Evaluation Of Sedation Characteristics With Intranasal Midazolam Versus Sublingual Midazolam In Paediatric Patients Undergoing Magnetic Resonance Imaging

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Citation

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Abstract

BACKGROUND ;-The purpose of this comparative study was to compare prospectively the sedation characteristics of intranasal midazolam to sublingual midazolam in paediatric patients up to 10 years undergoingmagnetic resonance imaging

(MRI).METHODS Sixty paediatric patients referred for body MRI were divided equally to one of two treatment group. The 30

patients of group I received 0.3 mg/kg intranasal midazolam spray in to each nostril 15 min before MRI whereas the 30 patients of group II received 0.3mg/kg sublingual Midazolam 15 min before MRI. The patients responses to drug administration, onset of sedation time (parent child separation time) were noted. Heart rate, oxygen saturation, respiratory rate and degree of sedation by Ramsay scale of sedation were recorded before procedure and at 2min and up to 30 min after the drug is given to the patient. Recovery score as per Aldrete criteria were also noted. Image quality was evaluated on a 4 point scale. RESULTS :In group I, 30/30 MRI examination [100%], were completed successfully without relevant adverse effect. In group II, 05/30 patients for MRI examination [07%] ,reduction of anxiety and sedation were insufficient and low dose I.V. Propofol 0.75mg/kg supplement was given. MRI sedation quality was rated higher among patients of group I compared to group II [p<0.05] which affected the better imaging quality as well. CONCLUSION ;- Therapeutic intranasal midazolam spray is an effective to overcome anxiety and provide better sedation than sublingual route in paediatric patient undergoing MRI and doses used in our study are optimum without any side effects.

INTRODUCTION

Although the architecture and design of magnets for magnetic resonance imaging (MRI) have profoundly changed over the last few years, staying enclosed in a magnet may trigger the fear and panic reaction in paediatric patients. Howsoever small the procedure, MRI causes a great amount of anxiety to both parents and the child. Fear of unpleasant procedures and separation from parents may result in lasting and untoward psychological consequences in children1. Hence, the investigation of paediatric patients in a MRI scanner still represents a challenge. According to the literature, up to 10% of all MRI examinations cannot be completed, or even started, because of fear and anxiety2,3. Although there are some alternative techniques to facilitate the MRI of claustrophobic patients (e.g. prism eyeglasses, verbal tranquillisation), medicamentous sedation and anxiolysis remain the most useful options in order to achieve good examination results. When medicamentous sedation for MRI is desired, benzodiazepines facilitate the separation of children from their parents and to reduce anxiety associated with unfamiliar persons and strange environment. The intranasal use of midazolam has been investigated in paediatric as well as adult populations4–9. Intranasal application has the following advantages compared to oral application: absent hepatic first-pass metabolisation, resulting in a faster onset of action and a higher bioavailability (of up to 83%), minor toxicity and improved controllability due to the missing peak concentration, and a lesser sedation5,9,10.

An ideal premedicant in children should have good patient and parent acceptance, predictable results and be free from any serious side effects. Midazolam which has been used for the last two decades as premedicant in children presents the unique property of a good premedicant because of its sedative and anxiolytic properties. It has proved to be an

excellent premedicant in children by various routes such as oral, rectal, intramuscular, intravenous, sublingual and intranasal routes11,12,13. Rapid and reliable onset of action, avoidance of painful injections, ease of administration and predictability, have made transmucosal route of administering premedication popular among the anaesthesiologists. The rich blood supply of mucosa allows rapid absorption of drugs directly into the systemic circulation with no first pass hepatic metabolism. Intranasal midazolam has been used for over a decade now for sedating children before anaesthesia, even though the main disadvantage of the nasal route is irritation of the nasal mucosa and crying following its administration. The aim of our study was to compare the safety, onset of sedation, degree of sedation produced by intranasal and sublingual administration of midazolam as premedication in children.

