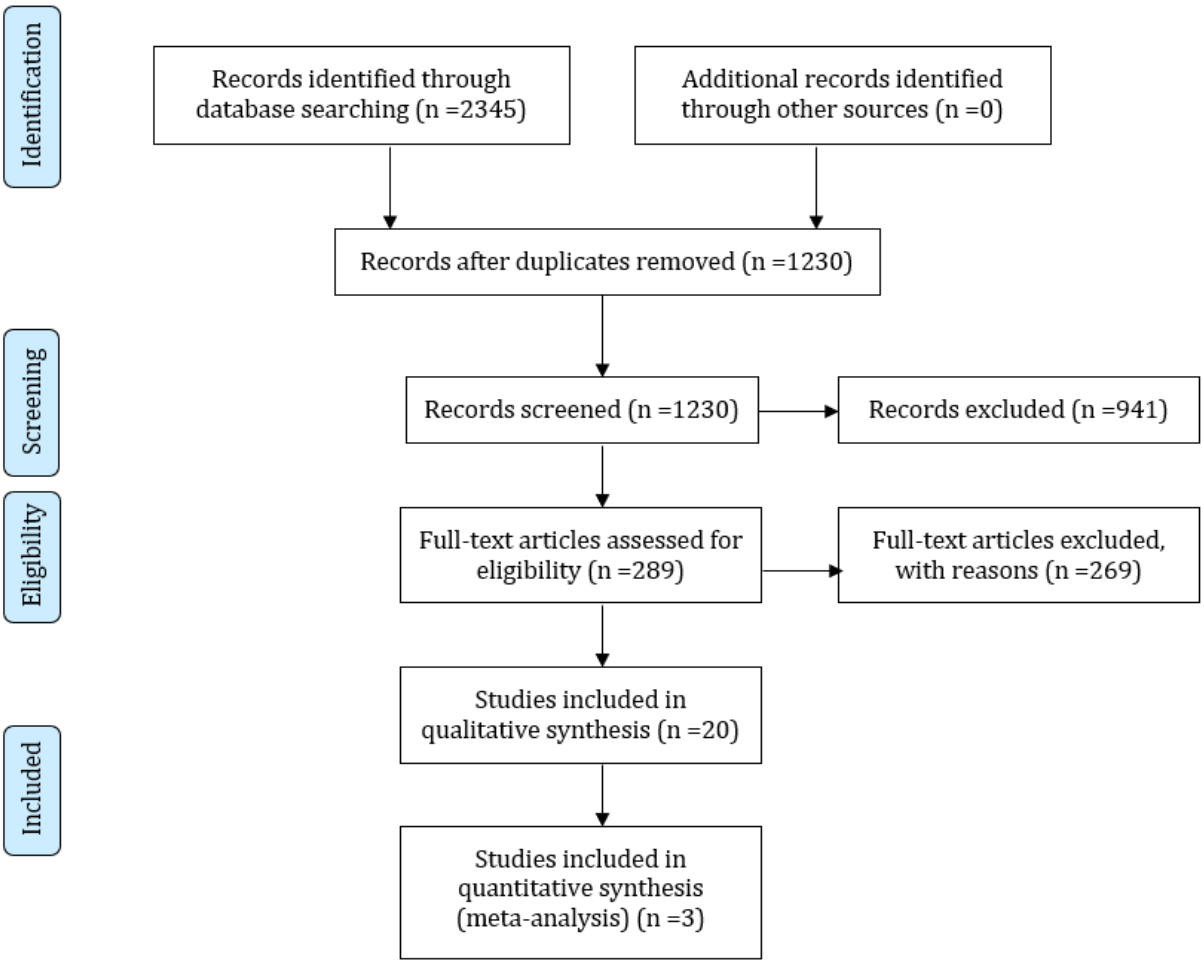

Fig 1. PRISMA Flow Diagram

Initially, 2,345 records were identified through electronic database searching. Duplicates were manually removed using a reference management program, resulting in 1,230 unique records. After screening of the titles and abstracts, 941 records were excluded for the following reasons: they did not meet the inclusion criteria, were unrelated to the research question, or lacked sufficient data. Afterward, 289 full-text articles were assessed for eligibility. Of these, 269 articles were excluded for various reasons, including: inadequate data for analysis, case report or cross-sectional study design, not involving human subjects, or being in languages other than English. The remaining 20 publications underwent full-text screening and were deemed eligible for qualitative synthesis. Three RCTs involving 215 children were included in the meta-analysis.***Risk of bias assessment:***

