Academic Emergency Medicine

SYSTEMATIC REVIEW

Non-Injectable Ketamine for Pediatric Sedation in the Emergency Department: A Systematic Review

Hadi Mirfazaelian[1,2] | Alireza Erfan Fazel[3] | Nima Azizi[3] | Komeil Mirzaei Baboli[4] | Rasoul Masoumi[5] | Mohammad Eftekhari[2]

[1]Department of Emergency Medicine, Tehran University of Medical Sciences, Tehran, Iran | [2]Prehospital and Hospital Emergency Research Center, Tehran University of Medical Sciences, Tehran, Iran | [3]Students' Scientific Research Center, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran | [4]Pathology Department, Harbor-UCLA Medical Center, Torrance, California, USA | [5]Independent Researcher, Tehran, Iran

Correspondence: Mohammad Eftekhari (smeftekhari@tums.ac.ir)

Received: 9 June 2025 | **Revised:** 19 September 2025 | **Accepted:** 25 September 2025

Supervising Editor: Michelle Macy

Funding: The authors received no specific funding for this work.

Keywords: Emergency Department | noninjectable ketamine | pediatric | procedural sedation and analgesia

ABSTRACT

Introduction: Ketamine is the most common medication for procedural sedation and analgesia (PSA) of pediatric patients in the emergency department (ED). Since ketamine injection is painful, some studies have assessed the routes other than intravenous and intramuscular. Therefore, this systematic review aims to evaluate the details of noninjectable ketamine (NIK) administration.

Methods: The review followed the Preferred Reporting Items for Systematic Review and Meta-Analysis for Systematic Review (PRISMA) guidelines. MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Web of Science Core Collection (SCIE and ESCI), and Scopus were searched for relevant studies from inception to 3 July 2025. All English original clinical research on PSA with NIK administration in pediatric populations in the ED was included. Risk of bias and certainty of evidence (COE) were also assessed.

Results: From 5617 identified records, 12 studies (7 interventional and 5 observational) with a total number of 1484 patients were included. Most of the studies evaluated laceration repair among children 2–12 years of age. Seven single-center double-blinded randomized controlled trials showed that oral ketamine (5–10 mg/kg) alone or in combination with other medications (mainly midazolam) provided the desirable level of sedation (COE: very low) relative to the oral comparators. It also resulted in faster onset of action (OA) (15–35 min) and shorter duration of action (DA) (60–265 min) (COE: low). Oral and nasal ketamine studies did not report any serious adverse event (SAE) associated with invasive interventions (COE: moderate to low).

Conclusion: Sedation with oral ketamine might have a desirable depth, faster OA, and shorter DA relative to the oral comparators. Furthermore, NIK probably showed no SAE during PSA. Nevertheless, the limited number of heterogeneous studies leaves uncertainty, highlighting the need for further research.

1 | Introduction

Pediatric patients in the emergency department (ED) experience anxiety and pain, especially during procedures. While nonpharmacological methods can be incorporated for sedation [1], procedural sedation and analgesia (PSA) is used widely to address the problem [2]. Ketamine is the drug of choice in pediatric ED patients for this purpose [3]. It is a

phencyclidine derivative and primarily acts as an N-methyl-D-aspartate receptor antagonist in the central nervous system [4]. Ketamine and its enantiomer (esketamine), which is four times more potent, provide hemodynamically stable anesthesia via central sympathetic stimulation while preserving respiratory function [5]. Although this medication has demonstrated good safety and sedation profiles, the pain associated with intravenous or intramuscular administration has motivated researchers to explore alternative routes such as per oral (PO), nebulization, and intranasal (IN) [4, 6, 7]. In addition, optimal dosing of ketamine in combination with other medications in these alternative routes is also under investigation [8–11].

In this systematic review, we aimed to assess the performance of noninjectable ketamine (NIK) for PSA of pediatric ED patients across different administration routes regarding its dosing regimens, onset of action (OA), duration of action (DA), recovery time, depth and quality of sedation as measured by sedation scales, additional medication for sedation (AMS), physician and patient satisfaction, as well as the short-term and long-term adverse events (AE).

2 | Methods

This report was registered in the International Prospective Register of Systematic Reviews (PROSPERO; registration number CRD420251081487) and followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Systematic Reviews (PRISMA) guideline. All studies which introduced or evaluated NIK or esketamine in pediatric (i.e., < 18 years old) PSA in the ED were considered eligible. Case reports, review articles, nonrandomized and/or pilot clinical trials, studies reported in abstract form, studies on ketamine for purposes other than PSA such as rapid sequence intubation, rapid tranquilization for acute behavioral disturbance, analgesic dose (subdissociative), and non-English studies of any type were excluded.

2.1 | Search Strategy

The search strategy was developed by a medical librarian. The key terms of "ketamine", "children", "pediatrics", "emergency department", "sedation", and "anesthesia" were used to develop a sensitive search strategy. Any additional relevant keywords identified during the search were integrated (Appendix S1). The following databases were included in the electronic search from the inception date to July 2025: MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Web of Science Core Collection (SCIE and ESCI), and Scopus. The reference lists of included studies were also reviewed.

2.2 | Study Records

All records were entered into Rayyan, a web-based screening application. After removing the duplicates by Endnote software or manually, two independent reviewers (NA and EF) assessed the inclusion criteria through evaluating the titles and abstracts. Any disagreement was resolved through discussion with a third reviewer who was an emergency medicine attending (HM or ME). In the next step, the full text of the included studies was scrutinized by the same reviewers in the previous stage. At this step, reasons for excluding the studies were recorded. Data extraction of the included studies was carried out manually by the same reviewers. The following data were extracted: publication year, country, study design, procedure type, sample size, sex, inclusion and exclusion criteria, American Society of Anesthesiologists (ASA) status of the patients, route, dose, depth, OA, and DA for sedative drugs, AMS, local analgesia, AE, and finally, patients', parents', and healthcare providers' satisfaction. All collected data underwent discussion and cross-verification with all the study members.

2.3 | Risk of Bias Assessment and Certainty of Evidence

The risk of bias in included studies was assessed independently by two reviewers (HM and ME) using the Cochrane Collaboration's Risk of Bias [12] for randomized clinical trials (RCTs) and Newcastle-Ottawa Scale (NOS) [13] for observational studies. Discrepancies were resolved by consensus.

The certainty of evidence was evaluated independently by two reviewers (HM and ME) using the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) approach [14]. This considers the domains of risk of bias, inconsistency, indirectness, imprecision, and publication bias for each outcome. The overall certainty of the evidence (COE) for each outcome was rated as high, moderate, low, or very low. Discrepancies were resolved by consensus.

2.4 | Data Synthesis

We presented the data qualitatively. In addition, descriptive statistics (e.g., proportion of patients with adverse events, mean and standard deviation of time to sedation) were used to summarize quantitative data, and the findings were presented in tables. Due to heterogeneity among the included studies, conducting a meta-analysis was not feasible.

