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Intranasal midazolam sedation as an effective sedation route in pediatric patients for radiologic imaging in the emergency ward: A single-blind randomized trial

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Abstract:

OBJECTIVES: Prevention and reduction of pain, anxiety, and fear during medical procedures is one of the most important factors that should be considered in pediatric emergencies. The aim of this study was to compare the efficacy of oral versus intranasal midazolam in sedation during radiologic imaging in the largest province of Iran, Kerman.

MATERIALS AND METHODS: Eighty children were enrolled in this single-blind clinical trial based on convenience sampling and were divided into two groups receiving 0.5 mg/kg midazolam in oral route administration and 0.2 mg/kg midazolam in intranasal route administration. Finally, 75 patients remained for evaluating medication acceptability, sedation level, onset time of sedation, additional sedative dose, adverse effects of sedation, and provider satisfaction.

RESULTS: Children in the intranasal group accepted medication more easily (89.8% vs. 36.9%; $P \leq 0.001$), while these children received a lower sedation dose, but the sedation level in both methods was similar ($P = 0.72$). Our findings showed that children in the intranasal sedation group had a faster onset of sedation compared to the oral group (17.94 ± 8.99 vs. 34.50 ± 11.45 ; $P \leq 0.001$). The frequency of midazolam side effects had no difference between the groups (29.7% vs. 15.8%; $P = 0.15$).

CONCLUSION: Intranasal midazolam with a lower sedation dose induces a faster onset and better acceptance. Intranasal midazolam can be used as an effective sedative method for pediatric patients, especially in emergency wards.

Keywords:

Emergency ward, intranasal, midazolam, radiologic imaging

Introduction

The patient's fear and anxiety may be caused by receiving medical interventions in the medical environment.

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The necessity of diagnostic/therapeutic procedures is difficult to be accepted by children, and this leads to fear and anxiety, thus making the procedures more difficult and problematic.^[1] Prevention and reduction of pain, anxiety, and fear

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Box-ED

What is already known on the study topic?

Prevention and reduction of pain, anxiety, and fear during medical procedures is one of the most important factors that should be considered in pediatric and the emergencies

The necessity of diagnostic/therapeutic procedures is difficult to be accepted by children, and this leads to fear and anxiety, thus making the procedures more difficult and problematic

What is the conflict on the issue? Has it importance for readers?

The use of midazolam in intranasal route may decrease the sedation onset time or some of the side effects, which was due to increased administration dose of midazolam by oral route among pediatric patients. The efficacy and safety of using a standard device for administration of intranasal midazolam is unclear.

How is this study structured?

This was a single-center, single-blind randomized clinical trial that includes data from approximately 74 pediatric patients.

What does this study tell us?

There was no difference in level of sedation, provider satisfaction, and dose administration in terms of sedation routes.

However, patients with an intranasal route easily accepted the medication, and the sedation onset time was faster for them.

during medical procedures is one of the most important factors that should be considered in pediatric medicine.^[2] These problems are common in children, and in order to control them, some methods such as talking to the child, making friendship, building rapport and trust as well as using sedative premedications can be used.^[3] If these preliminary methods are not taken into consideration, it can cause the procedure more difficult and time-consuming and make the child feared and anxious.^[3] On the other hand, using sedative methods result in a more comfortable situation and the resultant would be an acceptance on the part of children and parents concerning the diagnostic procedures in emergency wards.^[4]

It is necessary to consider some points in the selection of sedative drugs or premedications such as the rapid onset and short duration of actions as well as the minimum side effects.^[5] Benzodiazepines are one of the most important and common groups of medications used as sedative agents in medical interventions.^[6] Midazolam as a water-soluble benzodiazepine with the rapid onset of action and short half-life^[7] is used for procedural sedation analgesia/anesthesia which relieves anxiety and does not provide retrograde amnesia.^[3,4] Hence, it is superior to long-acting benzodiazepines such as diazepam

and lorazepam, and its sedative effects such as other benzodiazepines can be antagonized by flumazenil.^[8]