MATERIAL AND METHOD

The study was approved by the local ethics committee and written informed consent was taken from the parents of sixty ASA II to III children, aged up to 10 years prior to the MRI examination. Exclusion criteria were: age>10 years, general contraindications for MRI (i.e. cardiac pacemakers, neurostimulators, ferromagnetic implants etc.), general contraindications for the use of midazolam (i.e .myasthenia gravis, known reverse or allergic reactions etc.), participation in another study simultaneously, and the presence of otorhinolaryngeal diseases (e.g. status postsurgery, rhinitis, nasal polyposis).Children with respiratory and cardiac diseases or having upper respiratory tract infection were excluded from the study. All patients were brought to the reception area of MRI along with the parents and randomly allocated to one of the two groups of 30 patients each. Group I (Intranasal group) received intranasal midazolam 0.3mgkg-1 through ready-to-use midazolam spray (0.5% midazolam) in each nostrils (0.5mg in each nostril) in the semi recumbent position or in parent's lap 15 min before the MRI. In group II (Sublingual group), children were asked to touch the upper teeth with the tip of their tongue and then midazolam 0.3mgkg-1 diluted with honey was placed under the tongue 15 min before the MRI, not permitting the child to swallow the drug for 30 seconds. To avoid inter-observer variation the same anaesthesiologist was involved in all assessments. The MRI was performed on one of two 1.5-T scanners according to the corresponding examination protocol. All MRI protocols were standardised and consisted of various sequences without and with a contrast agent.

Each patient received a venous cannulation before the application of midazolam for safety reasons in order to assure venous access in case of adverse effects. Patients responses to drug administration was noted. Heart rate, respiratory rate and oxygen saturation were recorded before and at 2 minute intervals up to 30 minutes after administration of the drug. Degree of sedation also was assessed before and at 2 minute and intervals up to 45 minutes, using a Ramsay's sedation scale as shown in table -1.

Figure 1

FIG 1. RAMSAY'S SEDATION SCALE14

	SCORE
Anxious, agitated or restless	1
Co-operative, oriented and tranquil	2
Responding to command	3
Brisk response to command	4
Sluggish response to command	5
No response to command	6

MRI image quality of each MRI examination was assessed using the following five-grade scale: grade 0-very poor image quality; grade 1- poor image quality; grade 2-satisfactory image quality; grade 3-good image quality and grade 4- excellent image quality. Grade 0 or 1 was applied if the examination was of no or very little diagnostic usefulness because of extensive motion artefacts that were not caused by pulsation or normal peristalsis. Examinations classified as grade 2 allowed us to make the diagnosis, but some motion artefacts were still present. Examinations graded as 3 and 4 included a good or excellent image quality, with no or almost absent motion artefacts 15.

Recovery time and recovery score were noted according to Aldrete's recovery score as shown in below table.

The data was compiled and analysed statistically using a 'p' valve of <0.05 was considered significant.

Figure 2

FIG 2. POSTANESTHETIC ALDRETE RECOVERY SCORE16

VARIABLE EVALUATED	SCORE
1.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
2.BREATHING	
Able to breath deeply and cough freely	2
Dyspnea	1
Apnea	0
3.CIRCULATION	
Systemic blood 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
4.CONSCIOUSNESS	
Fully awake	2
Arousable	1
Not responding to command	0
5.COLOUR	
Normal	2
Pale, dusky	1
Cyanotic	0

RESULTS

The groups were comparable with respect to age, gender and weight, ASA grade[Table-1], total mean sedation score more (70%)achieved in children in intranasal group as compared to children in sublingual group(66%) which was statistically significant (p<0.05).

Figure 3

Table 1. Demographic Data

	Group I	Group II
Number	n= 30	n= 30
*Age (years)	3.3±3.1	3.1±2.3
*Weight (kg)	13.4±7.9	12.4±5.8
Sex (M/F)	13 / 17	14 / 16
ASA Grade II :III	10 : 20	6 : 24

*mean ±SD

Figure 4

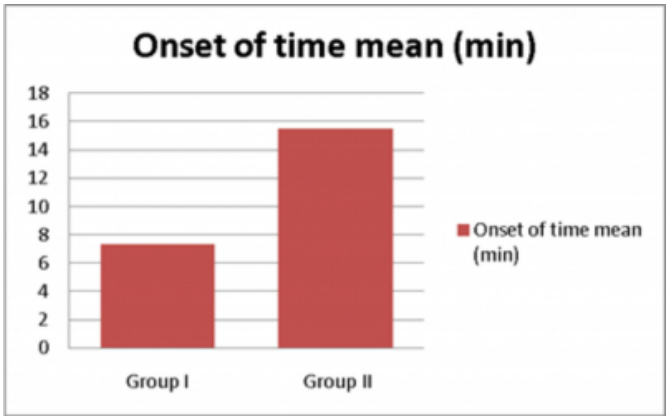
	Group I (n=30)	Group II (n=30)
Onset of sedation (min)(mean±SD)	7.3 ± 0.8*	15.5 ± 1.8
Total duration of study(min) (mean±SD)	29.9 ± 6.4	32.1 ± 4.6
Total sedation score (mean±SD)	3.6 ± 0.4*	3.3 ± 0.7