3 | Results

3.1 | Study Selection

Our database search identified 5617 studies. After deletion of duplicates, reviewers excluded 3119 studies by assessing titles and abstracts according to inclusion and exclusion criteria. Thirty-nine studies were scrutinized in full text. Twenty-seven studies were excluded; 12 were on ketamine injection [15–26], six were not in the ED [27–32], eight reported a method that did not fulfill the eligibility criteria [33–40], and one study was published in abstract only [41]. Finally, 12 studies were included in the analysis (Figure 1), seven interventional and five observational studies.

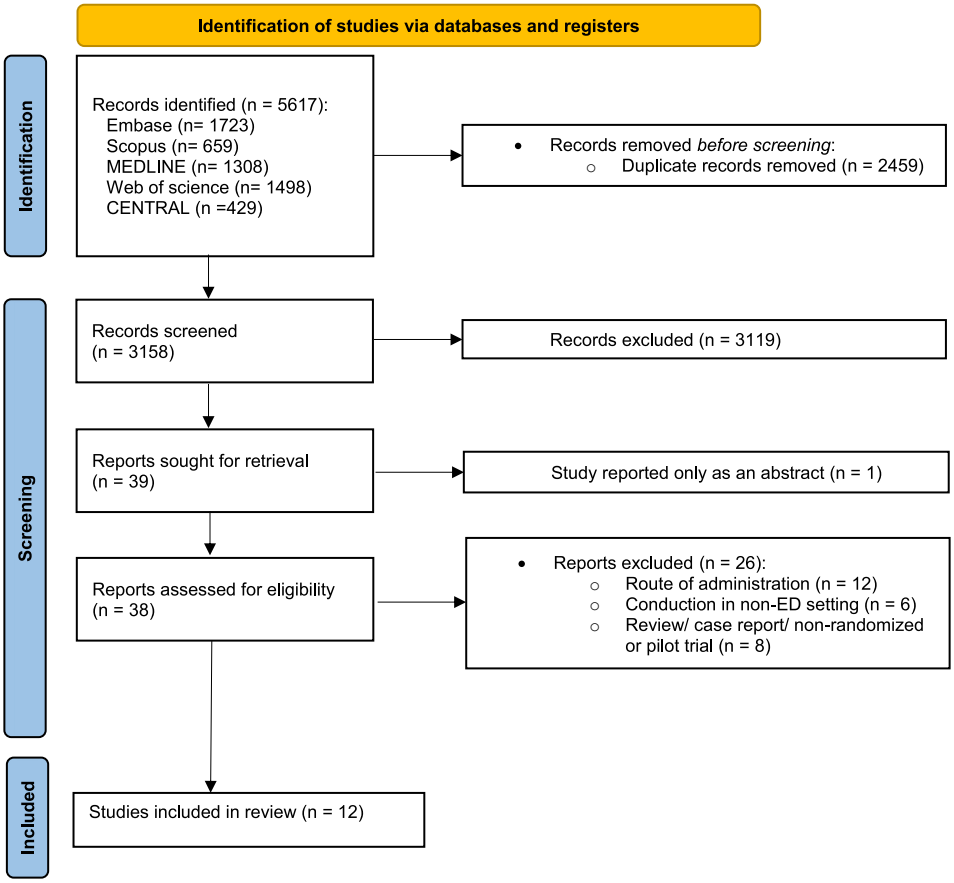

FIGURE 1 | PRISMA flow diagram.

3.2 | Study Characteristics

Studies were published from 1995 [42] through 2025 [43]. Five studies were conducted in Asia [44–48], four in North America [42, 43, 49, 50], and three in Europe [51–53]. Twelve included studies collectively enrolled a total of 1484 patients, of which 494 were involved in single-center double-blinded RCT studies and 990 in single-center cohort studies. Only one study investigated esketamine [52] (Tables 1 and 2).

The age of the patients in the RCTs was 1–10 years (Table 1). Most of the cohort studies evaluated the childhood period (i.e., 2–12 years) [54] except one study that included patients less than 3 months [50] (Table 2). All of the RCTs evaluated laceration repair except one study on radiology diagnostic procedures [48] (Table 1). In contrast, cohort studies evaluated various painful procedures such as laceration repair, arthrocentesis, lumbar puncture, burns, closed reduction, and radiological diagnostic procedures (Table 2). The RCTs evaluated oral ketamine (5–10 mg/kg) except one which compared IN ketamine (5 mg/kg) with IN midazolam (MDZ). Two studies on oral ketamine [42, 44] compared ketamine with placebo and 3 examined ketamine in combination with MDZ versus MDZ [44], MDZ in combination with promethazine [45], or diphenhydramine [47] (Table 1). Among cohort studies, two studies [43, 50] assessed oral ketamine (6 and 10 mg/kg) and three IN ketamine (3–5 mg/kg) [49, 51, 52] (Table 2).

3.3 | Risk of Bias Assessment

Due to insufficient information on blinding in the performance and detection domains, one interventional study [42] was rated as unclear risk of bias. Other RCTs were judged to have a low risk of bias (Appendix S2). Three [43, 50, 52] and two [49, 51] observational studies had good and fair scores of NOS, respectively (Appendix S3).

3.3.1 | Assessment of Anxiety, Sedation Depth, and Procedural Pain

Anxiety level before drug administration, preprocedural period after drug administration, and/or during procedure was reported in three studies [45, 47, 53]. They used mostly unvalidated tools [47, 53] or Houpt scale [45, 47] for this mean. A subdomain of overall anxiety, the 'Separation score' was reported in three studies [45, 48, 53]. There were no significant differences in anxiety levels between ketamine and comparator groups during the preprocedural period after drug administration. However, two out of three studies [45, 47] found a lower anxiety level in the ketamine group (Table 3).

Most of the RCT studies utilized sedation scales, although some were not validated [42, 44, 48, 53]. Among them, one employed the Ramsay sedation scale (RSS) [45] and one used the

TABLE 1 | Characteristics of the included interventional studies.

