Section: Pediatrics

Original Research Article

A COMPARISON OF INTRAVENOUS MIDAZOLAM AND INTRANASAL MIDAZOLAM FOR SEDATION IN RADIOLOGICAL PROCEDURES

Ashwini Kumar[1], Rajiv kumar Jha[2], Md Shahab Alam[1]

[1]Assistant Professor, Department of Pediatrics, Madhubani Medical College, Madhubani, Bihar, India.
[2]Associate Professor, Department of Pediatrics, Madhubani Medical College, Madhubani, Bihar, India.

Received : *25/12/2023*
Received in revised form : *10/03/2024*
Accepted : *27/03/2024*

Keywords:
(IN) midazolam, sedation, respiratory difficulty, short painless procedures, computed tomography

CorrespondingAuthor:
Dr.AshwiniKumar,
Email: ashwini.ucms@gmail.com

DOI: 10.47009/jamp.2024.6.2.115

Source of Support: Nil,
Conflict of Interest: None declared

Int J Acad Med Pharm
2024; 6 (2); 532-537

Abstract

Background: This study aimed to compare the effectiveness and safety of intravenous (IV) midazolam versus intranasal (IN) midazolam for sedation in pediatric patients undergoing radiological procedures. **Materials and Methods:** A randomized prospective clinical trial was conducted in the Department of Pediatrics and Radiology at Madhubani Medical College, Madhubani. Children aged 6 months to 8 years requiring sedation for computed tomography (CT) scans were included. A sample size of 100 patients was determined, with 50 patients allocated to each group (IV midazolam and IN midazolam). Randomization was achieved using envelope-based equal randomization. Parents provided informed consent prior to enrolment. Sedation was administered according to group allocation, and the radiological procedures were completed under sedation. The primary outcomes assessed were sedation efficacy and safety, including sedation onset time, sedation depth, procedure completion rate, adverse events, and recovery time. **Result:** Sedation was achieved faster in the intravenous group (mean time 27 minutes) than the intranasal group (mean time 32 minutes); there was no age and sex predilection for onset and duration of sedation. The overall success rate to complete the procedure was almost similar in both groups (88% in the IV midazolam group against 82% in the IN midazolam group). The intranasal group had faster recovery from sedation than the intravenous group (69.5 minutes in the intranasal group compared to 87.5 minutes in the intravenous group). Motion artifact on completion of the procedure was seen more in the intranasal group (2.7% in the IV group against 12% seen in the intranasal group).The total side effects observed, including the serious form such as desaturation and respiratory difficulty, were found more in the intravenous group than the intranasal group. **Conclusion:** Intranasal group has faster recovery from sedation than the intravenous group.(69.5 minute in intranasal group compared to 87.5 minute in intravenous group). Motion artefact on completion of procedure was seen more in intranasal group.(2.7% in IV group against 12% seen in intranasal group). Total side effects observed including the serious form (desaturation and respiratory difficulty) was found more in intravenous group than the intranasal group. Intranasal midazolam can be a simple and easily administered sedative for short painless procedures like CT scan, benefit it has fewer side effects (despite higher doses) and faster recovery.

INTRODUCTION

Sedation plays a crucial role in ensuring the successful completion of radiological procedures, particularly in pediatric patients who may experience anxiety and discomfort during imaging examinations. Among the various sedative agents used, midazolam, a benzodiazepine with sedative, anxiolytic, and amnestic properties, has gained widespread acceptance due to its efficacy and safety profile in pediatric settings. While intravenous (IV) administration has traditionally been the route of choice for midazolam delivery, intranasal (IN) administration has emerged as a promising alternative, offering advantages such as ease of administration and avoidance of needle-related anxiety.[1]

ISSN (O): 2687-5365; ISSN (P): 2753-6556

Numerous studies have investigated the efficacy and safety of intravenous midazolam in pediatric sedation for radiological procedures. However, limited data are available directly comparing intravenous and intranasal routes of midazolam administration in this population. Understanding the comparative effectiveness and safety profiles of these two administration routes is essential for optimizing sedation protocols and improving patient care.[2]

The current study aims to address this gap in the literature by conducting a randomized prospective clinical trial comparing intravenous midazolam with intranasal midazolam for sedation in pediatric patients undergoing radiological procedures, specifically computed tomography (CT) scans.[3] By evaluating parameters such as sedation onset time, sedation depth, procedure completion rate, adverse events, and recovery time, this study seeks to provide valuable insights into the optimal choice of midazolam administration route for pediatric sedation in radiological settings.

