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REVIEW ARTICLE

The effectiveness of intranasal midazolam for seizure treatment in emergency care: a systematic review

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ABSTRACT

Seizures are a critical medical emergency requiring prompt intervention to improve patient outcomes and prevent complications. Intranasal (IN) midazolam has emerged as a promising treatment due to its ease of administration and rapid onset. However, there is a lack of comprehensive systematic reviews assessing its effectiveness, particularly in prehospital settings compared to other treatments. This study aimed to systematically evaluate and compare the efficacy of IN midazolam in acute seizure management and patient outcomes in prehospital care and emergency departments. A comprehensive search was conducted, using the PICOS framework, including clinical trials and observational studies published between August 2014 and August 2024. Data were extracted using Covidence and organized into summary tables for analysis. Three out of 489 studies included 5,062 patients, all under 18 years, and 4,957 in prehospital settings. One study was a clinical trial and two were cohort studies. The main indicator of medication success was seizure termination within 10 minutes. One study reported a success rate of 88.2%. The second indicator was the reduction of seizure recurrence. Two studies noted the need for redosing, with the IN route with a risk difference of 11% and 95% CI. Despite the higher frequency of redosing, IN midazolam showed comparable efficacy to other routes. Adverse effects included respiratory depression, nasal irritation, somnolence, and vomiting. The majority of the studies reported that IN midazolam might be an effective, safe, and easily applicable treatment for acute seizures in adolescent and pediatric populations. However, it might require redosing compared to other routes.

Keywords: Effectiveness, intranasal midazolam, seizure treatment, emergency care, systematic review.

Introduction

A seizure is a sudden, temporary disruption of brain function caused by excessive neuronal activity and is classified into generalized, focal, and epileptic spasms [1]. Seizures are among the most common neurological emergencies encountered in emergency departments (EDs) and prehospital care [2], requiring prompt and effective management to prevent complications such as prolonged convulsive status epileptics, hypoxia, and long-term neurological damage [3-5]. Traditionally, intravenous administration of benzodiazepines, such as diazepam and lorazepam, has been the gold standard for acute seizure management [6,7]. However, establishing intravenous access in seizing patients can be challenging and time-consuming, particularly in prehospital and emergency settings.

Midazolam, a benzodiazepine with rapid onset and short duration, has sedative, anxiolytic, anticonvulsant, and amnesic properties. Administered through the highly vascularized nasal mucosa, it offers the advantages of quick absorption and ease of use without the need for IV access, making it an attractive option for emergency care providers [1].

The U.S. Food and Drug Administration has approved the use of midazolam nasal spray to treat seizure clusters in patients aged 12 years or older [2]. Midazolam has also

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been demonstrated to be effective in managing pediatric seizures in hospital wards [3]. Its advantages included ease of administration, rapid absorption, minimal pain, and avoidance of first-pass metabolism [4]. Research by Lahat highlighted that compared with intravenous routes, intranasal (IN) midazolam allows for quicker administration and a shorter time between hospital admission and seizure cessation [3]. This is particularly relevant in prehospital settings, where obtaining intravenous access in children is often challenging.

As a result, emergency medical services (EMSs) protocols recommended non-intravenous midazolam as a first-line treatment for pediatric status epilepticus. According to recently published evidence-based guidelines, in the absence of established vascular access, current National Association of State EMS Officials recommendations also advise the use of IN or intramuscular (IM) midazolam as first-line treatment for seizures [5].

A subgroup analysis restricted to longer EMS contacts and encounters with a physician impression of status epilepticus supported these outcomes. Additionally, their findings are consistent with earlier research assessing the use of IN antiseizure drugs in prehospital treatment. Existing evidence indicated that 0.1 mg/kg IN midazolam is a sub-therapeutic dose for the treatment of status epilepticus. Furthermore, 0.2 mg/kg IN midazolam has been demonstrated to be just as efficacious as intravenous benzodiazepines [6]. Numerous researchers have examined the safety of midazolam for respiratory or circulatory issues, and previous study does not show respiratory depression to be a significant side effect of midazolam [7].