Study (Year, country)	Study sample size	Average age	Male number (%)	Procedure type	Medications	Outcomes of interest	Comments
Qureshi (1995, USA)	30	3.4 ± 2[a]	26 (86.7%)	Laceration repair	Oral ketamine (10 mg/kg) vs. Placebo	Tolerance to lidocaine injection and suturing, Sedation depth, DA	Lidocaine 1% was injected subcutaneously. The maximum dose for oral ketamine was 250 mg
Younge (2001, United Kingdom)	59	4.1	NA	Laceration repair	Oral ketamine (10 mg/kg) vs. Oral MDZ (0.7 mg/kg)	Anxiety and tolerance scores, New behavioral disturbance within 2 weeks, OA, AE, Parental satisfaction	Lidocaine 1% injection or a gel containing epinephrine (1:2000) + cocaine (4.7%) was used for topical anesthesia
Barkan (2014, Israel)	59	5.0	32 (53.3%)	Laceration repair	Oral ketamine (5 mg/kg) + oral MDZ (0.5 mg/kg) vs. oral MDZ (0.5 mg/kg) + oral placebo	Sedation depth, Additional medication for sedation rate, OA, Procedure duration, DA, AE	LET cream was applied on arrival to the triage. Intradermal lidocaine (1%) prior to suturing
Soleimanpour (2014, Iran)	80	4.8	54 (67.5%)	Laceration repair	Oral ketamine (6 mg/kg) + oral MDZ (0.05 mg/kg) + oral atropine (0.02 mg/kg) vs. Oral diphenhydramine (1.25 mg/kg)	Sedation depth, AE	Lidocaine spray 4% was used. Local anesthesia injection was used if sedation depth was unacceptable after 45 min
Rubinstein (2016, Israel)	68	5.0	33 (48.5%)	Laceration repair	Oral ketamine (5 mg/kg) vs. Oral MDZ (0.7 mg/kg)	Sedation depth, Local anesthesia injection pain, Procedure pain by children, Parents and providers satisfaction, Additional medication for sedation, Procedure duration, OA, Adverse event	Lidocaine 1% was injected prior to suturing. The maximum dose for oral MDZ and ketamine were 20 mg and 70 mg, respectively
Bozorgi (2021, Iran)	102	5.7 ± 2.7[a]	49 (48%)	Surgical procedures (e.g., laceration repair)	Oral ketamine (5 mg/kg) + oral MDZ (0.5 mg/kg) vs. Oral promethazine (1 mg/kg) + oral MDZ (0.5 mg/kg)	Sedation depth, irritability and separation anxiety, Pain level during procedure, Crying in medication administration, Recovery time, AE	
Ziaei (2021, Iran)	95	4.0 ± 0.7[a]	45 (45.4%)	Radiologic diagnostic procedures in the ED	Oral ketamine (5 mg/kg) vs. Oral MDZ (0.5 mg/kg)	Sedation depth, Separation scores, DA, OA	

Abbreviations: DA, duration of action; ED, emergency department; MDZ, midazolam; NA, not applicable/not available; OA, onset of action; SD, standard deviation.
[a]Mean ± standard deviation.

TABLE 2 | Characteristics of the included observational studies.

Study (year, country)	Cohort design	Sample size	Age	Procedure	Exclusion criteria	Noninjectable ketamine dose	Outcomes of interest	Comments
Nemeth (2017, Germany)	Prospective	51 (IN: 51)	NA	Various (e.g., laceration)	Compromised vital functions (e.g., hypotension or respiratory depression), ASA ≥ III, and vascular access already in place	IN (esketamine): 4 mg/kg	Sedation depth, Time to sedation, AEs	Only patients for whom IV or other routes were not feasible. 47 patients nebulized with MDZ (0.5 mg/kg) and/or fentanyl (2 μg/kg)
Guthrie (2019, USA)	Retrospective	196 (IN: 196)	Median: 3.8 [IQR: 2.3, 7.2] years Range: 6 months to 18 years	Various (e.g., laceration repair, orthopedics procedure)	Hypersensitivity to ketamine, difficult airway, epistaxis, rhinitis, and ciliary dysfunction	IN: 2–5 mg/kg	Provider satisfaction (0–100 scale), AEs, need for additional medication for sedation, DA	They surveyed the providers for the satisfaction with the IN ketamine
Mills (2024, Canada)	Retrospective	14 (Oral: 3, IV: 2, IM: 1, IV and IM: 1)	Median: 45 days Range: 12–89 days	NA	NA	Oral: 10 mg/kg	AE	Midazolam was co-administered in addition to the oral ketamine
Gutiérrez (2024, Spain)	Retrospective	671 (IN: 44, IV: 627)	Mean: 7.2 (SD: 4.3) years	Painful procedures (e.g., arthrocentesis, lumbar puncture, burns, closed reduction, and radiological examinations)	ASA ≥ 3	IN: 3–5 mg/kg	PSA effectiveness by provider (3-level scale), AEs, need for additional medication for sedation, Pain assessment	Ketamine maximum dose was 100 mg. Used 3 different sedation scales. Unclear if the AEs were in the IN or IV group
Del Pizzo (2025, USA)	Retrospective	58 (Oral: 58)	Median: 4 years Range: 9 months to 17 years	Various (e.g., laceration repair, orthopedics procedure)	NA	Oral: 6 mg/kg	AE	56 patients also received MDZ (0.5 mg/kg). 75.9% received local analgesia

Abbreviations: AE, adverse event; ASA, American society of anesthesiology; BP, blood pressure; DA, duration of action; IM, intramuscular; IN, intranasal; IQR, inter-quartile range; IV, intravenous; MDZ, midazolam; NA, not available/applicable; N/V, Nausea and/or vomiting.

TABLE 3 | Results of interventional studies.

Study	Medication	Average OA (min)	Need for additional medication for sedation	Adverse events	Main findings
Qureshi et al.	Oral ketamine	35	0/15 (0%)	0/15 (0%)	Patients who received ketamine had higher tolerance to lidocaine injection and suturing with longer DA. No serious AE was observed
	Placebo	NA	2/15 (13.3%)	0/15 (0%)	
Younge et al.	Oral ketamine	30	NA	Dysphoria: 0/30 (0%) Behavioral disturbances: 6/30 (20%) Ataxia after discharge: 2/30 (6.7%) Vomiting: 6/30 (20%)	Tolerance to local anesthesia injection was higher in the ketamine arm with fewer dysphoric reaction and behavioral changes
	Oral MDZ	29	NA	Dysphoria: 6/29 (20.7%) Behavioral disturbances: 12/29 (41.4%) Ataxia after discharge: 2/29 (6.9%) Vomiting: 2/29 (6.9%)	
Barkan et al.	Oral ketamine and oral MDZ	14.6 ± 6.3[a]	2/31 (6.5%)	N/V: 3/31 (9.7%) Self-limited $SpO_2 < 90\%$: 1/31 (3.2%) Agitation after recovery: 2/31 (6.5%)	The combination of oral MDZ and ketamine led to deeper sedation and lower rate of sedation failure
	Oral MDZ and oral placebo	17.9 ± 6.9[a]	8/29 (27.6%)	Mild hypotension: 1/29 (3.4%) Agitation: 1/29 (3.4%)	
Soleimanpour et al.	Oral ketamine, oral MDZ, and oral atropine	85% became drowsy after 45 min	NA	0/40 (0%)	Ketamine was more effective in painful procedures in terms of sedation and has fewer psychological side effects after 2 weeks. There was no AE ensued
	Oral diphenhydramine	< 20% became drowsy after 45 min	NA	0/40 (0%)	
Rubinstein et al.	Oral ketamine	23.6 ± 9.2[a]	12/37 (32.4%)	Vomiting: 1/37 (2.7%) Nausea and vertigo: 1/37 (2.7%) Agitation: 2/37 (5.4%)	While no difference was found in the level of pain, sedation depth, and DA, oral ketamine needed more additional medication for sedation
	Oral MDZ	25.8 ± 10.5[a]	2/31 (6.5%)	Vomiting and hiccups: 1/31 (3.2%) Agitation: 1/31 (3.2%)	

