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MIDAZOLAM SEDATION IN PAEDIATRICS: COMPARATIVE STUDY OF INTRANASAL VERSUS SUBLINGUAL MIDAZOLAM ATOMIZER SPRAY IN PAEDIATRIC PATIENTS UNDERGOING MAGNETIC RESONANCE IMAGING

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ABSTRACT: INTRODUCTION: Magnetic Resonance Imaging (MRI) causes a great amount of anxiety to both parents and child. Fear of unpleasant procedures and separation from parents may result in lasting and untoward psychological consequences in children. So sedation and anxiolysis is required for children undergoing even for minor diagnostic procedures. **OBJECTIVES:** The objectives of our study was to compare safety, onset of sedation, degree of sedation produced by intranasal and sublingual administration of midazolam for premedication in children of 4-10 years undergoing MRI. **MATERIALS AND METHODS:** In this prospective randomized double blind study, the intranasal and sublingual administration of midazolam in pediatric patients who were to undergo MRI was evaluated in 60 children who were aged between 4-10 years with ASA physical status I and II by using a newer midazolam spray. The patients were divided into two groups of 30 patients each and they received Midazolam 0.3 mg/kg. Either intranasally or sublingually in a randomized manner. The heart rate, oxygen saturation (SpO₂), respiratory rate and the degree of sedation before and at 3 minutes intervals, recovery score, MRI image quality were recorded and compared. **RESULTS:** The respiratory rate, heart rate and the oxygen saturation was found from the baseline in both the groups ($p > 0.05$). A sedation score of >3 (approx.) was achieved in both the groups within 10 minutes of drug administration. The recovery score did not differ significantly between the two groups ($p > 0.05$). **CONCLUSION:** Both the intranasal and sublingual administration of Midazolam as sedative is safe and equally effective in pediatric patients.

KEYWORDS: Magnetic Resonance Imaging (MRI), Sedation, Pediatrics, Intranasal, Sublingual, Midazolam, Atomizer spray.

INTRODUCTION: MRI causes a great amount of anxiety to both parents and child.¹ Fear of unpleasant procedures and separation from parents may result in lasting and untoward psychological consequences in children.² The unfamiliar faces and the environment inside MRI, compound a sense of insecurity in children.³ In a busy radiology department time taken for the procedure becomes an important factor when choosing the technique used for sedation. Pharmacological agents are often helpful to minimize anxiety and to provide sedation.⁴

Midazolam was proved to be an excellent sedative by various routes such as oral, intramuscular, intravenous, rectal, sublingual and intranasal routes. Although most of these routes are effective and reliable, each has drawbacks. Oral route have a slow onset or may be spit out and drug taste is the main determinant for the success of administration. Intramuscular medications are painful and may result in sterile abscess. Intravenous medications may be painful during injection or

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at the start of infusion. Rectal medications may sometimes make the children feel uncomfortable and they may cause defecation and occasionally burning sensation.

Rapid and reliable onset of action, avoidance of painful injections, ease of administration and predictability, have made intranasal and sublingual route of administering sedation popular among anesthesiologists. Midazolam in the form of drops, spray and nebulization is tried by nasal route. We used a new midazolam atomizer spray for the study. In this spray, the drug is delivered in puffs which contain very minute particles which spread over a large surface area. The present study was designed to compare the safety, acceptability and degree of sedation which was produced by intranasal and sublingual midazolam as premedication in pediatric patients undergoing MRI.

MATERIALS AND METHODS: The present study was done in Govt. General Hospital in the department of Radiology, Rangaraya Medical College, Kakinada during 2013 June to 2014 January, after obtaining the Institutional Ethical Committee approval. Written and informed consent from the parents was taken. 60 ASA I and II children who were aged between 4 to 10 years prior to MRI examination were enrolled in the study. Thorough pre-anesthetic evaluation and investigations were carried out to find out any associated systemic illness. On arrival baseline pulse rate, respiratory rate and arterial oxygen saturation were recorded. In a Prospective randomized double blind study, 60 pediatric patients referred for body MRI were randomly allocated to one of the two groups of 30 patients each.