Midazolam can be administrated by the intravenous, intramuscular, intradermal, intranasal, oral, and rectal routes. Rectal and injection administrations are unpleasant for pediatric patients. In the oral route, time to reach the maximum effect (1 h), its longer duration of action (4 h), and variable depth of sedation make it unfavorable.^[9] Among all methods, intranasal administration is more comfortable^[10] and needs a short time to reach its maximum effect (10 min). In addition, it has a short duration of action (60 min).^[9] The total administered dose depends on the patient's medical conditions, patient's response, and body weight.^[11] In general, intranasal dose ranges from 0.2 mg/kg/dose (in 1-to-5-month-old children) to 10 mg/kg/dose (in teenagers or adults).^[12] Research findings show that 0.5 mg/kg/dose of midazolam may cause side effects including nausea, vomiting, rash,^[13] dizziness, or drowsiness and it should be used only under medical supervision.^[11]

Several studies have confirmed the effectiveness of midazolam and its intranasal administration.^[14] Manani *et al.* showed that intranasal midazolam can relieve anxiety over 3 min of administration.^[15] The results of a case series by Plum and Harris on two pediatric patients with nasal fractures showed that intranasal midazolam can offer effective anxiolysis for pediatric patients during reduction of nasal fractures.^[16] Likewise, Rostaminejad *et al.* in Iran recommended administration of intranasal midazolam before anesthesia for children aged 2–6 years.^[17]

According to the previous studies and upon pediatric cognitive and behavioral characteristics, achieving a situation which is appropriate for diagnostic and therapeutic procedures, as well as adopting an effective and low invasive sedative method, is ultimately important. In this regard, it seems that intranasal midazolam is a suitable method, but in many situations intranasal midazolam has generally been administrated in drop form by syringe which is difficult to keep in the nose. The present study was one of the first studies in Iran to compare the efficacy of oral versus intranasal midazolam which was administrated with a standard device for sedation during radiologic imaging in the trauma referral center of largest province of Iran, Kerman.

Materials and Methods

Study design

This study is a single-blind randomized clinical trial (the protocol of the study was registered in Iranian Registry of Clinical Trials, (code:IRCT20171009036661N3).

Subjects and setting

This study was undertaken among pediatric patients who were referred to the emergency ward and were candidate for radiologic imaging in Shahid Bahonar hospital in Kerman in 2018 (from August to October). This hospital is known as a trauma referral center in Southeast of Iran. The target population was pediatrics who were scared and anxious due to fear of medical environment, anxiety, and avoidance in parents and not being placed in suitable position for radiologic imaging. The inclusion criteria were: the American Society of Anesthesiologists I and II classification, who aged 1–14 years. Patients with a history of seizures or any neurological diseases were excluded. Finally, according to pediatric situation, the physician (first author) determined the sedation before radiologic imaging.

Patients' allocation

Of 100 patients, 20 children were not enrolled due to parents' disagreement before the randomized allocation. Finally, eighty patients were selected using convenience sampling method and divided into two subgroups (oral or intranasal midazolam) using random sequence [Figure 1].

Intervention

In the oral subgroup, children received 0.5 mg/kg/dose midazolam orally. Due to the absence of oral formulation of midazolam in Iran, the injectable form is used instead. After 30 min, the sedation level was evaluated by the physician. The sufficient sedation was mild-moderate sedation, and if these levels did not reach, the dose of midazolam raised 0.1 mg/kg any 30 min. The maximum dose of midazolam with this route was 0.7 mg/kg. In the intranasal subgroup, 0.2 mg/kg/dose of injectable form of midazolam was aerosolized with an atomization device (manufactured by Teleflex company). Half the dose was delivered into each nostril. The sedation levels were devalued by the physician any 15 min. If the sufficient sedation level did not reach, the dose of midazolam to 0.1 mg/kg any 15 min. The maximum dose of midazolam used for intranasal route was 0.5 mg/kg. If the expected sedation level after maximum midazolam dose did not reach, the patient omitted from study. The patient's level of sedation was determined based on the Richmond Agitation-Sedation Scale (RASS), as shown in Table 1. RASS is a reliable and valid tool that is intuitive, easy to use, and includes both agitation and sedation. Administration and evaluation of sedation level was done by different researchers.