This systematic review aimed to evaluate the effectiveness of IN midazolam in managing seizures in prehospital and emergency care settings, addressing a gap in the literature and exploring its underutilization in clinical practice.

Subjects and Methods

Eligibility criteria

Following the guidance of the Cochrane Handbook, the PICOS framework was employed to shape the research question and guide the literature search. The population included patients of all ages who experienced acute seizures either in prehospital environments or in the ED, regardless of sex, race, ethnicity, or origin. The intervention included IN midazolam which was administered by paramedics, EMS specialists, or other emergency healthcare providers, such as ER physicians. Comparison included alternative administration routes, such as intravenous or IM midazolam. Outcomes included an examination of seizure control and overall treatment effectiveness. Where primary outcome was the seizure cessation within 10 minutes of receiving IN midazolam, compared with other administration routes, and seizure recurrence. Secondary outcomes were time to seizure cessation, adverse effects, patient demographics, and longer-term outcomes, including neurological function at discharge and during follow-up (Table 1).

Search strategy

This review incorporated clinical trials and observational studies (cohort and case-control designs). Owing to the difficulties of conducting randomized controlled trials in pre-hospital settings, such as the urgent nature of seizure management, ethical concerns regarding consent, and logistical constraints, observational studies were included. Only studies published in the English language between August 2014 and August 2024 were considered for this review. The 10-year timeframe ensures that the review reflects current evidence, aligns with modern practices, and includes high-quality relevant data.

An electronic search was conducted in August 2024 across multiple databases, including the Cochrane Library, PubMed, MEDLINE, Embase, and Ovid, to

Table 1. *Key data extracted from the included studies.*

Category	Details
Population	– Demographic characteristics such as age and gender. – Patients experiencing active seizures treated in prehospital settings or ER. – Total sample size for each comparison group. – Details regarding withdrawals or losses to follow up, including reasons for these losses.
Intervention	– Administration details of IN midazolam (IN midazolam): – Number of doses. – Dosage. – Method of delivery in prehospital settings.
Outcomes	– Primary and secondary outcomes: – Effectiveness of IN midazolam, focused on seizure control. – Seizure cessation. – Need for redosing. – Overall patient health outcomes.
Study Characteristics	– Relevant details of study design: – Study duration. – Timing. – Country of origin. – Number of participants. – For clinical trials: – Randomization methods. – Allocation concealment. – Participant blinding to assess methodological quality.

identify relevant studies. A combination of medical subject headings and keywords were used to capture studies related to the effectiveness of IN midazolam for seizure management in prehospital settings.

Various search terms were used including emergency healthcare providers (paramedics, ER nurses, ER physicians, ER consultants, EMS specialists, and emergency technicians), prehospital emergency care, EMS, prehospital care, ambulance response, the ER, and the ED. Various terms describing seizure types and conditions, including epileptic seizures, generalized tonic-clonic seizures, myoclonic seizures, partial seizures, convulsions, complex partial seizures, and tonic-clonic seizures, were used. Furthermore, specific terms related to the use of midazolam administered nasally, such as IN midazolam, nasal midazolam, midazolam nasal spray, IN benzodiazepine, and nasal delivery of midazolam were also used to search the relevant studies.

Boolean operators were used to combine the keywords and ensure a comprehensive search. The reference lists of the included studies were also reviewed to identify any additional relevant articles.

Study selection

The authors determined the eligibility of articles for inclusion by screening the titles and abstracts of all identified studies during the search process. For any conflicts regarding eligibility, a meeting with the principal investigator was conducted to reach a consensus. Only papers that explicitly mentioned the intervention delivered and the intended population were included. Studies lacking clear definitions of the indication were excluded; for instance, studies measuring the efficacy of IN midazolam administered to patients in a peri-ictal state as a prophylactic medication were excluded. Additionally, studies with insufficiently robust designs, such as editorials, case reports, conference abstracts, and letters, were excluded from the final analysis. Papers that did not clearly outline the intervention or the settings in which the intervention was applied were also excluded. Eligible studies were those that measured and reported relevant outcomes, including seizure cessation and the need for redosing due to recurrent seizures. Studies focusing on irrelevant outcomes, such as healthcare provider metrics, cost-effectiveness analyses, or economic results, were excluded if they did not align with the inclusion criteria regarding patient outcomes.