[Table-2, chart- 1] shows onset of sedation (also count as child-parent separation time)in intranasal group (mean 7min) was rapid compared to sublingual group (mean-15min) which was statistically significant(p<0.0001)[table-2, chart-1].

Table 2. Results of sedation , duration of study, sedation score.*significant difference between groups (p<0.05).

Figure 5

CHART- 1 TIME OF ONSET OF SEDATION



There was no statistically significant difference in recovery score and image quality between the two group [table-3, chart- 2].

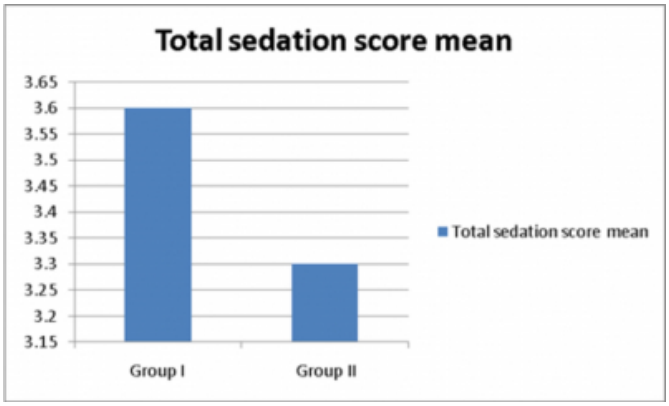
Figure 6

TABLE -3 Results of recovery score and image quality at the end of study

	GroupI(n=30)	Group II(n=30)
Recovery score (mean±SD)		
0 (min)	8.5 ± 0.8	8.2 ± 0.8
5 (min)	8.9 ± 0.7	9.1 ± 0.7
10 (min)	10 ± 0.0	9.9 ± 0.2
Image quality		
1	0	0
2	2	8
3	16	18
4	11	4

Figure 7

CHART- 2 MEAN SEDATION SCORE



The five children in sublingual group who were inadequately sedated received a low dose i.v. bolus propofol 0.75 mg/kg which was sufficient for adequate sedation during MRI. There was no statistically significant difference in 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. Changes in the heart rate, respiratory rate and sedation score after administration of the drug in the two groups are shown in [table -4]

DISCUSSION

Conscious sedation is one of the most important measures to help paediatric patients for co-operation with MRI examination. The term "conscious sedation" means that the patient is able to maintain his/her airway and respond appropriately to physical stimulation and verbal commands while sedated 17. For this purpose, midazolam is often used because its pharmacological properties are superior to other benzodiazepines (fast onset, better tissue compatibility, controllability of effect, short duration of action of 20 to 40 min, short elimination half-time of 1.5 to 3 h). Additionally, anxiolysis appears already at a low dosage and, usually, there are no relevant adverse effects, apart from a slight sedation 17 Midazolam may be administrated orally, intravenously, intra rectally or intranasal. For radiological examinations, in particular, to achieve conscious sedation in claustrophobic patients referred for MRI, midazolam is generally administrated via the oral or the i.v. route in most institutions. The advantage of oral administration compared to i.v. administration is the fact that it does not present an invasive procedure and most radiologists feel more comfortable with oral use than with i.v. use. On the other hand, i.v. use compared to oral application offers the advantage that there is no hepatic first-pass metabolism, Resulting in a faster onset of action and a higher bioavailability of the drug. In addition, i.v. administration is not influenced by the bowel contents and movement, resulting in an improved controllability18,19.