Group I: (Intranasal group) received intranasal midazolam 0.3 mg/kg through ready to use midazolam spray (each spray delivered 0.1ml or 0.5mg of drug preparation containing midazolam 5mg/ml i.e. 5%). Half of the dose was administered in each nostril (for a 13kg child on average four sprays in each nostril) in semi recumbent position or in parents lap 15 mins before MRI.

Group S: (Sublingual group) children were asked to touch their upper teeth with the tip of the tongue and then midazolam was sprayed 0.3 mg/kg (each spray delivered 0.1ml or 0.5mg of drug preparation containing midazolam 5mg/ml i.e. 5%) beneath the tongue while not permitting the children to swallow the drug for 20 seconds. To avoid interobserver variations, the same anesthesiologist was involved in all the assessments who was kept blind to the route of administration which was used by attending nurse.

EXCLUSION CRITERIA: Patients with general contraindications for MRI (i.e. cardiac pacemakers, neurostimulators, ferromagnetic implants etc) were excluded from the study. Patients with general contraindications for the use of midazolam (i.e. myasthenia gravis, known allergic reactions etc), presence of otorhinolaryngeal diseases (eg. Status post-surgery, rhinitis, nasal polyposis) children with respiratory and cardiac diseases or having upper respiratory tract infections, children on drugs which are enzyme inducers or inhibitors are also excluded from the study.

ASSESSMENT: The patient's responses to the drug administration were noted. The onset of sedation time (parent child separation time) were noted. Heart rate, oxygen saturation and degree of sedation by using Wilson's 5 point sedation scale. (Table-I) were recorded before the procedure and at 3 mins intervals and upto 30 mins after the drug is given to the patient. Recovery score as per Aldred

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criteria were also noted (Table-II) Image quality was evaluated on a point scale (Table III). A sedation score of 3 and above was considered as satisfactory and a score of 1 & 2 as unsatisfactory.

Statistical Analysis: The data was compiled and analyzed statistically by using the students't test and a 'p' value of <0.05 was considered as significant and $p < 0.01$ was considered as highly significant. All the scores in our study were analyzed by using the student's t test and standard error of difference between the two means and Chi-Square test. Statistical analysis was done by using Graphpad software.

RESULTS: The Groups were comparable with respect to age, gender and weight (Table IV). Mean age for group I was 3.3 ± 3.1 . Mean weight for group I is 13.4 ± 7.9 and for group S is 12.4 ± 5.8 . Both the groups are comparable as far as age, sex, weight and ASA physical status. There was no significant differences in pre-sedation vital parameters and base line sedation score ($p > 0.05$). Base line sedation score ranged from 1-2 in all children of both groups. There was no statistically significant difference in the heart rate, respiratory rate and oxygen saturation between the two groups before and after administration of the drug. ($p > 0.05$).

Adequate oxygen saturation (>95%) was maintained in all the children in both the groups throughout the study. 18 (60%) children in the intranasal group cried in response to the drug administration, as compared to only 5 (16.6%) children in sublingual group. A bitter taste was observed in 45% (14/30) of the patients who received midazolam by sublingual route. The difference between the two groups was statistically highly significant. ($p < 0.001$). Sedation score after the administration of the drug in the two groups are shown in Table V. Sedation score of 3 and above was considered as satisfactory and score of 1 and 2 as unsatisfactory (Bar diagram).

A slight increase in heart rate was observed in the intranasal group after drug administration as compared to that in the sublingual group. But there was no statistically significant variation in the heart rate and respiratory rate in both the groups when they were compared to the base line values ($P > 0.05$). After 10 minutes of drug administration, a sedation score of more than 3 was achieved in 80% of the children in the sublingual group, as compared to 82% children in the intranasal group which was statistically significant ($p < 0.05$).