MATERIALS AND METHODS

A randomized prospective clinical trial was conducted in the Department of Pediatrics and Radiology at Madhubani Medical College, Madhubani. Children aged 6 months to 8 years requiring sedation for computed tomography (CT) scans were included. A sample size of 100 patients was determined, with 50 patients allocated to each group (IV midazolam and IN midazolam). Randomization was achieved using envelope-based equal randomization. Parents provided informed consent prior to enrollment. Sedation was administered according to group allocation, and the radiological procedures were completed under sedation. The period of the study was January 2023 to December 2023. The primary outcomes assessed were sedation efficacy and safety, including sedation onset time, sedation depth, procedure completion rate, adverse events, and recovery time.

Inclusion Criteria

Children undergoing CT who need sedation aged between 6 month and 8 years. Head injury patients with GCS 13 and above who had CT Scan between this age group.

Exclusion Criteria

Patients with Rhino Pharyngitis. Patients with nasal pathology. Patients with history of allergy to the study drug. Patients on prior sedative medication. Patients with cardio-respiratory disorders. Patients with hepatic and renal disease. Head injury child with GCS 12 or less.

Intranasal Group: With the children sitting on the parents lap or trolley in the waiting area of radiology department, first dose of drug was administered through the nasal route with dose of 0.4mg/kg. The preparation of intranasal midazolam used was INSED atomizer{38} (midazolam 5mg/5 mL, each metered dose: 0.5 mg per spray, Samarth Pharma Private Limited, Mumbai, India). Total dose was divided into two aliquots and given in both the nostril using metered dose and assessed at 15 minutes through Ramsay sedation score for adequate sedation. Second and third dose of intranasal midazolam was considered in children not adequately sedated i.e. not achieved score of 4 through Ramsay sedation score. Second and third dose was 0.2-0.4mg/kg each depending on sedation score after the previous dose. Score of 4 was considered adequately sedated. Intranasal midazolam is marketed in India as metered dose inhaler.

Technique of administration: children were positioned such that the head was in the direction of reading book. Intranasal spray nozzle was inserted and spray was directed back and upward towards the eye and ear of that side to prevent the medicine from draining back to throat and irritating the child. Also child was asked not to sniff back and blow the nose after administering the drug.

Intravenous Group: Children with intravenous catheter in situ were administered 0.2mg/kg of IV midazolam and were assessed for adequate sedation (Ramsay Score OF 4 or more). Children not adequately sedated were repeated with same dose 0.2mg/kg up to total of three doses. Total dose for the completion of procedure was up to 0.6mg/kg.

In either group if after each three specified doses, required sedation was not achieved patient were given alternative drug/ anaesthetic agent to complete the procedure and the result was considered as failure.

The Ramsay Sedation Scale (RSS).[4]

The Ramsay Sedation Scale was the first scale to be defined for sedation and was designed as a test of reusability. The RSS scores sedation at six different levels, according to how rousable the patient is. It is an intuitively obvious scale and therefore lends itself to universal use, not only in the ICU, but wherever sedative drugs or narcotics are given.

Ramsay Sedation Scale,[4]

1 Patient is anxious and agitated or restless, or both
2 Patient is co-operative, oriented, and tranquil
3 Patient responds to commands only
4 Patient exhibits brisk response to light glabellar tap or loud auditory stimulus
5 Patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus
6 Patient exhibits no response

Patient will progress through sedation score 1-6 and the highest level reached will be recorded.

Statistical Methods: Data was entered in Microsoft Excel 2010.Statistical analysis was conducted using SPSS for windows software(version 26; SPSS). Categorical variables were presented as percentages, and continuous variables were presented as mean ± SD. Differences in proportions were analysed using chi square or Fischer's exact test. Student' t test or Wilcoxon ranksum test were used to evaluate

ISSN (O): 2687-5365; ISSN (P): 2753-6556

differences between continuous variables in the two groups for parametric and non-parametric data respectively. A p value of < 0.05 was considered as significant.

RESULTS

Table 1: Baseline characteristics for Comparison between IV midazolam and In Midazolam as Sedation in Paediatric Imaging (CT scan).