(Continues)

TABLE 3 | (Continued)

Study	Medication	Average OA (min)	Need for additional medication for sedation	Adverse events	Main findings
Bozorgi et al.	Oral ketamine and oral MDZ	NA	NA	N/V: 2/51 (3.9%)	MDZ + ketamine had deeper sedation and lower rates of irritability and separation anxiety with shorter DA
	Oral promethazine and oral MDZ	NA	NA	N/V: 0/51 (0%)	
Ziaei et al.	Oral ketamine	20	NA	NA	Two groups had same sedation depth and separation anxiety levels but ketamine arm showed a faster OA and shorter DA
	Oral MDZ	30	NA	NA	

Abbreviations: AE, adverse event; DA, duration of action; MDZ, midazolam; NA, not applicable/available; N/V, nausea and/or vomiting; OA, onset of action.
[a]Mean ± standard deviation.

University of Michigan Sedation Scale (UMSS) [46]. Two studies reported children's cooperation using a Likert-like scale [43, 47]. The seven RCT studies showed that oral ketamine (5 mg/kg) in combination with other drugs more frequently and significantly reached the desirable level of sedation [44, 45, 47] whereas oral ketamine alone at the same dose did not show a significant difference with the comparators [46, 48, 53] (Table 3). In contrast, sedation levels were reported in cohort studies in only one study that reported UMSS [52]. Three [43, 49, 52] out of five cohort studies reported an overall success rate in sedation with IN or oral ketamine in more than 80% of their patients (Table 4).

In three interventional studies, procedural pain was assessed through the Visual Analog Scale (VAS) by physicians and/or parents [44–46]. Two out of three studies showed no significant difference between "ketamine (5 mg/kg) + MDZ (0.5 mg/kg)" and MDZ (0.5 mg/kg) alone [44], and between ketamine (5 mg/kg) and MDZ (0.7 mg/kg) [46]. However, the ketamine and MDZ combination provided more comfort in comparison with "promethazine (1 mg/kg) + MDZ (0.5 mg/kg)" [45] (Table 3). Procedural pain was reported in only one observational study [51] (Table 2), in which 44 of 671 patients received IN ketamine and the remainder received IV sedation. Using age-appropriate scales, the investigators found that for procedures of shorter duration (10–15 min), the rate of unsatisfactory analgesia was significantly higher in the IN group (80%) in comparison to the IV group for procedures of longer duration (exceeding 20 min) (25.4%).

3.3.2 | Satisfaction Scale

Physicians and/or parents' satisfaction was the outcome of interest in four of the studies [46, 49, 51, 53] (Tables 1 and 2). While different approaches were incorporated for this assessment, no significant difference was observed between oral ketamine and MDZ [46, 53] (Appendix S4). Although parents' satisfaction with the IN route was high at approximately 90% [49], in another study, one third of the parents were unsatisfied when the procedures took longer than 15 min [51] (Table 4).

3.3.3 | Onset and Duration of Action

OA for the oral route was 15–35 min [42, 44, 46, 48, 53], and DA ranged from 60 to 265 min. However, studies that employed ketamine in combination with other drugs showed shorter OA and longer DA (Appendix S4). In addition, OA with IN esketamine was lower at 10 min [52]. DA for IN ketamine was 237.9 min in one study [49] (Table 4).

3.3.4 | Additional Medication for Sedation

AMS (rescue treatment) was defined as a repeated dose of ketamine in the same route (full or half of the initial dose), IV administration of ketamine or other medication, or any "additional analgesic or anesthetic drug use", at the physician's discretion.

Studies on IN ketamine either did not require AMS [52] or showed 13.6% need for it, similar to the rate in IV ketamine

TABLE 4 | Results of observational studies.

Study	Adverse events	Additional medication for sedation	Other outcomes
Nemeth et al.	No cardiopulmonary AEs	NA	Most patients had mild reaction to pain during procedure
Guthrie et al.	No cardiopulmonary AEs. Other AEs such as N/V, dizziness, drowsiness, and dysphoria were present	15/196 (7.7%)	Satisfaction: 90% DA: 237.9 min
Mills et al.	No AE was reported	NA	NA
Gutiérrez et al.	No serious AE. Laryngospasm: 2/671 (0.3%) Apnea 2/671 (0.3%) Other AEs such as N/V, emergence phenomena/delirium, myoclonus, elevated BP, and morbilliform rash had a rate of < 10%	6/44 (13.6%)	Satisfaction: 63.6%
Del Pizzo et al.	No cardiopulmonary AEs. Nonserious (e.g., emergence phenomenon and N/V): 4/58 (6.9%)	8/58 (13.8%)	NA

Abbreviations: AE, adverse event; ASA, American society of anesthesiology; DA, duration of action; NA, not applicable/available.

(14.8%) [51]. In an observational study of 58 children who received "oral ketamine (6 mg/kg) ± oral MDZ (0.5 mg/kg)"—of whom two received ketamine alone—8 patients (13.8%) required AMS [43]. In RCTs, when oral ketamine alone (10 mg/kg) was compared with placebo, no AMS was required [42]. However, oral ketamine at a lower dose (5 mg/kg) required more AMS when compared to oral MDZ (0.7 mg/kg) (12% vs. 6%) [46]. Interestingly, when oral ketamine at this lower dose (5 mg/kg) was combined with MDZ (0.5 mg/kg) and compared to MDZ alone (0.5 mg/kg), less IV AMS was required (6% vs. 27%) [44] (Table 3).

3.3.5 | Adverse Events

Studies typically categorized AE based on severity—minor/major or serious/nonserious—and timing, either during peri-sedation or delayed (days or weeks after sedation). Minor peri-sedation AEs (e.g., changes in vital signs, morbilliform rash, dizziness, nausea, vomiting, myoclonus, nystagmus, dysphoria, and unpleasant taste) had an incidence of < 10% [51]. Some of the ketamine AEs such as vomiting and ataxia in the ketamine group had no significant difference with MDZ and both were reported in 2% [53] and 9% [44], respectively. Interestingly, dysphoria was less common in ketamine in comparison to MDZ (0% vs. 21%) [53] (Tables 3 and 4).