Data extraction and management

The data collection and extraction were performed via Covidence, a specialized online tool from Cochrane that aids in conducting systematic reviews with precision [8]. The results from each study were organized into summary tables for a clear presentation. EndNote 20 was used to create and maintain a database of all relevant bibliographic references [9].

Quality assessment

The evaluation of the included studies required the use of the Critical Appraisal Skills Program tool, which utilizes the checklist for trials or cohorts, depending on the study type [10]. This tool was employed to assess various quality aspects of the studies. The number of withdrawals, dropouts, and follow-up losses in the trials was reviewed, and when justifications for missing data were provided, the analysis was based on participants with complete data [10,11].

The quality of the included studies was assessed based on clarity, precision, applicability, feasibility, and risk of bias. Ramgopal et al. [12] and Whitfield et al. [13] exhibited methodological limitations, including potential bias from transport time, confounding factors, and incomplete assessment of seizure recurrence. Maha Z. Mohammed et al. [14] followed a randomized design but was limited by its open-label nature, variability in patient settings, and lack of cost-effectiveness analysis. Detailed quality assessment criteria and scoring are provided in Supplementary Tables S1–S4.

Excluded studies

Of the 74 studies selected for full-text review, 71 were excluded for not meeting the eligibility criteria. The reasons for exclusion were inappropriate study setting (n = 13), inappropriate outcomes (n = 5), inappropriate indication (n = 1), inappropriate intervention (n = 2), inappropriate study design (n = 35), inappropriate patient population (n = 3), inappropriate route of administration (n = 1), and lack of access to the full text (n = 11) (Figure 1).

Results

A comprehensive search process was conducted for the published literature until September 30, 2024, and identified a total of 594 records. Of these, 70 from PubMed, 4 from Cochrane, 244 from Embase, 175 from Ovid, and 97 from Medline (Ovid). Additional studies were identified through reference research. Based on title and abstract screening, 74 studies were selected for full-text review. Ultimately, three studies comprising 5,062 pediatric patients met the inclusion criteria. Among the three included studies, one was a clinical trial, and two were cohort studies. Among the total patients, 4,957 were treated in prehospital settings, and 105 were treated in the ED.

The studies differ in their design and settings, with two being retrospective studies and one being a prospective randomized controlled trial. The study settings include both EMS and ED environments, and the study durations range from 2 to 7 years. The number of participants varied, with the largest study including 2,923 participants under the age of 18 years and the smallest involving 105 seizure episodes in children. The comparator groups were subjected to different administration routes for midazolam, including the IN, intravenous (IV), IM, intraosseous (IO), and buccal routes. The dosage for IN midazolam was 0.2 mg/kg in two studies [12,13] and 0.1 mg/kg in Whitfield's study, with the IV and IM routes using either 0.1 mg/kg or 0.2 mg/kg doses depending on the study [6]. The primary objectives were to compare the efficacy of different midazolam routes, specifically the need for additional doses, seizure cessation, and side effects associated with each route.