In the present study, we compared 0.5mg/kg intranasal midazolam spray with sublingual midazolam 0.3mg/kg, prepared from preservative free midazolam was mixed with honey and placed under the tongue; the patient was asked to hold it as long as possible before swallowing. The inferior result of the oral application regarding feasibility of the examinations, reduction of anxiety and image quality might be explained by the study of Biro et al. 20 found a marked interindividual variability of sedation and amnesia after orally administered midazolam prior to surgery. Additionally, anxiolysis was lacking in all orally administered doses, showing no difference compared to the placebo group, whereas sedation and amnesia were dose-dependent. The intranasal application of midazolam is well known in paediatric medicine, especially for painful procedures such as dental interventions, treatment of acute seizures, for premedication and trauma management6,7. In adults, the intranasal application of midazolam has been reported for sedation during upper gastrointestinal endoscopy, for premedication, as well as for the treatment of panic disorders4,8,9. However, the experience with midazolam in patients for radiological examinations and, in particular, in patients referred for MRI is limited. Moss et al. 21 presented their preliminary results using intranasal midazolam for claustrophobic MRI patients. This route of administration reduced the necessity for i.v. sedation from 67% to 17%. As in our study we were not using additive i.v. sedation in intranasal group. In sublingual group 05/30 patients for MRI examination reduction of anxiety and sedation was insufficient and low dose Propofol 0.75mg/kg supplement was given. Recently, Hollenhorst et al.3 showed, in a double-blind placebo controlled study, that intranasal applicator midazolam leads to a significant reduction in MRI-related anxiety, resulting in an improved MRI image quality. In the study of Hollenhorst et al.3, 54 consecutive patients scheduled for MRI of the head were divided into two groups receiving either 4 mg of midazolam intranasal or a placebo intranasal. No cancellation of MRI occurred in the midazolam group consisting of 27 patients, whereas 4/27 (14.8%) patients receiving the placebo panicked and terminated MRI earlier. Present study is in accordance with their study. Schweizer et al.4 reported an improvement of panic disorders in 4/5 patients using a total dose of 0.5– 1.0 mg of self-administrated intranasal midazolam drops. In our study patient became calm after giving study drug and no patient had failure of MRI. Hollenhorst et al. 3 showed the time delay between the application of the drug and the start of MRI. In their study, intranasal application of midazolam took place 15 min before MRI. In the study of Moss et al.21, patients received two drops per nostril of a midazolam solution (total 0.5 mg) prior to entering the scanner without a time definition. This dose could be repeated during the MRI procedures (total 1.0 mg). In our study, we administered the intranasal spray 15 min before MRI. According to the literature, the effect of the intranasal implicated midazolam starts in less than 5 min17. In our study onset of sedation mean time was 7.3 min compared with sublingual route it was 15.5 min. In a clinical setting, it is easier to administer the intranasal spray on the MRI table if the patient is complaining of claustrophobia. The excellent effect of the intranasal used midazolam may be explained by the

following reasons. In contrast to oral and rectal administration, intranasal midazolam administration has no first-pass effect in the liver and no interference with the bowel contents. Therefore the interindividual differences in the dose-related effects are much smaller. Using a nasal spray absorption through the nasal mucosa is fast and virtually complete (about 83%), resulting in a quite easily controllable midazolam application22. The fast and intense effect of the small and amphiphilic midazolam molecule may be explained by the supposed predominant fast paracellular transport through the nasal mucosa, as well as the easy passage through the blood–brain barrier23,24. According to the literature, the intranasal spray is also superior to nose drops, which are partially swallowed3,9,20; compared to i.v. administration, there is a lower toxicity due to decreased peak concentration and its usage is easier and less painful 3, 22. Although intranasal application is an off-label use and not yet approved by the authorities, it seems to be safe. As also described by other authors, there were no major adverse effects requiring further therapy, only a local temporary burning sensation after intranasal spray application was detected. This is probably due to the used preserving agent (benzyl alcohol) and the low pH value (3.3) of the aqueous midazolam solution 17. In our study we used Ramsay's sedation score to assess sedation which was higher in intranasal route was (3.6 mean) compared to sublingual route (3.3 mean).which was statically significant so, it can be concluded that intranasal midazolam produce better sedation compared to sublingual midazolam.

CONCLUSION

We conclude from our study that both intranasal and sublingual routes of administration of midazolam are effective, and provide adequate sedation for easy separation from the 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 favours use of intranasal route to provide better sedation compared to sublingual route in children.

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