Figure 2 presents the risk of bias assessment for all 20 included studies. Evaluation of the overall risk of bias was conducted using the revised Cochrane ROB-2 tool, which categorized eight studies as having a low risk

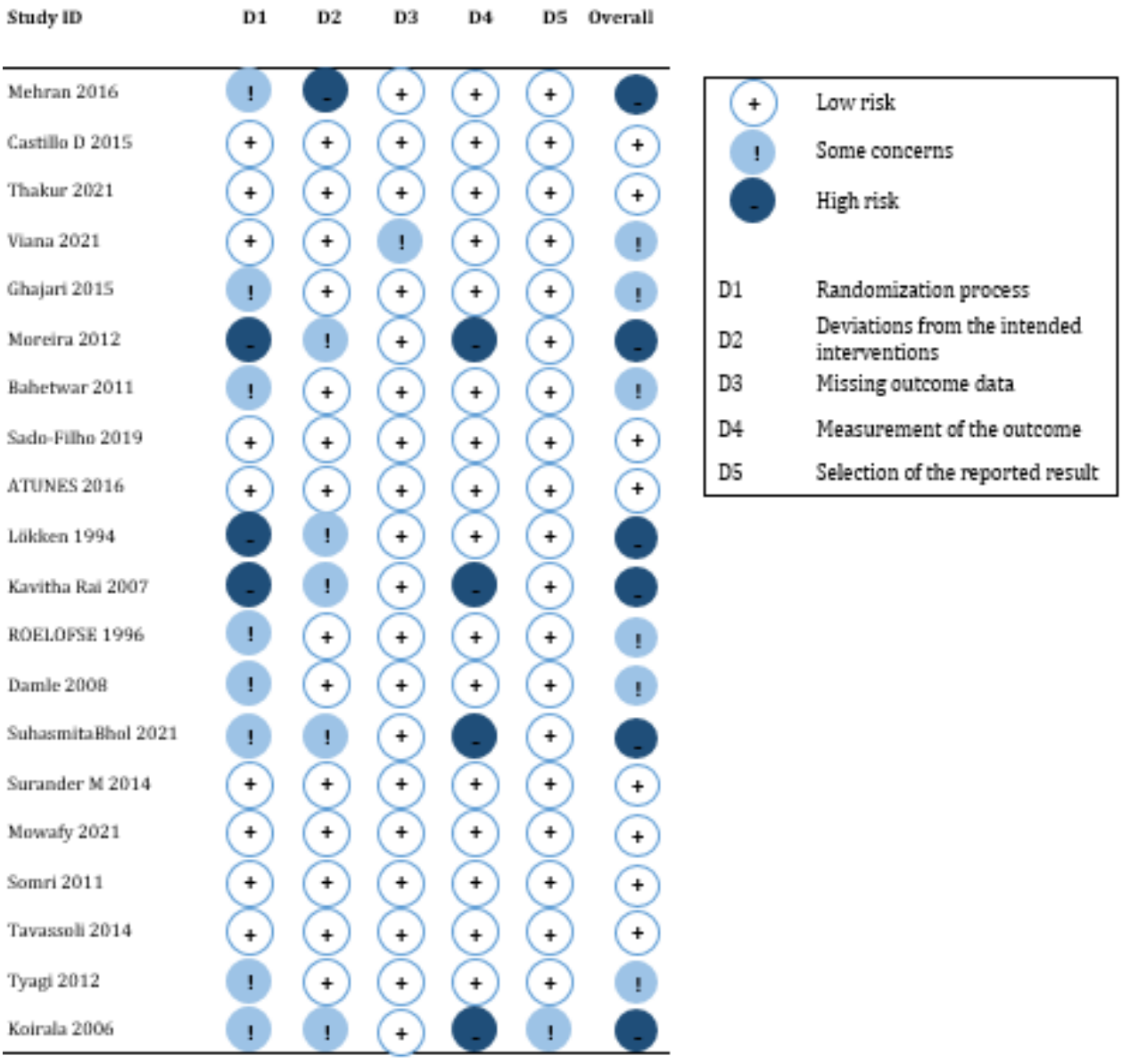

Fig 2. Risk of bias assessment

of bias, six studies with some concerns, and six studies with a high risk of bias rating.