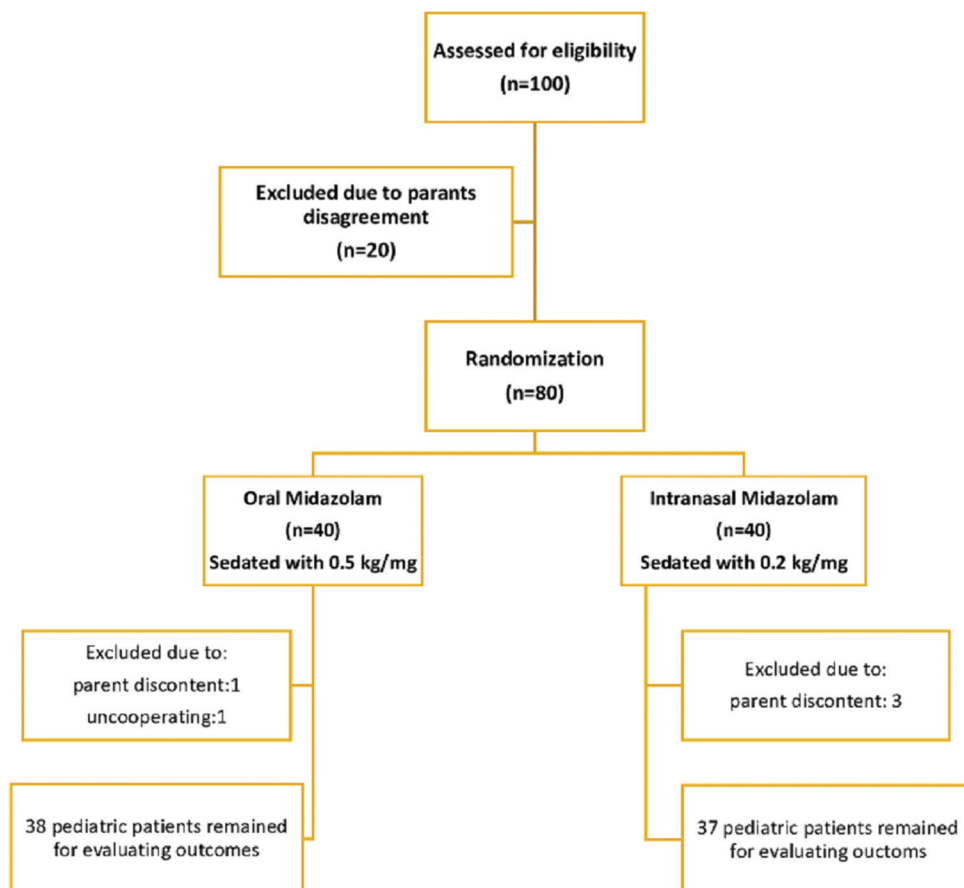


Figure 1: Flow diagram of progress through the phases of assessment of intranasal midazolam for sedation among pediatric patients

As the sufficient sedation reached, children were transferred to the radiology ward. The staff of radiology who measured the duration of radiologic imaging were also masked from patients' allocation. Before and after midazolam administration, vital signs (systolic blood pressure, pulse rate, respiratory rate, and temperature) were recorded.