Some studies considered events like emergence phenomena as major complications. However, serious adverse events (SAE) were generally defined as those requiring an intervention, particularly invasive interventions beyond basic airway maneuvers [51, 52]. Nevertheless, neither interventional nor observational studies reported any case of serious cardiopulmonary AE that needed invasive procedures such as intubation after NIK administration. Partial airway obstruction was reported in 1.7%, and laryngospasm and apnea were described in 0.3% of the population in two cohort studies [43, 51] (Tables 3 and 4).

The most commonly studied delayed AE was behavioral changes 2 weeks after sedation. Using the post-hospitalization behavioral questionnaire (PHBQ) by two studies, oral ketamine had a significantly lower rate of behavioral changes compared with MDZ alone [53] or the combination of MDZ, atropine, and diphenhydramine [47] (Table 3).

3.4 | Certainty of Evidence

We selected eight outcomes based on our aims of study and the results of the systematic review. Four efficacy outcomes—OA, DA, depth of sedation, and AMS with oral ketamine—were assessed exclusively using data from RCTs to decrease heterogeneity. The remaining four outcomes—parents and physician satisfaction, as well as short- and long-term adverse events—were evaluated from all studies but RCTs and cohort studies (Table 5).

Since the number of relevant studies in each outcome was lower than 10, publication bias was rated as less important for all studies. Table 5 presents the ratings for the remaining domains, with a detailed discussion of each outcome, domain, and overall certainty of evidence (COE) provided in Appendix S5. Briefly, oral ketamine alone or in combination with other oral drugs might provide the desirable sedation depth, faster OA, and shorter DA relative to oral comparators. Regarding AMS, either higher doses of oral ketamine alone (10 mg/kg) or lower doses (5 mg/kg) in combination with MDZ might be associated with a reduced need for an AMS. In addition, NIK probably had no SAE and might have a higher rate of physician satisfaction.

4 | Discussion

This systematic review on PSA of ED pediatric patients showed that oral ketamine (5–10 mg/kg) alone or in combination with

TABLE 5 | Certainty of evidence assessments based on (Grading of Recommendations Assessment, Development, and Evaluation) GRADE system.

Number of studies and design(s) (sample size)	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Certainty (overall score)
Outcome: Oral ketamine onset of action: oral ketamine alone or in combination might have faster onset of action						
6 RCT on oral ketamine (392)	Not serious	Not serious	Serious	Serious	Less important	Low
Outcome: Oral ketamine duration of action: oral ketamine alone or in combination might have shorter duration of action						
7 RCT on oral ketamine (494)	Not serious	Not serious	Serious	Serious	Less important	Low
Outcome: Depth of sedation with oral ketamine: oral ketamine alone or in combination might provide the desirable depth of sedation						
7 RCT on oral ketamine (494)	Not serious	Serious	Serious	Serious	Less important	Very low
Outcome: Additional medication for sedation: oral ketamine, at higher doses alone (10 mg/kg) and "lower doses (5 mg/kg) + midazolam" doses, might be associated with a reduced need for additional medication for sedation						
3 RCT on oral ketamine (158)	Not serious	Serious	Serious	Serious	Less important	Very low
Outcome: Parental satisfaction: IN ketamine might provide a higher parental satisfaction but oral ketamine did not show a significant difference						
2 RCT on oral ketamine (127)	Not serious	Serious	Not serious	Serious	Less important	Very low
1 cohort on IN ketamine (196)	Not serious	Not serious	Serious	Serious	Less important	Very low
Outcome: Physician satisfaction: NIK might provide a higher physician satisfaction						
1 RCT on oral ketamine (68)	Not serious	Not serious	Not serious	Serious	Less important	Moderate
2 cohort on IN ketamine (867)	Not serious	Serious	Not serious	Not serious	Less important	Very low
Outcome: Short-term AE needed an invasive intervention: NIK probably had not serious AE						
7 RCT on oral ketamine (494)	Not serious	Not serious	Not serious	Serious	Less important	Moderate
3 cohort on IN ketamine (918)	Not serious	Not serious	Not serious	Serious	Less important	Moderate
2 cohort on oral ketamine (72)	Not serious	Not serious	Serious	Serious	Less important	Low
Outcome: Long-term AE[a]: prevalence of long-term AE of NIK might be lower than comparisons						
2 RCT on oral ketamine (139)	Not serious	Not serious	Serious	Serious	Less important	Low

Abbreviations: AE, adverse events; IN, intranasal; MDZ, midazolam; NIK, noninjectable ketamine; RCT, randomized controlled trial.
[a]Adverse events occurred after discharge.

other medications (mainly MDZ) might provide a desirable level of sedation, faster OA, and shorter DA relative to the oral comparators (mainly MDZ). Additionally, the need for AMS might be lower when ketamine was administered alone at higher doses or at lower doses in combination with MDZ. Furthermore, the included studies showed that oral and nasal ketamine probably had no SAE needing an invasive intervention.

Approaches with minimal patient contact are preferable, as they induce less stress. Noninjectable routes such as nitrous oxide gas require some degree of physical restraint. Therefore, the oral route can be considered "contactless sedation" as a subgroup of "needleless sedation". However, additional factors—including adequate sedation depth, AMS, OA, DA, and AE—must also be considered. In our review, oral ketamine

provided either superior sedation depth or showed no significant difference with the comparator groups among children (mostly 2–12 years). Two studies found no significant difference in sedation depth between ketamine and MDZ. This lack of difference—according to MDZ's absence of analgesic properties—may be reasonable: one study assessed sedation during imaging [48], while the other used local anesthesia prior to suturing without reporting pain during injection [46]. Therefore, we can conclude that oral ketamine alone or combined with MDZ might provide a desirable level of sedation for painful procedures (COE: very low). However, the need for AMS can serve as a proxy for noninjectable sedation failure, as it most often involves another painful intervention like IV access. Three studies evaluated AMS, indicating that oral ketamine dosing played a key role in this regard. Fewer AMS might be required when oral ketamine was administered alone at higher doses (10 mg/kg) [42] or at lower doses (5 mg/kg) in combination with MDZ [44] (COE: very low). About the timing properties of oral ketamine, whenever it has been compared with a nonplacebo group, the studies might suggest relatively faster OA (15–35 min) and shorter DA (60–265 min) (COE: low). Regarding AEs, the oral route probably was not associated with any SAE needing an invasive intervention (COE: moderate to low).

Adequate sedation depth with a slower OA with oral ketamine is supported by a study comparing oral ketamine (15 mg/kg) to IM ketamine (5 mg/kg) for premedication in ~5-year-old patients under Bispectral Index monitoring; after approximately 20 min, sedation depth was found to be similar between groups [55].

Regarding the IN route, a 2017 systematic review [36]—mainly in pediatric dental settings—reported successful sedation in 85% of patients, with OA and DA ranging from 3.6 to 11.6 min and 7 to 69 min, respectively. No SAE was observed, and vomiting was the most common AE.