Study characteristics:

The RCTs included children who were younger than 14 years of age. A total of 780 uncooperative children were evaluated across 20 RCTs. At the onset of the study, all children in these RCTs were identified as uncooperative. The drugs used for the interventions included midazolam, ketamine, and a combination of midazolam and ketamine, administered through various routes such as oral, intranasal, buccal, rectal, and intravenous routes.

Oral sedation:

In seven trials, oral administration was used as the route of sedation administration. Among these, three studies had a high risk of bias, one had some concerns, and three had a low risk of bias. In a study by Damle et al, [33] oral midazolam provided significantly better anxiolysis compared to oral ketamine (Table 1-*Supplementary*). Rai et al. [38] reported that midazolam had the longest duration of action but was less effective in terms of treatment completion due to increased movements and crying. The highest level of cooperation during the procedure was achieved with ketamine (Table 1-*Supplementary*). Antunes et al. [37] showed higher efficacy of moderate sedation with midazolam (OR: 2.9, 95% CI: 1.2–6.9) and midazolam/ketamine (OR: 4.3, 95% CI: 1.6–11.4) for improvement of children's behavior (Table 1-*Supplementary*). Another study found that a combination of midazolam and ketamine was more effective than midazolam alone [34]. This combination made the children more cooperative during the treatment session, enabled longer sessions, and yielded consistent behavior scores (Table 1-*Supplementary*). Koirala et al, [35] in another study compared midazolam, ketamine, and their combination as sedative agents. The midazolam-ketamine group had the best sedative scores and the most convenient treatment experience. The onset of sedation was fastest in the midazolam-ketamine group, while the midazolam group had the shortest recovery time (Table 1-*Supplementary*). Thakur et al. [36] evaluated the effectiveness of different doses of the combination of oral ketamine and midazolam. All three groups showed similar behavior scores during treatment, with excellent and easy treatment completion observed with 0.3mg/kg oral midazolam +3mg/kg oral ketamine (83.3%). The wake-up behavior scores, according to the Modified Observer's Assessment of Alertness/Sedation MOASS scale, were calm and cooperative with 0.3mg/kg oral midazolam +3mg/kg oral ketamine (91.7%) (Table 1-*Supplementary*). Somri et al. [39] conducted a study to optimize the dose of oral midazolam for sedation and found that an oral dose of 0.75mg/kg of midazolam appeared to be optimal in terms of effectiveness, acceptability, and safety for dental treatments in pediatric patients (Table 1-*Supplementary*).

Oral/intranasal sedation:

Four studies compared the effectiveness of oral and intranasal routes of drug administration [32,40-42]. One study [40] had a low risk of bias, two [32-41] had some concerns, and one [42] had a high risk of bias. Fallahinejad Ghajari et al. [32] found that intranasal midazolam-ketamine combination was more satisfactory and effective than the oral route, particularly for sedating uncooperative children (Table 2-*Supplementary*). Sado-Filho et al. [40] assessed the efficacy of intranasal and oral ketamine-midazolam combinations compared to oral midazolam. They showed that intranasal ketamine-midazolam achieved a quiet behavior for at least 60% of the session length in 50.0% of the cases, while oral ketamine-midazolam achieved this in 46.4% of the cases, compared to 32.1% with oral midazolam. The differences were not statistically significant (Table 2-*Supplementary*). Viana et al. [41] compared oral midazolam-ketamine, intranasal midazolam-ketamine, and oral midazolam. They observed a predominance of negative behavior in both the intranasal midazolam-ketamine and oral midazolam groups. In terms of sedation level, there was a predominance of moderate sedation in all groups, with no child exhibiting deep sedation (Table 2-*Supplementary*). Bhol et al.

[42] compared oral midazolam-ketamine with intranasal midazolam-ketamine. They found that the intranasal route achieved an adequate depth of sedation in 93% of the cases and satisfactory completion of treatment in 89% of the cases. However, oral sedation procedures achieved a deeper level of sedation (98%) with a longer recovery time of 45 minutes to 1 hour, making it suitable for more invasive or prolonged procedures. The intranasal route was effective for modifying behavior in mildly to moderately anxious children, but for more complex cases, the oral route was recommended (Table 2-*Supplementary*).