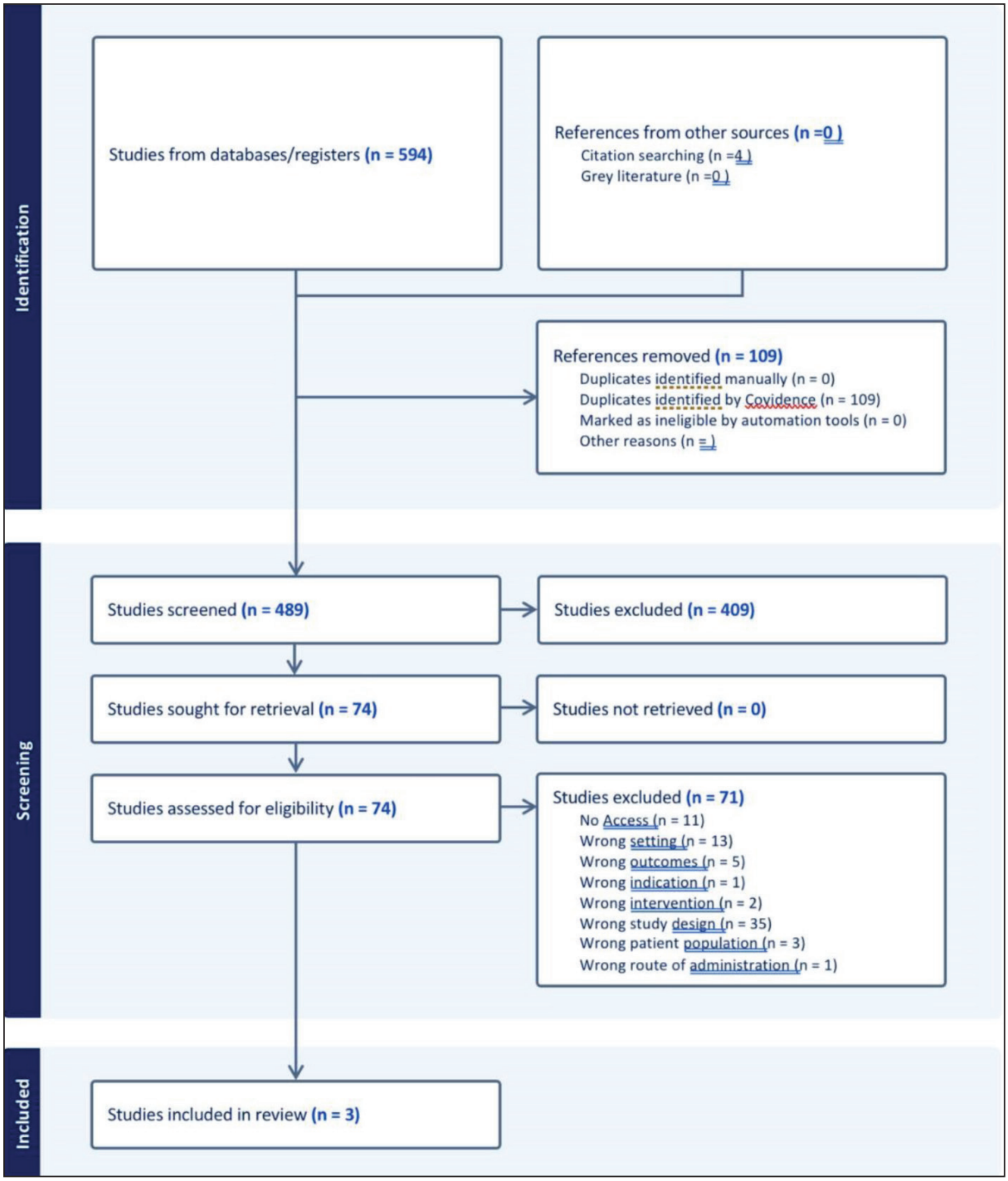

Figure 1. *PRISMA flow chart of the included and excluded studies [12].*

The side effects observed across the studies included respiratory depression, somnolence, vomiting, agitation, and nasal irritation. A study by Whitfield et al. [6] indicated that respiratory depression occurred in 6.7% of patients receiving IN midazolam compared with 5.6% of those receiving IV or IM doses [6]. Furthermore, two studies reported that IN-midazolam was associated with a greater likelihood of requiring additional doses of midazolam [12,13]. These studies provided valuable insights into the use of IN-midazolam in pediatric seizure management and emphasized its potential advantages in prehospital and ER settings (Table 2).