About other combinations with ketamine for pediatric sedation, a meta-analysis [56] on ketamine–dexmedetomidine, compared to MDZ-ketamine, propofol-ketamine, dexmedetomidine, or ketamine, found that the ketamine–dexmedetomidine combination offered better sedation outcomes than dexmedetomidine or ketamine alone by significantly shortening the OA and recovery times while maintaining hemodynamic and respiratory stability and a low incidence of AE.

Although no SAEs requiring invasive intervention were observed in our review, most studies did not employ a standardized definition. Over the past decade, researchers have established standardized frameworks by using evidence like the Pediatric Sedation Research Consortium (PSRC) [57]. Utilizing this structure, the largest multicenter study to date evaluated 12,780 pediatric patients who received ketamine sedation in the ED over a 20-year period [5]. The study reported the incidence of critical and high-risk events as 0.016% (95% CI, 0.0019–0.057) and 0.52% (95% CI, 0.41–0.66), respectively.

For reducing AEs, literature showed that a nil per os (NPO) status was not recommended prior to ED PSA. An observational study of PSA in ED involving 2570 patients, of whom 1177 were under 21 years of age, found that NPO $\geq$8 h was associated with similar or worse outcomes compared to NPO $<$8 h.

4.1 | Future Research

Based on the included RCTs, we are only able to discuss efficacy outcomes for oral ketamine compared to other oral medications. Ketamine has mostly been evaluated in combination with or in comparison to MDZ, and there are no studies in ED on NIK against or in combination with agents such as dexmedetomidine or nitrous oxide. Before conducting RCTs on various routes and drug combinations, dose–response studies for NIK and esketamine are necessary. As demonstrated in our study and the systematic review of IN ketamine [36], meta-analysis remains impossible until standard dosing is established and evaluated in comparable populations. Outcomes must also be reported consistently. In addition to AE and scales for pain and sedation depth, timing outcomes such as DA should be reported uniformly to enable meaningful comparisons. The OA was defined variably across studies, ranging from the time between ketamine administration and the appearance of nystagmus [46], to the achievement of a specified sedation level [44, 47]. Similarly, recovery definitions make the DA comparisons between the studies challenging. Some studies used recovery time interchangeably with discharge criteria and observed patients until various endpoints such as return to baseline consciousness [52], verbal and motor skills [53], or tolerance of oral fluids [45, 46]. Therefore, we need dose–response studies for NIK and esketamine and more RCTs on various routes and drug combinations with consistent outcome definition.

5 | Conclusions

Oral ketamine (5–10 mg/kg), alone or combined with other agents, might provide effective sedation in pediatric ED patients with faster OA and shorter DA relative to other oral comparators. Fewer AMS might be needed when oral ketamine was administered alone at higher doses or at lower doses in combination with MDZ. Studies on NIK likely did not report any SAE requiring invasive intervention. Of note, further research is needed to determine the optimal NIK dose and route for pediatric ED sedation, using a consistent sedation depth scale and timing definition.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1. N. García-Aracil, J. D. Ramos-Pichardo, M. E. Castejón-de la Encina, L. José-Alcaide, R. Juliá-Sanchís, and Á. Sanjuan-Quiles, "Effectiveness of Non-Pharmacological Measures for Reducing Pain and Fear in Children During Venipuncture in the Emergency Department: A Vibrating Cold Devices Versus Distraction," *Emergencias* 30, no. 3 (2018): 182–185.

2. R. Fallah, F. Ferdosian, and A. Shajari, "Non-Parenteral Medications for Procedural Sedation in Children-A Narrative," *Iranian Journal of Child Neurology* 9, no. 3 (2015): 1.

3. N. E. White, W.-J. Wendt, A. Drendel, and P. S. Walsh, "Sedation With Ketamine, Propofol, and Dexmedetomidine in Pediatric Emergency Departments," *American Journal of Emergency Medicine* 93 (2025): 21–25, https://doi.org/10.1016/j.ajem.2025.03.027.

4. M. A. Peltoniemi, N. M. Hagelberg, K. T. Olkkola, and T. I. Saari, "Ketamine: A Review of Clinical Pharmacokinetics and Pharmacodynamics in Anesthesia and Pain Therapy," *Clinical Pharmacokinetics* 55 (2016): 1059–1077.

5. S. M. Green, D. S. Tsze, and M. G. Roback, "Emergency Department Ketamine Sedation: Frequency and Predictors of Critical and High-Risk Adverse Events," *Annals of Emergency Medicine* 86 (2025): 600–605, https://doi.org/10.1016/j.annemergmed.2025.05.003. Epub ahead of print. PMID: 40481829.

6. S. Prakash, A. K. Gupta, J. P. Meena, and R. Seth, "A Review of the Clinical Applications of Ketamine in Pediatric Oncology," *Pediatric Blood & Cancer* 68, no. 1 (2021): e28785.

7. P. Reddy, M. Ramburuth, and R. Rodseth, "Ketamine and Midazolam as Procedural Sedation in Children: A Structured Literature Review and Narrative Synthesis," *Southern African Journal of Anaesthesia and Analgesia* 26, no. 1 (2020): 10–16.

8. D. Dallimore, D. W. Herd, T. Short, and B. J. Anderson, "Dosing Ketamine for Pediatric Procedural Sedation in the Emergency Department," *Pediatric Emergency Care* 24, no. 8 (2008): 529–533, https://doi.org/10.1097/PEC.0b013e318180fdb5.

9. M. C. Howes, "Ketamine for Paediatric Sedation/Analgesia in the Emergency Department," *Emergency Medicine Journal* 21, no. 3 (2004): 275–280, https://doi.org/10.1136/emj.2003.005769.

10. E. Melendez and R. Bachur, "Serious Adverse Events During Procedural Sedation With Ketamine," *Pediatric Emergency Care* 25, no. 5 (2009): 325–328, https://doi.org/10.1097/PEC.0b013e3181a341e0.

11. R. B. Mistry and M. C. Nahata, "Ketamine for Conscious Sedation in Pediatric Emergency Care," *Pharmacotherapy* 25, no. 8 (2005): 1104–1111, https://doi.org/10.1592/phco.2005.25.8.1104.

12. J. P. Higgins, D. G. Altman, P. C. Gøtzsche, et al., "The Cochrane Collaboration's Tool for Assessing Risk of Bias in Randomised Trials," *BMJ (Clinical Research Ed.)* 343 (2011): d5928.

13. G. A. Wells, B. Shea, and D. O'Connell, "The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-Analyses," 2000.

14. G. Guyatt, A. D. Oxman, E. A. Akl, et al., "GRADE Guidelines: 1. Introduction—GRADE Evidence Profiles and Summary of Findings Tables," *Journal of Clinical Epidemiology* 64, no. 4 (2011): 383–394.