Intranasal sedation:

Three studies investigated the use of intranasal route for medication administration [43-45]. One of these studies had a high risk of bias [43], one had some concerns [44], and one had a low risk of bias [45]. Mehran et al. [43] found that ketamine (0.5mg/kg) resulted in fewer movements, less crying, and increased sleepiness when compared to midazolam (0.2mg/kg). However, there were no significant differences between the two drugs in terms of children's overall behavior and sedation efficacy. Both drugs demonstrated positive efficacy for sedating children during dental treatments (Table 3-*Supplementary*). Bahetwar et al. [44] reported that the onset of sedation was rapid with ketamine compared to midazolam and midazolam-ketamine, with a statistically significant difference between ketamine and midazolam. The overall success rate was 89% with ketamine, 84% with midazolam-ketamine, and 69% with midazolam, with a statistically significant difference between the success rates of ketamine and midazolam (Table 3-*Supplementary*). According to Surendar et al, [45] both midazolam and ketamine, when used individually, can be safely and effectively administered through the intranasal route for induction of moderate sedation in uncooperative pediatric dental patients (Table 3-*Supplementary*).

Rectal sedation:

Two studies explored the use of rectal route for drug administration [46,47]. One of these studies [46] had a high risk of bias, while the other [47] raised some concerns. Lökken et al. [46] conducted a comparison between midazolam and a combination of midazolam and ketamine. They found that addition of ketamine to midazolam significantly increased amnesia and drowsiness. Moreover, this combination appeared to be more effective in alleviating anxiety and preventing pain (Table 4-*Supplementary*). Roelofse et al. [47] compared midazolam administered alone to midazolam combined with ketamine. Both drugs provided satisfactory sedation and anxiolysis. However, when evaluating postoperative recovery, it was noted that a statistically significant number of children who received midazolam alone were fully awake upon admission to the recovery room and 30 minutes later, as compared to those who received the drug combination (Table 4-*Supplementary*).

Subcutaneous sedation:

Only one study with a low risk of bias investigated the use of subcutaneous route for drug administration [48]. Flores-Castillo et al. [48] examined subcutaneous midazolam with and without ketamine. They observed that the percentage of children who did not cry was consistently higher in the group receiving midazolam-ketamine compared to the group receiving midazolam alone, but this difference did not reach statistical significance. In terms of body movement, the percentage of children without movement was higher in the midazolam-ketamine group, but this effect was only observed for the first 10 minutes. There were no significant differences at 20, 30, and 40 minutes, but after 40 minutes, body movement was lower in the midazolam group (Table 5-*Supplementary*).

Buccal/intranasal sedation:

One single study with a low risk of bias compared buccal and intranasal routes for drug administration [49]. Mowafy et al. [49] evaluated the effectiveness of midazolam spray administered through the buccal and intranasal routes. Their findings indicated that aerosolized buccal midazolam was better tolerated by patients. On the other hand,

intranasal aerosolized midazolam had a quicker onset of sedation (Table 6-*Supplementary*).

Buccal/oral sedation:

Only one single study with a low risk of bias compared buccal and oral sedation. Tavassoli-Hojjati and collogues [50] compared oral and buccal midazolam and revealed no significant difference in physiological factors between the medication groups at different time points (0, 10, 20, and 30 minutes, and discharge). Additionally, there was no significant difference between the two groups in terms of behavioral parameters. Most parents rated both sedative agents as "effective" or "very effective," and the children were generally minimally anxious or not anxious at all (Table 7-*Supplementary*).

Oral/ IV sedation:

One single study that had some concerns in risk of bias assessment compared intravenous (IV) and oral midazolam sedation [51]. Tyagi et al. [51] reported that patients who received IV midazolam exhibited significantly improved post-administration behavior in aspects such as sleep, crying, and movement. The overall behavior scores for patients in the IV midazolam group were significantly higher compared to the other three groups (Table 8-*Supplementary*).