Outcomes and data collection

Level of sedation, provider satisfaction (Likert scale), patient's acceptance, onset of sedation, duration of radiologic imaging (the time between patients' entrance and exist to radiologic room), total dose of midazolam, and any adverse effects due to sedation such as delayed awaking, hypotension, respiratory depression, restlessness, nausea or vomiting, tachycardia, hypoxia, bradycardia, delusion, and hiccups were compared among participants as the outcomes.

Acceptability

Acceptance of medication administration was recorded as follows: (1) readily accepted, (2) accepted with grimacing, (3) accepted with complaint, and (4) rejected completely (rejected the entire dose). If the participants rejected the entire dose or accepted with complaint, it was recorded as "difficult" acceptance and the others as "easy" acceptance.

Provider satisfaction

Provider satisfaction (radiology ward staff) was recorded on a four-point Likert scale as weak, medium, good, and excellent.

Data analysis

Data were described using mean (standard deviation) and frequency. The normality of quantitative data was checked through Kolmogorov–Smirnov test. For comparison of demographic and clinical characteristics of pediatric patients and also the outcomes of the study, we used Mann–Whitney U-test, Chi-square test, and Fisher's exact test. We used SPSS® software (version 23, IBM Company, Los Angeles, CA) for data analysis. The significance level was considered as $P \leq 0.05$ for two-sided hypotheses.

Results

Characteristics of participants

Eighty children were enrolled, and 75 remained for evaluating the outcomes [Figure 1]. The age, sex, and weight distribution were similar between the two groups ($P = 0.18, 0.28,$ and $0.35,$ respectively). The main reason for referring ($P = 0.73$) and the type of radiologic imaging were also the same ($P = 1$) [Table 2].

Main outcomes

Findings revealed that the easy acceptance level in

the intranasal group was high ($n = 33, 89.2\%$), but in the oral group, it was low ($n = 14, 36.9\%$) ($P \leq 0.001$). Comparing to the oral group, patients in the intranasal group had faster sedation onset ($P \leq 0.001$) [Figure 2]. Between the oral and intranasal groups, the level of sedation ($P = 0.72$), provider satisfaction ($P = 0.79$), duration of procedure ($P = 0.07$), and the number of dose administration ($P = 0.30$) were similar [Table 3].

Restlessness ($n = 7, 9.3\%$), delayed awaking ($n = 4, 5.3\%$), nausea/vomiting and hiccup ($n = 2, 2.7\%$), and respiratory depression and elusion ($n = 1, 1.3\%$) were reported as adverse effects of sedation with midazolam which were reported equally by the two groups ($P = 0.15$). Furthermore, results showed that adverse effects were related to the total dose in the oral group ($P = 0.03$). Conversely, in the intranasal group, there was no relationship between the total dose and adverse effects ($P = 0.63$) [Table 4].

Table 1: Richmond Agitation-Sedation Scale

Score	Term	Description
4	Combative	Overtly combative or violent; immediate danger to staff
3	Very agitated	Pulls on or removes tube (s) or catheter (s) or has aggressive behavior toward staff
2	Agitated	Frequent non-purposeful movement or patient-ventilator dyssynchrony
1	Restless	Anxious or apprehensive but movements not aggressive or vigorous
0	Alert and calm	
-1	Drowsy	Not fully alert, but has sustained (more than 10 s) awakening, with eye contact, to voice
-2	Light sedation	Briefly (<10 s) awakens with eye contact to voice
-3	Moderate sedation	Any movement (but no eye contact) to voice
-4	Deep sedation	No response to voice, but any movement to physical stimulation
-5	Unarousable	No response to voice or physical stimulation

Table 2: Characteristics of pediatric patients referred to the emergency ward for radiologic imaging in the oral and intranasal groups