DISCUSSION: Conscious sedation is one of the most important measures to help pediatric patients for Co-operation with MRI examination.⁵ For radiological examinations, to achieve conscious sedation in claustrophobic patients referred for MRI, midazolam is generally administered via the oral or the IV route in most institutions.⁶ Midazolam, is a potent imidazo – benzodiazepine, has got all the required properties, namely sedative, hypnotic and anxiolytic activities. Midazolam is used for pre-operative sedation by the intramuscular,⁷⁻⁹ per rectal,^{10,11} oral¹² and sublingual routes^{13,14} but each route has its own advantages and disadvantages. The use of intranasal or sublingual midazolam for sedation has come into practice right from early nineties.^{15,16}

Intranasal Midazolam, in this regards has got some advantage owing to its high mucosal vascularity, the intranasal route offers a rapid and virtually complete absorption within one to two hours into the system circulation.¹⁷ As Midazolam has high hepatic clearance, the avoidance of the hepatic first pass metabolism offers greater systemic bioavailability.¹⁵⁻¹⁷

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It has a faster onset than the oral or rectal route. Although sedation was achieved with 0.2 mg/kg midazolam intranasally, the sedation by the sublingual route of same dose was inadequate (there were chances of partly swallowing it).

Thus a dose of 0.3mg/kg was selected for both the routes to make it comparable. The heart rate and the respiratory rate in both the groups remained stable and they did not show any significant variation from the baseline values in our study. These findings indicated the safety of Midazolam which was given by either route and in the doses which were studied. Minor respiratory depression was observed by Fulkuta et al¹⁸ with 0.3 mg/kg of intranasal midazolam.

Similarly Mallnovsky et al¹⁹ reported a case of respiratory depression in a 30 month old child which was given intranasal midazolam, attributing that to ethmoidal passage of the drug which resulted in high CSF levels. In many studies, it was noted that the oxygen saturation remained above 95% in a majority of the cases which were premedicated with transmucosal midazolam.

This was confirmed in our study also, where the oxygen saturation was maintained above 95% in all the children, irrespective of whether they were sedated by the nasal or the sublingual route. However the desaturation to less than 93% with 0.3mg/kg intranasal which was noted by Karl et al²⁰ in a small percentage of children, suggested close respiratory monitoring and the availability of resuscitation equipment when the intranasal route was used.

Adequate sedation (score >3) after 10 minutes of drug administration, which was noted in a majority of children in the sublingual groups as compared to the intranasal group in our study, was in concordance with the finding of many studies, including the study of Karl et al²⁰. Although the total buccal and sublingual area is small and it has a pH of 6.2 to 7.4, it has a potential for the rapid absorption of drugs, since these areas are rich in blood and lymphatic vessels. The drug directly passes into the systemic circulation and thus the first pass metabolism of the drug can be avoided.

The lower incidence of adequate sedation through the intranasal route, as was observed in our study also could be attributed to the shorter stay time of the drug in the nasal mucosal surface as was suggested by DeBoer et al²¹. Majority of the children in our study were calm and relaxed (Score >3). Nasal irritation and crying was found in 56% of the patients. in Group I immediately after drug administration.

A bitter taste was reported in 50% of the patients in Group S. The increased incidence of crying with respect to the nasal route has been attributed by these authors¹³ to the low pH of midazolam (pH 3.3), which causes burning or irritation of the nasal mucosa on administration.

CONCLUSION: Thus we conclude that both the intranasal and sublingual routes of administration of midazolam are equally effective and they provide adequate sedation for easy separation from parents and co-operation from children during MRI. However lower incidence of onset of sedation and sedation score caused by sublingual route compared to intranasal route favors use of intranasal route to provide better sedation compared to sublingual route in children undergoing MRI.

REFERENCES:

1. Beeby DG, Huges JOM. Behaviour of unsedated children in the anaesthetic room. *Br J Anaesthesia* 1980; 52:279-81.
2. Korsch BM. The child and the operating room. *Anesthesiology* 1975;431:251-57.