15. S. F. Wasfy, R. M. Hassan, and R. M. Hashim, "Effectiveness and Safety of Ketamine and Midazolam Mixture for Procedural Sedation in Children With Mental Disabilities: A Randomized Study of Intranasal Versus Intramuscular Route," *Egyptian Journal of Anaesthesia* 36, no. 1 (2020): 16–23, https://doi.org/10.1080/11101849.2020.1727669.

16. J. J. Brown, J. M. Gray, M. G. Roback, U. Sethuraman, A. Farooqi, and N. Kannikeswaran, "Procedural Sedation in Children With Autism Spectrum Disorders in the Emergency Department," *American Journal of Emergency Medicine* 37, no. 8 (2019): 1404–1408.

17. M. E. Cudny, N. E. Wang, S. L. Bardas, and C. N. Nguyen, "Adverse Events Associated With Procedural Sedation in Pediatric Patients in the Emergency Department," *Hospital Pharmacy* 48, no. 2 (2013): 134–142.

18. Y. Lubin and G. Weiser, "Nighttime Sedations in the Pediatric Emergency Department: A Single-Center Experience," *Pediatric Emergency Care* 39, no. 9 (2023): 698–701.

19. E. A. Lucich, N. S. Adams, P. C. Goote, J. A. Girotto, and R. D. Ford, "Pediatric Procedural Sedation in the Emergency Setting," *Plastic and Reconstructive Surgery. Global Open* 8, no. 4 (2020): e2735.

20. S. E. Mace, A. Ulintz, B. Peterson, A. S. Nowacki, J. Worley, and S. Zamborsky, "Fifteen Years' Experience With Safe and Effective Procedural Sedation in Infants and Children in a General Emergency Department," *Pediatric Emergency Care* 37, no. 9 (2021): e500–e506.

21. T. Morrison, C. Carender, B. Kilbane, and R. W. Liu, "Procedural Sedation With Ketamine Versus Propofol for Closed Reduction of Pediatric Both Bone Forearm Fractures," *Orthopedics* 40, no. 5 (2017): 288–294.

22. C. Stewart, A. Bradley, J. Faulkner, and A. Jatan, "The Use of Ketamine Sedation for the Treatment of Nail Bed Repairs in the Pediatric Emergency Department," *Pediatric Emergency Care* 39, no. 4 (2023): 265–267.

23. S. F. Tel-Dan, D. Shavit, R. Nates, N. Samuel, and I. Shavit, "Emergency Physician-Administered Sedation for Thoracostomy in Children With Pleuropneumonia," *Pediatric Emergency Care* 37, no. 12 (2021): e1209–e1212.

24. J. G. D. Waterman, M. S. Leder, and D. M. Cohen, "Adverse Events in Pediatric Ketamine Sedations With or Without Morphine Pretreatment," *Pediatric Emergency Care* 22, no. 6 (2006): 408–411.

25. K. Wells and V. Calleo, "Safety and Depth of Sedation With Ketamine Alone Versus Ketamine With Midazolam in Pediatric Fracture Reduction: A Retrospective Chart Review," *Pediatric Emergency Care* 40 (2023): 717–721.

26. S. Majidinejad, M. Ebrahimi, R. Azizkhani, et al., "The Effects of Different Doses of Submucosal vs. Intravenous Ketamine for Conscious-Sedation in Children Candidates for Diagnostic-Therapeutic Procedures in Emergency Department," *Frontiers in Emergency Medicine* 5, no. 1 (2021): 315 (In English), https://doi.org/10.22114/ajem.v0i0.315.

27. A. Abdullahi, R. Abdulmalik, M. Rabiu, A. Mohammmed, and O. Taiwo, "Oral Midazolam Plus Ketamine Versus Midazolam for Conscious Sedation in Paediatric Ambulatory Dentistry: Use and Safety in a Limited Resource Clime," *African Journal of Anaesthesia and Intensive Care* 19, no. 2 (2019): 9–15.

28. A. Agarwal, A. A. Ansari, R. Nath, et al., "Comparative Evaluation of Intranasal Midazolam-Ketamine, Dexmedetomidine-Ketamine, Midazolam-Fentanyl, and Dexmedetomidine-Fentanyl Combinations for Procedural Sedation and Analgesia in Pediatric Dental Patients: A Randomized Controlled Trial," *Journal of Dental Anesthesia and Pain Medicine* 23, no. 2 (2023): 69–81, https://doi.org/10.17245/jdapm.2023.23.2.69.

29. N. Arun, A. Choudhary, and M. Kumar, "Comparative Study of Intranasal Dexmedetomidine Versus Intranasal Ketamine as Premedicant in Children," *Cureus* 14, no. 7 (2022): e26572.

30. K. E. J. Brunette, B. J. Anderson, J. Thomas, L. Wiesner, D. W. Herd, and S. Schulein, "Exploring the Pharmacokinetics of Oral Ketamine in Children Undergoing Burns Procedures," *Pediatric Anesthesia* 21, no. 6 (2011): 653–662, https://doi.org/10.1111/j.1460-9592.2011.03548.x.

31. D. Buonsenso, G. Barone, P. Valentini, F. Pierri, R. Riccardi, and A. Chiaretti, "Utility of Intranasal Ketamine and Midazolam to Perform Gastric Aspirates in Children: A Double-Blind, Placebo Controlled, Randomized Study," *BMC Pediatrics* 14 (2014): 67, https://doi.org/10.1186/1471-2431-14-67.

32. B. Grossmann, A. Nilsson, F. Sjöberg, and L. Nilsson, "Rectal Ketamine During Paediatric Burn Wound Dressing Procedures: A Randomised Dose-Finding Study," *Burns* 45, no. 5 (2019): 1081–1088, https://doi.org/10.1016/j.burns.2018.12.012.

33. C. Deasy and F. E. Babl, "Intravenous vs Intramuscular Ketamine for Pediatric Procedural Sedation by Emergency Medicine Specialists: A Review," *Pediatric Anesthesia* 20, no. 9 (2010): 787–796.

34. A. Heath, J. D. Rios, E. Pullenayegum, et al., "The Intranasal Dexmedetomidine Plus Ketamine for Procedural Sedation in Children, Adaptive Randomized Controlled Non-Inferiority Multicenter Trial (Ketodex): A Statistical Analysis Plan," *Trials* 22, no. 1 (2021): 15.

35. V. Pansini, A. Curatola, A. Gatto, I. Lazzareschi, A. Ruggiero, and A. Chiaretti, "Intranasal Drugs for Analgesia and Sedation in Children Admitted to Pediatric Emergency Department: A Narrative Review," *Annals of Translational Medicine* 9, no. 2 (2021): 189.

36. N. Poonai, K. Canton, S. Ali, et al., "Intranasal Ketamine for Procedural Sedation and Analgesia in Children: A Systematic Review," *PLoS One* 12, no. 3 (2017): e0173253.