Dose-response meta-analysis:

Dose-response meta-analysis was conducted to study the effect of oral midazolam dose on duration of treatment (in minutes). One-stage random effects model was used and the effect size was reported as standardized mean difference (SMD). In order to find the starting point of the chart (Fig. 3), one observation was added to each study including dose zero, mean zero, SD zero and similar sample size. According to the quadratic model, each 1mg/kg was associated with a 29.1-unit increase in SMD; while each one square of dose (mg/kg) was associated with a 16.9-unit decrease in SMD (Table 9). Considering the simultaneous effects of dose and square of dose, the increasing trend was up to about 0.8mg/kg dose (Fig. 3).

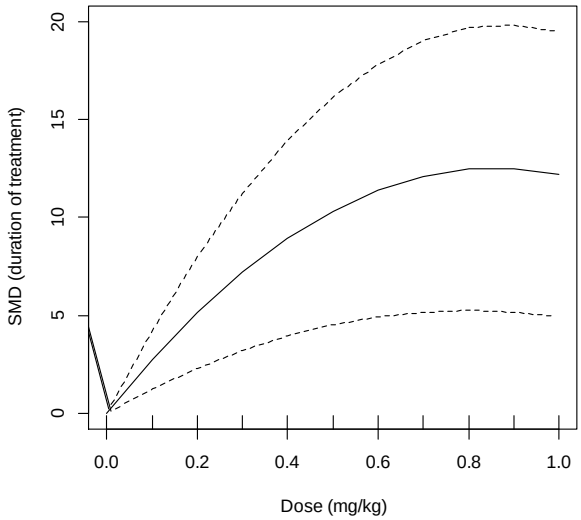

Fig 3. Dose-response meta-analysis to study the effect of oral midazolam dose on duration of treatment, SMD: standardized mean difference, the error bounds indicate 95% confidence interval.

DISCUSSION

The results of our systematic review suggest that combining oral midazolam with ketamine is more effective than using either drug alone (32–37). Additionally, the intranasal combination of midazolam and ketamine appears to offer superior outcomes compared to their oral combination (32, 40). Regarding the rectal route, both midazolam alone and the midazolam–ketamine combination were effective; however, the combination showed greater sedation depth and amnesic effect, though not all studies reported statistically significant differences (46). In the subcutaneous route, one study reported higher rates of sedation success and reduced movement during the initial treatment period with the combination, although the difference did not remain significant over time (48). Ketamine has been explored as a supplementary drug when combined with

Table 9. Dose-response meta-analysis to study the effect of oral midazolam dose on duration of treatment

Predictor	Estimate	SE	z	P (>|z|)	95% CI LB	95% CI UB
Dose	29.107	8.152	3.57	<0.001	13.129	45.085
Square of dose	-16.894	4.468	-3.78	<0.001	-25.651	-8.137

SE: standard error, P: P value, CI: confidence interval, LB: lower bound, UB: upper bound

midazolam during the perioperative phase. This approach is based on the belief that midazolam's anxiolytic effects enhance the sedative and analgesic properties of ketamine, with limited increase in side effects [52]. Intranasal ketamine appears to outperform intranasal midazolam, but due to the high risk of bias in some studies, the data may not be entirely reliable [43,44].

Given the limitations in terms of study sample size and variations in sedation evaluation scales, it is challenging to recommend a specific administration route or determine which drug combination is the most effective for sedation. Therefore, future studies are recommended to include larger participant trials and establish standardized criteria for sedation assessment to ensure more robust and reliable results. The findings of this systematic review suggest that when it comes to ease of treatment and clinical efficacy, the combination of midazolam and ketamine is superior to using midazolam or ketamine alone.

CONCLUSION

This systematic review suggests that the combination of oral midazolam and ketamine is more effective than either drug alone, with intranasal administration showing superior results compared to the oral route. In both rectal and subcutaneous routes, the drug combination also demonstrated greater effectiveness. Ketamine, when paired with midazolam, enhances sedation and analgesia with minimal increase in side effects. However, due to high risk of bias and variations in study designs, the data may not be entirely reliable. Larger studies with standardized sedation assessment criteria are needed to draw definitive conclusions. Overall, the combination of midazolam and ketamine appears to offer superior clinical efficacy compared to individual use of each drug.

CONFLICT OF INTEREST STATEMENT

None declared.

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