Patients characteristics	Intravenous midazolam groupN=50,mean ± SD	Intranasal midazolamgroupN=50,mean ± SD	P value
1. Age in months, mean (±SD)	34±21.8	39.38±22.5	0.29
2. Sex, n (%) Male Female	 34(68) 16(32)	 32 (64) 18(36)	0.67
3.Weight in kilograms	12.99 (±4.43)	14.23(±4.92)	0.19
4. Type of examination, n (%) a.NCCT Head b.CECTHead c.CECTThorax d.CECT Abdomen	 22(44) 22(44) 3(6) 3(6)	 22(44) 21(42) 4(8) 3(6)	 0.98
5. Diagnosis, n (%) a.Screening for intracranial bleed b.Seizure disorder c.Respiratory disorder d.Meningitis e.Acute abdomen f.Liver abscess g.Sub acute intestinal obstruction h.Stroke	 19(38) 24(48) 3(6) 1(2) 1(2) 0(0) 2(4) 0(0)	 20(40) 19(38) 5(10) 2(4) 2(4) 1(2) 0(0) 1(2)	 0.29
6.Midazolamdose in mg/kg	0.49(±0.10)	0.99(±0.21)	<0.01
7. GCS score, n (%) 13 14 15	 3(6) 9(18) 37(74)	 0(0) 7(14) 43(86)	 0.21
8. Type of enrolment, n (%) IPD OPD	 33(48%) 17(54%)	 35(52%) 15(46%)	 0.67
9. Type of procedure, n(%) Emergency Routine	 25(50) 25(50)	 27(54) 23(46)	 0.69

Table 2:Association between route of administration and outcome

Group	Success	Failure	P value
IV	44 (88%)	6	0.4
IN	41 (82%)	9	

88% of the patients receiving intravenous midazolam were able to complete the procedure while 82%completed the procedure in intranasal group. The results suggested that IN midazolam is as good as IV group (p=0.4).

Table 3: Correlation between route of administration and sedation score achieved>4(ability to sedate the child)

Group	Sedation score ≥ 4	Sedation score < 4	P value
IV	45	5	
IN	42	8	0.79

84% percent of the total patient among intranasal group were able to achieve the desired sedation score of 4 or more in comparison to intravenous group where 86 % achieved the desired score. The difference was statistically insignificant.(p=0.78).

Table 4: Association between routes of administration and mean sedation score

Group	Mean sedation score	P value
IV	4.2	0.01
IN	3.9	

Mean Ramsay sedation score achieved with two or three doses was maximum in intravenous group (4.2) compared to (3.9) in intranasal group and the result was statistically significant. (p=0.01).

ISSN (O): 2687-5365; ISSN (P): 2753-6556

Table 5: Association between route of administration and duration to achieve maximum sedation score

Group	Mean duration(min.)	P value
IV	27	<0.01
IN	32	

The mean duration to achieve the Ramsay sedation score of 4 or more was 32 min in intranasal group compared to 27 min in intravenous group which was significant statistically.(p value =<0.01).

Table 6: Association between route of administration and total dose

Group	Mean total dose(mg/kg)	P value
IV	0.49	<0.01
IN	0.99	

Mean total dose required for completion of procedure in intravenous group to achieve primary outcome was 0.49 mg/kg (81.6% of the maximum dose of 0.6mg/kg) while in intranasal group it was 0.99mg/kg (that is 82.5% of the maximum recommended 1.2mg/kg.).

Table 7: Association between drug route and number Of doses required for achieving outcome

No. Of doses	IV	IN	P value
1 dose	0	0	0.42
2 dose	28	24	
3 dose	22	26	

Among the two groups association with number of dosesrequiredto achieve the outcome , it was found that in IVM group 28 patients(56 %) completed the procedureusing two doses, while22(44%)patients required 3rd doses for completion, similarly in INM group 24 (48%)patients completed the procedureusing two doses and 26(52%)required third dose for completion. None of the patient in both group was able to achieve the outcome with single dose. This association was statistically insignificant. p=0.42.

Table 8: Association between drug route and side effects

Group	Total no. Of side effects	P value
IV	21	0.04
IN	10	

Between the two groups side effects observed was maximum in intravenous group's total of 21 no. against 10 in intranasal group (p= 0.04).

Table 9: Association between route of administration and time to regain orientation as per Ramsay scale.

Group	Mean time(min.)	P value
IV	87.5	<0.01
IN	69.5	

Total duration to regain consciousness /to get oriented as per Ramsay score was 87.5 minute in intravenous group and 69.5 min in intranasal group. (P value <0.01).