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3. Kian ZN. Perioperative psychological trauma in children. In the Chapter, Complication in Anaesthesia, 1st edn. Philadelphia: W.B. Saunders, 1990:982-85.
4. Rita L, Cox JM, Seleny FL et al. Ketamine hydrochloride for pediatric Pre-medication: comparison to pentazocine. *Anesth Analg* 1974;53:375.
5. Hollenhorst J, Munte S, Friedrich L, Heine J, Leuwer M, Becker H, Piepenbrock S. Using intranasal midazolam spray to prevent claustrophobia induced by MR imaging. *AJR Am J Roentgenol* 2001; 176:865–868.
6. Moss ML, Buongiorno PA, Clancy VA. Intranasal midazolam for claustrophobia in MRI. *J Comput Assist Tomogr.* 1993 Nov-Dec; 17(6):991-2.
7. Rochette A, Julia IM, Evrard O et al. Intra-muscular midazolam as Pre-medication in newborn children and infants. *Ann Fr Anaesth Reanim* 1984;3:346-50.
8. Rita L, Selemey FL, Mazure KA, Rabins R. Intra-muscular midazolam for paediatric pre-anaesthetic sedation: a double blind controlled study with morphine. *Anesthesiology* 1986;63:528-31.
9. Taylor MB, Vine PR, Hatch DJ. Intra – muscular midazolam Pre-medication in small children. *Anaesthesia* 1986;41:21-26.
10. Saint-Maurice C, Esteve C, Holzer J et al. Pre- Pre-medication with rectal midazolam: effective dose in paediatric anaesthesia. *Ann Fr Anaesth Rearim* 1984;3:181-83.
11. Saint-Maurice C, Meistleman C, Ray E et al. Pharmacokinetics of rectal midazolam for Pre – medication. *Anesthesiology* 1886;65:5436.
12. Raubould D, Bradshaw BG. Pre-Medication for day care surgery. *Anaesthesia* 1987;42:591-95.
13. Karl HW, Rosenburger JL, Larach MG, Ruffle JM. Transmucosal administration of midazolam for the Pre-medication of paediatrics patients. Comparison of nasal and the sublingual routes. *Anesthesiology* 1993;78:885-91.
14. Khalil S, Phibrook L, Rabb M et al Sub-lingual midazolam Pre-medication in children: a dose response study paediatric. *Anaesth* 1998;8:461-65.
15. Nail CTW, Leigh J, Rosen DR, Pandit UA. Pre-anesthetic sedation of preschool children by using intranasal midazolam. *Anesthesiology* 1988;69:972-75.
16. Davis PJ, Tome JA, McGowan FX Jr et al. Preanesthetic medication with intranasal midazolam for very brief paediatric surgical procedures: effect on recovery and hospital discharge time. *Anesthesiology* 1995;82:2-5.
17. Bojrkmán S, Rigemar G, Idvall J. Pharmacokinetics of midazolam when it is given as intranasal spray to adult surgical patients. *Br J Anaesth* 1997;79:575-80.
18. Fukuta O, Braham RL, Yanase H et al. Intranasal administration of midazolam: pharmacokinetic and pharmacodynamic properties and sedative potential. *J Dent Child* 1997;64:89-98.
19. Malinovsky JM, Populărie C, Cozian A et al. Effects of the intranasal, rectal and oral routes on the plasma midazolam concentrations. *Anaesthesia* 1995;50:351-54
20. Karl HW. Rosenberger JL, Larach MG et al. Transmucosal administration of midazolam for the pre-medication of paediatric patients. comparison of nasal and sublingual routes. *Anesthesiology* 1993;78:885-91.
21. DeBoer G, De Leede LG, Breimer DD. Drug adsorption by the sublingual and the rectal routes. *Br J Anaesth* 1984;56:69-82.