Seizure cessation within 10 minutes was used as the primary indicator of drug effectiveness, with cessation defined as the absence of abnormal motor activity, as confirmed by either a caregiver or physician and accompanied by partial or full recovery of consciousness. The clinical trial included in the review reported a seizure cessation success rate of 88.2% within 10 minutes following the administration of intranasal midazolam (in-MDZ), with a statistically non-significant result (p-value = 0.509) [13]. This outcome highlighted the potential efficacy of in-MDZ in rapidly controlling seizures in prehospital and emergency care settings (Table 3).

Table 2. *Characteristics and main findings of the included studies.*

Author and year	Study duration	Study setting	Study design	Participants (*N*)	Dose	Side effect	Comparator
Whitfield et al. [6]	7 years	EMS	Retrospective observational	2034 patients (Age <14)	IN/IM/IV: 0.1 mg/kg	Respiratory depression	IV/IO/IM routes
Ramgopal et al. [12]	4 years	EMS Agencies	Retrospective Cohort Study	2923 patients (Age <18)	IN/IM: 0.2 mg/kg IV: 0.1 mg/kg	Airway compromise	IV/IM/IN routes
Mohammed et al. [13]	2 years	ED	Prospective, randomized, controlled trial	105 participants Nasal: *N* = 34 (Age <10)	IN/IM/Buccal: 0.2 mg/kg max	Somnolence, vomiting, and agitation	IV/IM/IN/Buccal routes

IM: intramuscular, IN: intranasal, IV: intravenous, N: number of participants, EMS: Emergency medical services.

Table 3. *Primary outcome – seizure cessation within 10 minutes after in-MDZ administration.*

Study	Main finding	Conclusion
Mohammed et al. [14]	No significance was found (*p*-value = 0.509) when comparing the therapeutic success rate between IN midazolam and the other routes.	It is efficient to use IN midazolam to stop seizures within 10 minutes likewise the other routes.

Table 4. *Secondary outcome – the necessity for redosing after the recurrence of a seizure.*

Study	Main Finding	Conclusion
Whitfield et al. [6]	Redosing of midazolam was 11.0% more likely (95% CI: 6.7%-15.3%) following an initial IN dosage compared to administration via other injection routes.	IN-Midazolam (0.1 mg/kg) was less effective than IM, IV, and IO administration at the same dose for managing pediatric seizures in prehospital settings.
Ramgopal et al. [12]	IN-Midazolam was 39% more likely to require additional benzodiazepine doses (95% CI: 10%-76%).	The provision of IN midazolam was associated with an increased need for additional benzodiazepine doses.
Mohammed et al. [13]	There is no significance regarding the need for another dose.	No differences were found between all routes regarding the number of rescue doses, need for further antiepileptic treatment, and recurrence of seizure activity.

The second primary outcome was the need for redosing. Two studies noted that IN midazolam was associated with a greater likelihood of requiring further administration of benzodiazepines (Table 4).

According to Ramgopal, IN-midazolam was associated with greater odds of requiring additional doses of benzodiazepines (OR = 1.39, 95% CI = 1.10-1.76) [12]. Additionally, a retrospective non-inferiority analysis revealed that the use of IN-midazolam was associated with more subsequent midazolam use throughout an EMS call. The same study reported an increased likelihood of requiring midazolam redosing of 2.0 (95% CI = 1.6-2.6) compared with the first delivery of midazolam via IV or IM routes [6]. A subsequent dose of midazolam was administered to 25% of patients who received an initial IN dose, compared with 14% of those who received their first dose by IM, IV, or IO. The risk difference for redosing midazolam after an initial IN dose, compared with injections via other routes, was 11.0% (95% CI 6.7-15.3%) [6].

Despite the higher frequency of redosing, IN midazolam has demonstrated comparable efficacy to other administration routes, especially in pediatric and adolescent populations [12]. In all included studies, confidence intervals were typically specified at the 95% confidence level, which is consistent with the standard threshold for statistical significance (*p*-value = 0.05). Concerning potential complications, three studies reported various adverse events occurring after IN midazolam administration. Whitfield reported that, compared with 5.6% of those who received initial midazolam via another route, 6.7% of patients receiving IN-midazolam required bag-mask ventilation in the field, resulting in a 1.1% (95% CI 1.4 ~ 3.7%) risk difference [6]. Other observed adverse effects included respiratory depression and nasal irritation [12], whereas one study reported somnolence and vomiting [13].