Table 10:Association between route of administration and artefact

Group	No artefact	artefact	P value
IV	43	1	0.06
IN	36	5	

Artefact seen in intravenous group was 2.27% against 12% seen in intranasal group and was statistically insignificant. (P value .06)

DISCUSSION

There is continuous search for an ideal sedative agent for procedural sedation in children. Intravenous midazolam has been in use for procedural sedation for quite a long time and is established mode of delivery for sedation.Intranasal form of midazolam has been introduced recently in India and is used in various procedural sedation in the emergency department.

We used Ramsay sedation scale for quantitating the depth of sedation. The Ramsay Sedation Scale, scores sedation at six different levels (1- anxious /restless or both, 4-brisk response to light glabellar tap or loud auditory stimulus, 6-no response). Adequate sedation was defined as Ramsay score of 4 or more. In our study achieving desired sedation with INM was in 84%compared to 90% in IV group. The difference was not statistically significant (p=0.78). We used high doses of intranasal midazolam for procedural sedation in our study citing other study which used less doses leading to unsuccessful results using INM. Fallah et al,[5] conducted similar study utilizing Ramsay sedation scale score comparing the efficacy of oral chloral

ISSN (O): 2687-5365; ISSN (P): 2753-6556

hydrate and INM in children for sedation during elective brain CT scan. Desired Ramsay score(>4) achieved was 40% in INM group and 93% in chloralhydrate group, p=0.001.The lower efficacy of INM group compared to chloral hydrate group in sedation in this study was probably related to low dose (0.2mg/kg) of INM used. Khatavkar etal,[2]conducted similar study where desired sedation score(sedation scale adapted from wilton and colleagues,[6] achieved in group A (INM 0.2mg/kg) was 80%and in group B(IVM +IVK) was94%. The difference was statistically significant, p<0.005.The comparatively lower efficacy of INM in this study compared to the other group (IVKM) can be explained by the fact that they used lower doses in INM group(0.2mg/kg)[7] and presence of two intravenous drugs in the other group (IVKM).

We also evaluated the maximum sedation score achieved in the two groups. The maximum sedation score achieved was higher in intravenous group compared to intranasal group (4.2 ± 0.7 vs. 3.9 ± 0.6, p<0.05).The maximum sedation achieved by any sedative agent has its own merits and demerits. Greater depth of sedation allows the procedure to be done easily. But at the same time, it may also be associated with problems of respiratory depression and delayed recovery. Delayed recovery also increases the duration of hospitalization. Our study shows that although INM administration led to lower depth of sedation compared to IVM but at the same time as far as ability to complete the procedure was concerned both were equivalent and the recovery was faster in INM group. This results were comparable to Acworth et al,[8][2001] where mean sedation score in IVKM group was 2.5 and 3.5 in INM group on sedation score1-5(1=unconscious,5= very agitated) p <0.01.

Time to achieve maximum sedation score was longer in intranasal midazolam group compared to IV midazolam group.Children in INM group were able to achieve maximum sedation score at mean duration of 32.0 ± 8.9 minutes compared to intravenous group where duration was 27.0 ± 6.3 minutes, p=0.0001. This can be explained by the fact that the bioavailability of IV medication is always better than any other route (IN in our case). These results were comparable to Filho et al,[9]who in their study found that time to achieve sedation via intranasal route for those who required 2 or more doses was 28.4 minutes, averaged 15.2 minutes(SD 9.4 minutes, median 12.0 minutes, range 5.0-).In one another study by Roelofse etal.[10] Intranasal midazolam group achieves maximum sedation at 20 minute. The wide variability seen in various studies regarding the onset of adequate sedation could be explained by the variability of doses, interval between doses, different sedation scores used and the heterogeneity in patient population (outpatient or inpatient or both).

We also evaluated the presence of artefacts at the end of the CT Scan after sedation in each group. Artefacts on completion of procedure were observed in 2.3% in IV group compared to 12% in IN group. The difference was not statistically significant but approached significance closely, p=0.05. This could be a matter of concern if the final outcome of the radiological procedure is not as per desire. No study comparing INM with other medications has evaluated artefacts in radiological procedure. Filho et al,[9] evaluated the safety and efficacy of INM and showed that 93.3%of scans using IN midazolam showed no motion artefact. More well powered studies are needed before concluding that INM is associated with increased frequency of artefacts.

