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Original Research Article

Comparison of sedation scores after nebulized and intravenous Midazolam in children

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ABSTRACT

Background: An efficacious, reliable, and non-invasive route of administration for midazolam, a drug used for sedation and pre-anesthetic medication, would have obvious advantages. This study compares the sedation achieved by nebulized route and intravenous route as procedural sedation.
Methods: A randomized double-blinded interventional study was designed to compare the effect of nebulized midazolam with intravenous midazolam as a sedative medication in 86 children undergoing imaging procedures like CT scan, MRI scan, EEG. Ramsay sedation scores and parameters of cardiovascular and respiratory function were measured over 20 min and summarized
Results: The mean sedation score in both groups was comparable at baseline, 10 minutes and 20 minutes with p values of 0.1, 0.1, 0.09 respectively. Parameters of cardiovascular and respiratory function were comparable in both the groups.
Conclusion: Present study showed that nebulized midazolam when given at a higher dose of 1 mg/kg was found to be as potent as intravenous midazolam, opening up a door for a sedative which is easier to administer, has better acceptance with lesser complication.

Keywords: Intravenous, Midazolam, Nebulised, Sedative

INTRODUCTION

Paediatric sedation is a global challenge. The delivery of paediatric sedation has expanded over the last decade in both volume and demand.[1] However most of the current sedation guidelines are contradictory and many of the newly developed sedatives are not approved for paediatrics.[1] The need of the hour is to identify the best method to acquire and maintain sedation. The challenge encountered in paediatrics is that the standard sedation scales cannot be applied. Pharmacokinetics and dynamics vary with age and it is often difficult to differentiate pain from distress in children. Midazolam being a water-soluble drug is the shortest acting benzodiazepines and is frequently used as an intravenous sedative.[2] In this study we have evaluated the efficacy of inhaled midazolam to provide sedation in children. The advantage of nebulized approach for administration of sedatives is that it is non-invasive, needs minimal expertise and more comfortable for the child.

Midazolam is a water-soluble drug, which is the shortest acting in relation to other benzodiazepines and is often used as an i.v. sedative.[3] By activating γ-aminobutyric acid, benzodiazepines produce sedation, anxiolysis, amnesia, and anticonvulsant effects. After administration, respiratory depression should be watched for. Time to peak effect for midazolam is brief with i.v. administration (2-3 minutes) and duration is short (45-60 minutes).[4] Although intranasal midazolam is safe and effective in

reducing anxiety and stress in children, it may cause nasal burning, irritation, and lacrimation during instillation. Nebulized midazolam may offer a more comfortable and easy to use route of administration.[3]

METHODS

A randomised double-blinded interventional was conducted at A. J. Institute of Medical Sciences, Mangalore during a 12-month period between September 2016-August 2017.

The aim of the study was to compare effectiveness of nebulized midazolam as an alternative for procedural sedation in comparison with intravenous midazolam with the help of sedation scoring system.

Inclusion criteria

All children between the ages of one month to six years who are required to undergo either a CT scan, MRI scan or EEG under sedation.

Exclusion criteria

Children with respiratory distress, including asthma, atopy, or on any long-term medication and GCS <10.

62 children fitted into the inclusion criteria and were taken up for the study. Ethical committee approval was sought and received. Baseline characteristics like age, gender, weight was recorded. A detail past history was taken in order to rule out any drug allergy, any medications or cardiac disorders. After placement of routine monitoring (electrocardiograph, non-invasive blood pressure and pulse oximetry), children were randomly assigned to either of the two groups alternately.

Group 1 received midazolam by nebulisation at the dose of 1 mg/kg (upto a maximum of 5 mg) diluted in 5 ml normal saline and administered as nebulisation through pediatric mask. The nebulisation was administered via a compressed air operated jet nebulizer connected to oxygen administered at 10 L/minute for a period of 5 minutes. Following the completion of nebulisation, 0.1ml/kg of normal saline was given intravenously. The treating doctor administered the nebulisation over a period of 5 minutes and the score was noted at the end of intravenous injection.

Group 2 received 5 ml of placebo (normal saline) as nebulisation followed by intravenous midazolam injection at the dose of 0.1mg/kg (upto a maximum of 6 mg). The baseline score was taken at the end of the intravenous injection. The commercially available intravenous preparation containing 1mg per 1 ml midazolam has been used in both the routes.