Discussion

This was a systematic review that included three studies out of 489 studies involving 5,062 patients. They were all classified as pediatrics or adolescents, as their age was younger than 18 years. Most of these patients received treatment in the prehospital setting, and a few were treated in the ER. Two of the studies that were chosen for inclusion were cohort studies, and one was a randomized clinical trial.

The main factor influencing the effectiveness of the drug was the cessation of seizures within 10 minutes. Only the clinical trial reported the superiority of IN-midazolam with a *p*-value of 0.002 for stopping prominent visible seizure activity within 10 minutes of administration [13]. The need for redoing was the second main outcome. IN-midazolam was associated with an increased likelihood of requiring additional benzodiazepine administration, according to two studies [6,12]. IN-midazolam was associated with a greater likelihood of needing additional benzodiazepine dosages (OR = 1.39, 95% CI = 1.10-1.76),

as stated by Ramgopal et al. [12]. Using IN-midazolam was also linked to more subsequent midazolam use during an EMS call, according to Whitefield's study [6]. This was mainly due to the low dose of midazolam, which is used as an IN. Midazolam has been shown to have effective outcomes in preventing seizures, similar to other routes when it is adjusted to a higher dose [14].

This article reviewed three studies that were considered strong according to the critical appraisal skill program checklist. First, Mohammed's research strength was the randomization in the clinical trial, which helped reduce bias and ensure that the treatment effects were not influenced by other variables [13]. Moreover, regular monitoring of vital signs and systematic assessment of side effects have contributed to understanding the safety profile of midazolam [13]. Both cohort studies shared the benefit of having a large sample size, which improved the statistical power and generalizability [6,12]. To add to the Ramgopal study, the confounders were adjusted by controlling crucial factors such as age and heart rate, adding validity to the comparisons [12]. Additionally, the findings align with existing research on IM and IV midazolam, adding credibility by having consistent results with other evidence [12].

On the other hand, several limitations of these studies, such as the short follow-up period after the administration of IN midazolam, should be noted. These studies focused primarily on short-term seizure cessation without addressing longer-term efficacy, safety, or recurrence rates after 24 hours, which are crucial for comprehensive treatment evaluation. Furthermore, the two observational studies cannot establish causal relationships, and a lack of randomization and blinding increases the risk of bias.

Seizures are among the most life-threatening conditions in emergency settings, particularly in prehospital environments, where the uncontrolled nature of care poses unique challenges. The need for treatments that are rapid, easy to administer, and effective emphasizes the importance of continually updating the literature. Although intravenous benzodiazepines offer the advantage of quicker administration, significantly impacting seizure cessation time, IN offers faster administration and avoids delays associated with obtaining IV access, which balances the benefits of IN over IV in the prehospital setting [14,15].

According to published findings, IN delivery of midazolam is effective at preventing seizures and shortens the total time between hospital entrance and seizure elimination, ultimately contributing to faster seizure cessation than IV/rectal benzodiazepines [16]. As a result, IN-midazolam might be regarded as a viable therapeutic choice for acute seizures in young patients. This approach mitigates the hazards and limits associated with the IV approach. In clinical and prehospital settings, IN midazolam can be utilized to manage seizures [16]. A placebo-controlled trial demonstrated that midazolam nasal spray (MDZ-NS) outperformed a placebo in terms of achieving immediate and sustained seizure suppression among patients with seizure clusters in an outpatient environment while also exhibiting a favorable safety profile [17].