Variables	Oral group (n=38), n (%)	Intranasal group (n=37), n (%)	P
Age (months)	37.10±18.36	37.72±17.22	0.18 ^a
Weight (kg)	12.64±2.99	13.18±3.23	0.35 ^a
Sex			
Male	20 (52.6)	24 (64.8)	0.28 ^b
Female	18 (47.4)	13 (35.2)	
Reasons for referring			
Trauma	18 (47.3)	14 (37.8)	0.73 ^c
Surgical	1 (2.7)	1 (2.8)	
Others	19 (50)	22 (59.4)	
Radiologic imaging			
CT scan	18 (47.3)	17 (45.9)	1 ^c
Ultra sound	20 (52.7)	19 (51.3)	
X-ray	0	1 (2.8)	

^aMann-Whitney U-test, ^bChi-square test, ^cFisher's exact test

Discussion

The results of this study show that pediatric patients easily accepted the intranasal sedation method, although the level of sedation was similar between different sedation methods. Although in sedation with intranasal midazolam, patients received a lower total sedation dose, they experienced a faster sedation onset. The additional dose of midazolam, provider satisfaction, and time of radiologic imaging was similar between patients with different sedation methods. The adverse consequences after radiologic imaging were not different among patients.

While our findings support this matter that intranasal sedation with mucosal atomizer is easier to use and has

high acceptability,^[18] in some studies, children preferred to take the liquid form of midazolam, especially syrup in contrast to intranasal form.^[19,20] Fewer patients sedated with oral midazolam accepted this sedation method more easily because children usually resist taking medications, especially liquid or tablet forms due to bitter taste.^[21] The oral liquid forms have different tastes due to added flavors and sweeteners which make them pleasant to be taken by children, and this may be the reason for different acceptance. Although midazolam is a safe and suitable to use oral, buccal, and nasal routes and provides a wide area for clinical applications,^[22] the oral liquid form of midazolam is not available in pharmaceutical market and the injection formulation is used for oral administration which has bitter and irritating taste.

The time of sedation onset is an important factor for choosing the sedation method, and this issue is more important and noticeable in pediatric patients. The pain-related fear during medical procedures makes children more and more anxious. Anxiety from the radiology environment, separation from parents, and crying lead to the lack of cooperation, and these factors may prolong the length of medical procedures.^[23,24] Therefore, using a sedation method which has a faster onset with adequate procedural sedation decreases the anxiety of children and consequently facilitates the medical procedures. Based on the related studies, intranasal method compared to other sedation methods is more effective for reducing anxiety and stress and

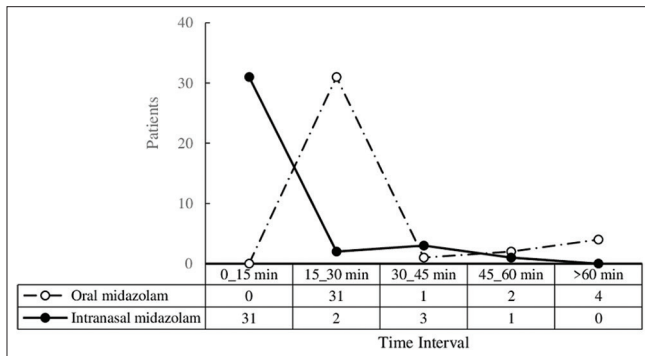


Figure 2: Comparison of sedation onset between the oral and intranasal groups

Table 3: Comparison of clinical characteristics and the efficacy of sedation method between the oral and intranasal groups

Variables	Oral group (n=38), n (%)	Intranasal group (n=37), n (%)	P
Acceptance			
Easy	14 (36.9)	33 (89.8)	0.001 ^a
Difficult	24 (63.1)	4 (10.2)	
Sedation level			
Mild	23 (60.5)	20 (54)	0.72 ^b
Moderate	15 (39.5)	16 (43.2)	
Deep	0	1 (2.8)	
Provider satisfaction			
Weak	4 (10.5)	3 (8.1)	0.79 ^b
Medium	5 (13.1)	3 (8.1)	
Good	8 (21.1)	11 (29.7)	
Excellent	21 (55.2)	20 (54.1)	
Dose administration			
1 st	31 (81.6)	33 (89.2)	0.30 ^b
2 nd	7 (18.4)	3 (8.1)	
3 rd	0	1 (2.7)	
Additional dose (mg/kg)	0.10	0.17±0.09	0.05 ^c
Duration of procedure (min)	4.84±2.83	4.10±3.01	0.07 ^c
Interval between receiving dose and starting the procedure (min)	34.50±11.45	17.94±8.99	0.001 ^c
Adverse effects			
Negative	32 (84.2)	26 (70.3)	0.15 ^a
Positive	6 (15.8)	11 (29.7)	