The patient's vital signs: heart rate, blood pressure, respiratory rate and pulse oximetry are recorded before and after administration of midazolam. One trained observer blinded to the route of administration was to score all the patients at baseline (after iv injection administered), at 10 minutes and 20 minutes according to Ramsay Sedation Score of 1 to 6 as shown in Table 1.[3]

Table 1: Ramsay sedation score.

Level	Response
1	Awake and anxious, agitated, or restless
2	Awake, cooperative, accepting ventilation, oriented, or tranquil
3	Awake, responds only to commands
4	Asleep, brisk response to light, glabella tap or loud noise
5	Asleep, sluggish response to light, glabella tap or loud noise
6	Asleep, no response to light, glabella tap, or loud noise

Statistical analysis

The collected data were entered and analyzed using SPSS software version 18.0. Descriptive statistics and qualitative data were analysed using student t-test and chi square test. A p value of <0.05 was considered to be significant.

RESULTS

86 children were eligible for the study out of which 6 were excluded. The parents of 4 children had not consented for the study and 2 children developed respiratory depression during the study. The rest of the 80 children were randomised into 2 groups. Each group had 40 children. The two groups were comparable with respect to demographic data collected like age, sex, weight of the child (Table 2).

Table 2: Demographic data.

Variable	Group A	Group B	P value
Age	3.125	3.867	0.2
Sex			
Males	29	28	0.8
Female	11	12	
Weight	12.675	13.625	0.394

The mean heart rate, respiratory rate and systolic and diastolic blood pressure in Group 1 and Group 2 were statistically comparable, p value of 0.1, 0.16, SBP of 0.2 and DBP of 0.4 respectively just after administration of the drug. There was no variation in the mean spO2, p value of 0.599, noted either.

The baseline sedation scores taken were 1 or 2 in all the patients in both the groups. The mean sedation score which was taken just after the completion of intravenous injection of all the patients was noted to be 2.125±0.892 in Group1 and 2.925±0.625 in Group 2 which was comparable p value of 0.112. The heart rate, blood pressure and spO2 showed no significant changes at 10 as well as 20 minutes,

p value of 0.268 and 0.622 for heart rate, 0.512 and 0.544 for spo2, 0.41 and 0.40 for systolic blood pressure, 0.11 and 0.10 for diastolic blood pressure respectively. However, the respiratory rate was noted to be slower in the group which was administered intravenous midazolam at 10 minutes, although the p value revealed no statistical significance p = 0.053 and at 20 mins p value of 0.4 (Table 3).

Table 3: Baseline variables.

Variables	interval	Group A	Group B	P value
Heart rate	0 minutes	107.8±17.813	105.2±17.186	0.1
	10 minutes	105.2±16.651	103.1±16.401	0.2
	20 minutes	102.5±16.522	101.7±16.042	0.6
Respiratory rate	0 minutes	27.6±5.926	26.7±6.152	0.1
	10 minutes	27.1±5.377	22.7±5.739	0.053
	20 minutes	24.1±5.250	22.1±5.834	0.4
Spo2	0 minutes	98.610±0.802	98.650±0.834	0.59
	10 minutes	98.515±0.774	99.550±0.597	0.51
	20 minutes	99.400±0.496	99.475±0.595	0.54
Systolic BP	0 minutes	100.350±3.732	98.750±8.848	0.2
	10 minutes	96.650±3.984	97.9±8.863	0.4
	20 minutes	96.0±3.974	97.35±9.264	0.4
Diastolic BP	0 minutes	65.600±4.325	66.550±6.835	0.4
	10 minutes	64.300±4.121	65.475±6.733	0.1
	20 minutes	64.575±4.212	65.871±7.434	0.1

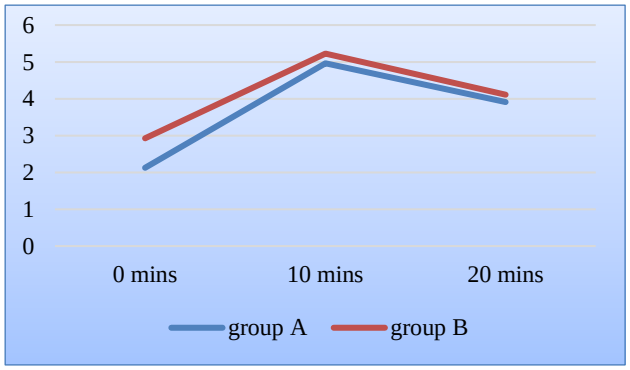

Figure 1: Mean sedation score at different intervals.