Numerous researchers examined the health risks of midazolam concerning pulmonary or cardiovascular issues. A newly published systematic review revealed that previous studies do not show respiratory depression to be an existential issue with midazolam [7]. In addition, the non-inferiority criteria were not met by IN midazolam dosed at 0.1 mg/kg, which was linked to a greater incidence of redosing in comparison to midazolam given via the IV, IO, and IM routes [6].

Additional research is necessary to directly compare the efficacy of midazolam across delivery routes using the suggested IN dose of 0.2 mg/kg. The numerous benefits of IN-midazolam, such as its quick, needle-free administration, might further justify its use as the recommended treatment for prehospital pediatric seizure control if non-inferiority is proven for this dosage [6].

Midazolam makes it possible to address children's seizures quickly and painlessly in the prehospital scenario if it is comparable to IV or IM methods. When IV access and IM administration are difficult or impractical, IN medications provide a secure, noninvasive method of quickly delivering medications. The following can be a vital substitute in the prehospital context for time-sensitive circumstances such as managing trauma, seizures, and agitated patients [18]. Nevertheless, there is an inadequate amount of data describing its effectiveness in this setting.

This review highlighted the lack of studies on IN midazolam for seizure control, particularly in prehospital and adult settings. Further research is needed to evaluate its effectiveness, safety, and long-term outcomes, as well as its potential advantages in terms of rapid administration and ease of use during emergencies. Policymakers should consider incorporating it into emergency protocols with proper training for healthcare providers, supported by large-scale trials to ensure its efficacy across diverse populations and settings. Evidence indicated that intranasal midazolam (in-MDZ) is effective in halting seizures in adults, with a success rate of 72.7% after the first dose [14]. However, it is less effective than treatments such as rectal diazepam (89%-100%) and IN al diazepam (63%). The highest success rate with in-MDZ was observed with a 10 mg dose.

The recurrence rate following the first dose of in-MDZ was 36.5%, which was lower than that following the first dose of placebo (61%-63%) or intravenous midazolam (43%). While in-MDZ is effective, it might not be as optimal as other treatments for both seizure termination and preventing recurrence [14]. Hence, higher doses of in-MDZ were more likely to provide the necessary pharmacological response to effectively control seizures, whereas under-dosing with benzodiazepines often results in suboptimal drug levels and treatment failure in the adult population. This finding reinforces the importance of using appropriate dosing strategies to optimize outcomes and reduce the need for redosing [14].

To enhance patient outcomes, further studies focusing on adult populations in emergency settings are needed to refine dosing recommendations and improve treatment efficacy.

Additionally, future research should focus on evaluating the safety and efficacy of MDZ-NS in children under 12 years of age, its interaction with clobazam, and its stability across temperatures [19]. Expanding benzodiazepine formulations and delivery methods tailored to seizure type, age, comorbidities, and drug interactions is vital for optimizing treatment and outcomes [19]. IN midazolam provides rapid, effective seizure control in out-of-hospital emergencies, often surpassing rectal and IV diazepam, but its faster elimination might heighten the risk of seizure recurrence [20].

Future research should compare its long-term outcomes with those of other benzodiazepines, optimize dosing to balance efficacy and recurrence risk, and assess its use by nonmedical personnel in real-world emergency settings [20]. The IN, IM, and buccal routes deliver drugs faster than the intravenous or rectal routes do, especially in outpatient settings, although overall effectiveness remains similar across routes. Future studies should prioritize comparing the total time to seizure cessation and assessing the effectiveness of various routes of administration to determine the best approach for seizure management [21].

Several limitations should be considered, which might impact the interpretability and applicability of the findings. The reliability of a systematic review hinges on the quality of included studies, as flaws, variability, and subjective pooling decisions can introduce bias or inconsistencies [22]. The focus on pediatric populations only, and variability in settings and designs, reduced generalizability. A major limitation in evaluating intranasal midazolam was the variability in study metrics, including inconsistent criteria for seizure cessation, recurrence prevention, and rescue medication use. Differences in dosing, administration techniques, and patient populations further hinder uniform conclusions about its efficacy. Furthermore, IN-midazolam was associated with higher redosing rates and adverse events, such as respiratory depression and nasal irritation, raising safety concerns. Inconsistent outcome measures and underreporting of adverse events further limit reliability.