37. M. Pruc, A. Navolokina, and L. Szarpak, "Intranasal Ketamine for Pediatric Emergency Department Lacerations," *American Journal of Emergency Medicine* 68 (2023): 206.

38. D. S. Tsze, D. W. Steele, J. T. Machan, F. Akhlaghi, and J. G. Linakis, "Intranasal Ketamine for Procedural Sedation in Pediatric Laceration Repair: A Preliminary Report," *Pediatric Emergency Care* 28, no. 8 (2012): 767–770.

39. S. Jafarnejad, I. Mehrabi, M. Rezai, and H. K. Ebrahimi, "Comparison of Intranasal Ketamine and Midazolam in Peripheral IV Access in Children Presenting to the Emergency Department, a Randomized Clinical Trial," *Pakistan Journal of Medical Sciences* 14, no. 3 (2020): 1412–1417.

40. S. Rached-d'Astous, Y. Finkelstein, B. Bailey, et al., "Intranasal Ketamine for Procedural Sedation in Children: An Open-Label Multicenter Clinical Trial," *American Journal of Emergency Medicine* 67 (2023): 10–16.

41. N. Poonai, K. Canton, S. Elsie, G. Joubert, A. Shah, and M. Rieder, "Intranasal Ketamine for Procedural Sedation in Children: A Randomized Controlled Pilot Study," *Annals of Emergency Medicine* 4 (2017): S109.

42. F. A. Qureshi, P. T. Mellis, and M. A. McFADDEN, "Efficacy of Oral Ketamine for Providing Sedation and Analgesia to Children Requiring Laceration Repair," *Pediatric Emergency Care* 11, no. 2 (1995): 93–97.

43. J. Del Pizzo and J. A. Fein, "Oral Ketamine and Midazolam for Procedural Sedation in the Pediatric Emergency Department: A Retrospective Study," *Pediatric Emergency Care* 41, no. 2 (2025): 122–126, https://doi.org/10.1097/pec.0000000000003291.

44. S. Barkan, R. Breitbart, G. Brenner-Zada, et al., "A Double-Blind, Randomised, Placebo-Controlled Trial of Oral Midazolam Plus Oral Ketamine for Sedation of Children During Laceration Repair," *Emergency Medicine Journal* 31, no. 8 (2014): 649–653.

45. F. Bozorgi, I. Gholikhatir, S. J. Mousavi, M. Rahiminejad, and A. Lali, "A Comparison of Oral Midazolam and Ketamine With Oral Midazolam and Promethazine in Paediatric Sedation," *Medical Studies* 37 (2021): 33–41.

46. O. Rubinstein, S. Barkan, R. Breitbart, et al., "Efficacy of Oral Ketamine Compared to Midazolam for Sedation of Children Undergoing Laceration Repair: A Double-Blind, Randomized, Controlled Trial," *Medicine* 95, no. 26 (2016): e3984.

47. H. Soleimanpour, A. Mahmoodpoor, F. Eftekhari Milani, K. Shahsavari Nia, R. Mehdizadeh Esfanjani, and S. Safari, "Effectiveness of Oral Ketamine, Midazolam, and Atropine Cocktail Versus Oral Diphenhydramine for Pediatric Sedation in the Emergency Department," *Iranian Red Crescent Medical Journal* 16, no. 9 (2014): e21366, https://doi.org/10.5812/ircmj.21366.

48. M. Ziaei, M. Keykha, F. Kazemi, and A. Abdolrazaghnejad, "Comparing the Sedative Effect of Oral Midazolam Versus Oral Ketamine on Children Aged 1–7 Years in Need of Radiologic Procedures," *Journal of Medicinal and Chemical Sciences* 5, no. 2 (2022): 177–187 (In English), https://doi.org/10.26655/JMCHEMSCI.2022.2.5.

49. A. M. Guthrie, R. A. Baum, C. Carter, et al., "Use of Intranasal Ketamine in Pediatric Patients in the Emergency Department," *Pediatric Emergency Care* 37, no. 12 (2021): e1001–e1007, https://doi.org/10.1097/pec.0000000000001863.

50. L. A. Mills and H. M. Kuntz, "Adverse Events in Patients Aged 90 Days or Younger Receiving Ketamine in the Emergency Department," *Pediatric Emergency Care* 40, no. 9 (2023): 665–667.

51. M. A. M. Gutiérrez, M. F. Camuñas, J. A. R. Domínguez, et al., "Sedoanalgesia With Ketamine in the Emergency Department: Factors Associated With Unsatisfactory Effectiveness," *Pediatric Emergency Care* 40, no. 9 (2023): 654–659.

52. M. Nemeth, N. Jacobsen, C. Bantel, M. Fieler, R. Sumpelmann, and C. Eich, "Intranasal Analgesia and Sedation in Pediatric Emergency Care-A Prospective Observational Study on the Implementation of an Institutional Protocol in a Tertiary Children's Hospital," *Pediatric Emergency Care* 35, no. 2 (2019): 89–95.

53. P. A. Younge and J. M. Kendall, "Sedation for Children Requiring Wound Repair: A Randomised Controlled Double Blind Comparison of Oral Midazolam and Oral Ketamine," *Emergency Medicine Journal* 18, no. 1 (2001): 30–33.

54. A. P. Hardin and J. M. Hackell, "Age Limit of Pediatrics," *Pediatrics* 140, no. 3 (2017): e20172151, https://doi.org/10.1542/peds.2017-2151.

55. R. Singh and B. Pradhan, "A Comparative Study of Intramuscular Ketamine and a Combination of Intramuscular Dexmedetomidine and Ketamine as Premedication in Paediatric Anesthesia," *Birat Journal of Health Sciences* 8, no. 1 (2023): 1967–1972.

56. H.-p. Li, K.-p. Liu, and L. Yao, "Dexmedetomidine in Combination With Ketamine for Pediatric Procedural Sedation or Premedication: A Meta-Analysis," *American Journal of Emergency Medicine* 50 (2021): 442–448, https://doi.org/10.1016/j.ajem.2021.08.073.

57. J. R. Grunwell, C. Travers, C. E. McCracken, et al., "Procedural Sedation Outside of the Operating Room Using Ketamine in 22,645 Children: A Report From the Pediatric Sedation Research Consortium," *Pediatric Critical Care Medicine* 17, no. 12 (2016): 1109–1116, https://doi.org/10.1097/pcc.0000000000000920.

Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Appendix S1:** acem70163-sup-0001-AppendixS1.docx. **Appendix S2:** acem70163-sup-0002-AppendixS2.docx. **Appendix S3:** acem70163-sup-0003-AppendixS3.docx. **Appendix S4:** acem70163-sup-0004-AppendixS4.docx. **Appendix S5:** acem70163-sup-0005-AppendixS5.docx.