The mean sedation scores at 10 minutes was found to be 4.962±0.722 In group 1 and 5.225±0.534 in group 2. The p value of 0.1 which was insignificant; showing that the sedation achieved through nebulisation and intravenous midazolam was almost the same at 10 minutes. At 20 minutes the mean sedation remained almost the same in both the groups 3.911±0.132 in group 1 and 4.112±0.241 in group 2 respectively with p value of 0.09. No child was observed to have a greater sedation by waiting for more than 10 minutes (Figure 1).

DISCUSSION

Infants show greater hemodynamic, immune, hormonal and metabolic stress responses. For a child undergoing a procedure, a major deciding factor is whether it is painful or not. Pure sedation is sufficient for imaging studies without analgesia. Sedation is required to allay the anxiety and movement. Coaxing and physical restraint is not an alternative and this may make the procedure not only difficult but also unsafe for the child. Moreover, the psychological trauma may be severe enough to even lead to stress disorder.[4]

In recent years there has been increasing interest in the sedation of children about to undergo distressing therapeutic procedures.[5]

Midazolam has a controlled sedation with quicker recovery time. The safety and tolerability profile of midazolam in pediatric patients is comparable/superior to that observed in adults.[6] Despite its common use, the preferred route of administration remains in dispute. The most popular routes being oral and rectal. Other routes include intranasal administration, sublingual, intramuscular and jet injection.[7]

The bioavailability of intranasal midazolam in children has been estimated at 55%, but using a concentrated nasal spray it may reach 83% and 87%, 18%, 27%, respectively, for the i.m., rectal, and oral routes in children.[8-10] In a study done by McCormick et al, in adult, showed that the absolute bioavailability of nebulized midazolam was not determined in their study, but these results indicate that it is about 34% of that by nasal instillation but the decreased bioavailability of the nebulized route may be in part due to inefficiency of the jet nebulizer system.[3] Nebulizer efficiency depends on several factors: (a) the proportion of

respirable particles produced during nebulization; (b) the proportion of aerosol released during inhalation; and (c) minimizing the residual 'dead volume' of drug remaining in the nebulizer, which may be as much as 66% of the original solution.[3] Very few studies have been published on the use of nebulised midazolam in pediatric patients. Among IV sedatives, benzodiazepines are considered because of the sedative effect, anti-anxiety and amnesia it provides. Midazolam is considered especially for its short half-life and fewer side effects.[11] To our knowledge, this is the first study comparing the nebulized route to oral route of midazolam for procedural sedation.

In a study done by McCormick et al, comparison of sedation scores in 10 healthy adults whom were given either intranasal midazolam or nebulised midazolam showed that nebulised midazolam caused less discomfort to the patient and is a good alternative to oral administration. However, the bioavailability is lesser than when given orally and probably requires a higher dose when given through nebulisation. In the present study, the sedation was better found with nebulised midazolam when compared to oral midazolam. [3]

In a study done by Kaabachi et al, comparing the effect of midazolam nebulizations with two different doses found that mask nebulisation with 1 mg/kg midazolam seems to be an effective, rapid and safe route for premedication in children.[7] In the present study the sedation was better achieved with nebulized midazolam at 1 mg/kg dosage. In a study done by McCormick et al, there was no significant difference in oxygen saturation between the intranasal and nebulized phases.[3] Mean heart rate and diastolic arterial pressure were both significantly higher in the intranasal phase of the trial, with a trend also towards higher systolic pressure. These findings may reflect the discomfort caused by this route of administration. But in our study the, heart rate, respiratory rate, oxygen saturation and blood pressure were comparable in both groups. This also infers the ease and comfort of administration of midazolam by nebulisation.

Nasal irritation appears to be a major disadvantage of instilling midazolam into the nasal passageway and this unpleasant side-effect is well documented in children. Administration by nebulizer will help to overcome this obstacle.[3]

Limitation of the study includes that the study requires to be done on a larger scale with a larger population in order to monitor the changes in the vitals of the child. Although we had found a slight lowering of the respiratory rate in the group receiving intravenous medication, its significance needs to be studied further.

CONCLUSION

In conclusion, the present study shows that nebulised midazolam when given at a higher dose of 1 mg/kg shows open up a door for a sedative which is easier to administer, better acceptance and has lesser complication. However, it requires further studies in paediatrics on a larger scale in the form of lower doses and better nebuliser delivery.

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