In addition, a limitation in older children was that administering midazolam at a dose of 0.2 mg/kg requires a larger drug volume, which can be challenging to deliver and often leads to local side effects, such as mucosal irritation [23]. Another limitation pertains to the prehospital and ED settings, where the lack of accurate data on EMS response times, seizure duration, time from patient's place to hospital, and patient follow-up after ED admission poses a challenge. These factors are critical for effectively evaluating the management and outcomes of seizures, particularly in patients with status epilepticus. Without these comprehensive data, assessing the timeliness and effectiveness of interventions, as well as understanding patient recovery, becomes difficult [24].

Conclusion

The studies have consistently demonstrated that in-MDZ is an effective and accessible treatment for terminating seizures in prehospital and emergency care settings, with an 88.2% success rate within 10 minutes of administration. Its non-invasive nature, ease of use, and rapid absorption through the nasal mucosa make it particularly advantageous for pediatric and uncooperative adult patients. Its effectiveness is comparable to that of other routes, such as IV midazolam and rectal diazepam. in-MDZ is favored for its practicality and suitability in challenging clinical scenarios. However, the increased likelihood of requiring additional doses compared to IV or IM administration highlighted the need for optimized dosing strategies. Although its safety profile is generally favorable, potential adverse effects, including respiratory depression and nasal irritation, necessitate careful monitoring.

Evidence increasingly supports IN midazolam for managing seizures in emergency settings, especially prehospital care. However, more research is needed on adult populations, as studies have largely focused on children. High-quality RCTs with extended follow-up periods are essential to assess their long-term efficacy, safety, and impact on outcomes like seizure recurrence and quality of life. By addressing these key areas, future studies could significantly improve clinical practices for seizure management in adults, offering a safer, more effective alternative for rapid intervention in emergency settings.

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List of abbreviations

EDs	Emergency departments
EMS	Emergency medical services
ER	Emergency room
IM	Intramuscular
IN	Intranasal
in-MDZ	Intranasal Midazolam
IO	Intraosseous
IV	Intravenous

Conflict of interests
The authors declare that there is no conflict of interest regarding the publication of this article.

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Table S1. *Risk of bias and quality assessment.*

Author year	Study did not addressed a clearly focused issue	Poorly recruited cohort	Exposure maximizes the bias	Outcomes maximize the bias	Poor confounding control	Follow-up bias
Ramgopal et al. 2024 [12]	🔴	🔴	🔴	🟢	🟡	🟡
Whitfield et al. 2022 [6]	🔴	🔴	🔴	🟡	🟡	🟡

🔴 Does not meet the criteria 🟢 Meet the criteria 🟡 Partially meet the criteria

Table S2. *Results and applicability assessment.*

Author year	Clarity of the findings	Precised results	Findings are applicable	Results fit with available evidence	Clear implication for future research
Ramgopal et al. 2024 [12]	🟢	🟢	🟢	🟢	🟡
Whitfield et al. 2022 [6]	🟢	🟢	🟢	🟢	🟡

🔴 Does not meet the criteria 🟢 Meet the criteria 🟡 Partially meet the criteria

Table S3. *Risk of bias and quality assessment.*

Author, year	Clear research question	The assignment of participants were randomized	Double blinding	Description of dropouts	Study groups treated equally	Power analysis	Intention to treat	Jaded score
Mohammed et al. 2024 [13]	🟢	🟢	🔴	🟢	🟢	No	Yes	3

🔴 Does not meet the criteria 🟢 Meet the criteria 🟡 Partially meet the criteria

Table S4. *Results and applicability assessment.*

Author year	Clarity of the findings	Precised results	Findings are feasible	The intervention is feasible	The benefits worth cost and risks
Mohammed et al. 2024 [13]	🟢	🟢	🟢	🟢	🟡

🔴 Does not meet the criteria 🟢 Meet the criteria 🟡 Partially meet the criteria