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By using Wilson's five-point sedation scale, the degree of sedation was assessed	
1.	Agitated: Patient was clinging to the parents and / or crying.
2	Alert: Patient was aware but was not clinging to the parents. Might have whimpered but had not cried.
3	Calm: Sitting or lying comfortably, with spontaneous eye opening
4	Drowsy: Sitting or lying comfortably with eyes closed, but responding to minor stimulation.
5	Asleep: Eyes closed, arousable, but did not respond to minor stimulations.
Table I: Showing Wilson's sedation scale	

VARIABLE EVALUATED	SCORE
• ACTIVITY	
Able to move four extremities on command	2
Able to move two extremities on command	1
Able to move no extremities on command	0
• BREATHING	
Able to breathe deeply and cough freely	2
Dyspnoea	1
Apnoea	0
• CIRCULATION	
Systemic bold pressure <20% of the preanesthetic level	2
Systemic blood pressure 20-50% of the preanesthetic level	1
Systemic blood pressure >50% of the preanesthetic level	0
• CONSCIOUSNESS	
Fully awake	2
Arousable	1
Not responding to command	0
• COLOUR	
Normal	2
Pale, dusky	1
Cyanotic	0
Table II: Showing Aldrede's Recovery Score	

Grade 0	Very poor image quality
Grade 1	Poor image quality
Grade 2	Satisfactory image quality
Grade 3	Good Image quality
Grade 4	Excellent Image quality

Table III: Showing MRI image quality five grade scale

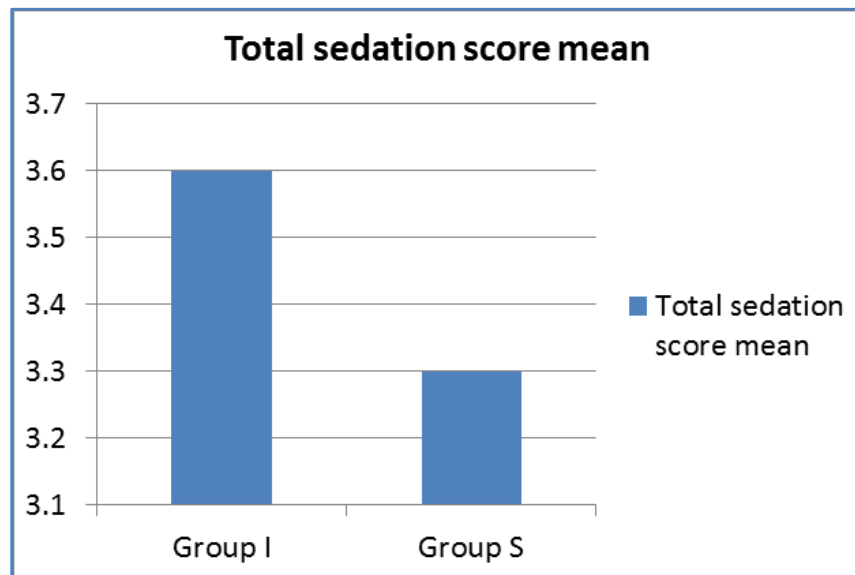
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	Group I	Group S
Number	N=30	N=30
Age	3.3 + /-3.1 (Mean ± SD)	3.1 + /-2.3 (Mean ± SD)
Weight	13.4+/-7.9 (Mean ± SD)	12.4+/-5.8 (Mean ± SD)
Sex (m/f)	13/17	14/16
ASA grade I: II	10:20	6:24

Table IV: Showing age, weight, gender and ASA grading

	Groups I (Mean ± SD)	Group S (Mean ± SD)	p value	Significance
Sedation Score at 0 min	1.58 ± 0.497	1.60 ± 0.498	0.87	N.S
Sedation Score at 5 min	2.11 ± 0.695	2.17 ± 0.747	0.74	N.S
Sedation Score at 10 min	3.6 ± 0.4	3.3 ± 0.7	0.046	S

Table V: Showing Sedation Score



Bar diagram showing sedation score

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