On evaluation of association with number of dosesrequiredto achieve the outcome it was found that in IVM group 56 % (28) patients completed the procedureusing two doses, while44% (22) patients required 3rd doses for completion, but in INM group48% (24)patients completed the procedureusing two doses and 52%(26)required third dose for completion. None of the patient in both group was able to achieve the outcome with single dose. This association was statistically insignificant, p=0.42. Consideration for high dose in our study was in accordance with previous studies comparing INM with other drug where low dose of intranasal midazolam used has resulted in poor outcome. It was observed that despite higher dose of INM used in our study side effects were less in comparison to IV group and the success was also high almost comparable to IV group. Fallah et al,[5] conducted study comparing chloral hydrate and INM for efficacy and safety in sedation for CT scan. They used single dose of chloral hydrate and 0.2mg/kg single dose of INM for sedation. Concluding INM to be less efficacious this was attributed to low dose of drug used.

CONCLUSION

Sedation was achieved faster in intravenous group(mean time 27 minute) than the intranasal group (mean time 32 minute).There was no age and sex predilection for onset and duration of sedation.

Overall success rate to complete the procedure was almost similar in both groups, (88% in IVM group against 82% in INM group). Intranasal group has faster recovery from sedation than the intravenous group.(69.5 minute in intranasal group compared to 87.5 minute in intravenous group). Motion artefact on completion of procedure was seen more in intranasal group.(2.7% in IV group against 12% seen in intranasal group). Total side effects observed including the serious form (desaturation and respiratory difficulty) was found more in intravenous group than the intranasal group. Intranasal midazolam can be a simple and easily administered sedative for short painless procedures like CT scan, benefit it has fewer side effects (despite higher doses) and faster recovery.

ISSN (O): 2687-5365; ISSN (P): 2753-6556

REFERENCES

1. Cravero JP, Blike GT, Beach M, et al. Incidence and nature of adverse events during pediatric sedation/anesthesia for procedures outside the operating room: report from the Pediatric Sedation Research Consortium. Pediatrics. 2006;118(3):1087-1096.
2. Malviya S, Voepel-Lewis T, Tait AR. Adverse events and risk factors associated with the sedation of children by nonanesthesiologists. AnesthAnalg. 1997;85(6):1207-1213.
3. Havidich JE, Beach M, Dierdorf SF, Onega T, Suresh G, Cravero JP. The incidence and nature of adverse events during pediatric sedation/anesthesia with propofol for procedures outside the operating room: a report from the Pediatric Sedation Research Consortium. AnesthAnalg. 2007;104(3):543-553.
4. Ramsay MAE, Savege TM, Simpson BRJ & Goodwin R. Controlled sedation with alpaxalone-alphadolone. British Medical Journal 1974; 2: 656 – 659.
5. Fallah R1, Nakhaei MH, Behdad S, Moghaddam RN, Shamszadeh A. Oral chloral hydrate vs. intranasal midazolam for sedation during computerized tomography.IndianPediatr. 2012 Feb;50(2):233-5.
6. Wilton NCT, Leigh J, Rosen DR, Pandit UA. Preanesthetic sedation of preschool children using intranasal midazolam. Anesthesiology. 1988;69:972–975.
7. BaldawaNM,PadviAV,DaveNM,Garasia MB. Atomised intranasal midazolam spray as premedication in pediatric patients: comparison between two doses of 0.2 and 0.3 mg/kg. J Anesth 2012 Jun; 26(3):346-50.
8. Acworth J P, Purdie D, Clark R C Intravenous Ketamine plus midazolam is superior to intranasal midazolam for emergency pediatric procedural sedation, Emerg Med J 2001;18:39–45.
9. Mekitarian Filho E1, de Carvalho WB, Gilio AE, Robinson F, Mason KP. Aerosolized intranasal midazolam for safe and effective sedation for quality computed tomography imaging in infants and children. J Pediatr. 2013 Rose E1, Simon D, Haberer JP Premedication with intranasal midazolam in pediatricanesthesia Ann Fr AnesthReanim. 1990;9(4):326-30.
10. RoelofseJA,ShiptonEA,de la Harpe CJ,Blignaut RJ. Intranasal sufentanil/midazolam versus ketamine/midazolam for analgesia/sedation in the pediatric population prior to undergoing multiple dental extractions under general anesthesia: a prospective, double-blind, randomized comparison. Anesth Prog. 2004;51(4):114-21

ISSN (O): 2687-5365; ISSN (P): 2753-6556