^aChi-square test, ^bFisher's exact test, ^cMann-Whitney U-test

Table 4: Comparison of the total doses based on adverse effects in the oral and intranasal groups

Groups	Adverse effect	Total dose (mg/kg), mean±SD	P
Oral	Negative	0.57±0.20	0.03 ^a
	Positive	0.80±0.32	
Intranasal	Negative	0.22±0.08	0.63 ^a
	Positive	0.27±0.21	

^aMann-Whitney U-test. SD=Standard deviation

provides sufficient sedation.^[25,26] Although intranasal method is widely used, it might be uncomfortable for children and buccal is a safe and acceptable method of midazolam transmucosal sedation, especially in pediatric dentistry^[27] and young patients.^[28] Therefore, the interval between the administration of sedative medication and beginning radiologic procedures can be reduced significantly.

Rapid mucosal absorption is the main reason for the faster onset of sedation in intranasal method in comparison to other midazolam sedation methods. In fact, in intranasal administration, midazolam passes directly from the nasal mucosa to the central nervous system (CNS) in contrast to oral and some intravascular administrations. The intranasal route provides efficient sedation as the drug directly transports into the CNS. Drug molecule characteristics which affect crossing the blood-brain barrier are pH, ionization state, lipophilicity, and molecular weight.^[29,30] Based on nasal mucosal absorption of midazolam, its intranasal administration largely bypasses hepatic first-pass metabolism and permits rapid and predictable clinical effects compared with oral and some intramuscular administrations. Therefore, due to the faster onset of intranasal midazolam sedation method, a lower total sedation dose is needed subsequently which was supported by our findings.

Vomiting, agitation, hypoxia, and apnea are common adverse effects of sedation with midazolam that were reported in some studies with different rates.^[31,32] Our results showed that lower than one-quarter of the patients suffered from adverse effects, which was similar between the two groups. This finding is consistent with the results of the study conducted by Klein *et al.*^[26] Research findings show that a higher total dose of midazolam among patients sedated orally can trigger more adverse effects.^[33]

Limitation

Several limitations of this study should be noted. First, we had to use injection formulation for oral sedation method for pediatric patients as oral liquid formulation of midazolam is not available in pharmaceutical market of Iran. Another limitation was the assessment of subjective outcomes such as level of sedation and provider satisfaction which led to potential bias.

Furthermore, nonblinded participants may interrupt results, and it cannot be claimed that our findings are generalizable to all patients.

Conclusion

Faster sedation onset, adequate sedation with a lower dose, and high acceptance rate were the advantages of administering intranasal midazolam for sedation of pediatric patients who were scared and anxious before radiologic imaging. This indicates that intranasal midazolam can be used as an effective sedation method for pediatric patients, especially for radiologic imaging in emergency ward.

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Author contribution

All authors contributed toward data analysis, drafting, and revising the paper and agree to be accountable for all aspects of the work (conception – Masoud Mayel and Ehsan Mohajeri, design – Masoud Mayel, Mehdi Ahmadinejad, and Mehdi Sadeghi Khabaz, and analysis and interpretation of data – Maliheh Sadat Bazrafshani).

Consent to Participate

All patients consented to participate to the study. Signed consent forms available from the authors.

Conflicts of interest

None Declared.

Ethical Approval

This study was approved by the Ethics Committee of Kerman University of Medical Sciences (Code number: 96000190).

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