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ROLE OF ORAL MIDAZOLAM AS A PROCEDURAL SEDATIVE IN CHILDREN AGED 6 MONTHS TO 12 YEARS

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ABSTRACT

Pediatric procedural sedation is a safe, effective and humane way to facilitate appropriate medical care. We conducted a prospective, open-label randomized controlled trial in 272 children in the age group of 6 months to 12 years who need to undergo a procedure requiring pain or anxiety management. The objective was to evaluate the efficacy and safety profile of oral midazolam in comparison with intravenous midazolam. Out of 272 children, 42.5% children underwent invasive procedures and the rest non-invasive. For non-invasive procedures, 79% subjects in the oral group were adequately sedated, compared to 63% in the intravenous group. For invasive procedures, 71% subjects were adequately sedated with oral midazolam and 78% in intravenous group. 85% procedures were successfully completed in oral group compared to 79% in intravenous. Occurrence of adverse effects like desaturation, apnea and paradoxical hyper agitation was less with oral midazolam compared to intravenous.

KEY WORDS: **Procedural sedation, analgesia, midazolam, children.**

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INTRODUCTION

Pediatric procedural sedation has evolved rapidly over the last two decades because of increased awareness about the presence of the procedure-related anxiety and pain even in the youngest children. The management of acute pain and anxiety in children undergoing therapeutic and diagnostic procedures outside the operating room has developed substantially in the past 15 years[1].Over the last 20 years, many newer sedative drugs and routes of administration have emerged. Different medications and combinations of medications can be used to achieve the desired effect. It is important to distinguish the goals for procedural sedation: pain relief, anxiolysis or both. Consideration should also be given to the fasting recommendations and monitoring guidelines before administering the sedation.[2] Procedural sedation refers to a technique of administering sedatives or dissociative agents with or without analgesics to induce a state that allows the patient to tolerate unpleasant procedures while maintaining the cardiopulmonary function. [3]Several observational and objective methods have been described for assessment of the level of sedation as reliable and valid measures. The University of Michigan Sedation Scale (UMSS)[4] is an observational tool that scores the patient's responsiveness to stimuli in a manner consistent with recognized definitions. This tool has been tested for inter-rater and test-retest reliability, and construct and criterion validity in small samples of children aged 6 months to 12 years, supporting its use during procedural sedation.[5] The injectable midazolam preparation used orally has proven very successful in producing light sedation, anxiolysis and amnesia.[6, 7] Respiratory depression is rare with orally administered midazolam.[6] Studies done by F C Davies et al [8] have shown that at 0.5 mg/kg, oral midazolam appears safe and is effective in sedating most children for minor procedures.In the recent years, there has been a drive to find an effective, safe, short acting, non-injectable sedative. Oral midazolam has emerged as such an agent. It has been used with success as a procedural sedative since 1990. [9] Till date, the injectable preparation of midazolam is being widely used orally and is found to be effective. Considering the published literature, it was unethical to compare oral midazolam with placebo, since the former is known to be effective. [8] Few studies are published comparing efficacy of drugs like clonidine[10], ketamine among others in oral and intravenous routes for surgical premedication and sedation. There are very few studies in the literature comparing the effectiveness of midazolam in oral and intravenous routes for procedural sedation in children; hence an attempt has been made to study the efficacy and safety profile of oral midazolam.

METHODS

SETTING & PERIOD: It was a prospective, open label randomized controlled trial with stratification and blocking, conducted between April 2010 and March 2012, in the department of pediatrics of a tertiary care, multi-specialty, referral hospital in private sector in south India. About 150 to 200 children visit the out-patient and emergency department per day. In our Pediatric Intensive Care Unit (PICU), invasive procedures like lumbar puncture (~20 per month), bone marrow aspiration/biopsy (~5 per month), central line insertions and venous cut downs (~10/ month) are done regularly. We have in-house facilities for CT & MRI scans (~25 per month). All our pediatric residents are Pediatric Advanced Life Support (PALS) trained and perform all procedures under the guidance of intensivists available round the clock. The study was approved by the Institute's Ethics Committee.

ENROLLMENT

Children in the age group of 6 months to 12 years undergoing procedures that require pain and/or anxiety management were included in the study. This included invasive procedures like lumbar puncture, bone marrow biopsy/ aspiration, venous cut down and central line insertions as well as non-invasive procedures like CT and MRI scans in potentially uncooperative children. Children with a history of allergy to benzodiazepines, or to any of its components and those who had been sedated

within 4 hrs of presentation were excluded from the study. A pre-sedation evaluation comprising the child's medical history and physical examination was done. Informed consent was taken from the parents in accordance with the institutional policy.

SAMPLE SIZE

Sample size was calculated based on a pilot study. With power of 90% and alpha error of 5%, it was estimated that a sample size of 130 (n=129.2) in each group would be sufficient.

RANDOMIZATION

Stratification was done for age groups (6 mo-6 yrs and >6 yrs-12 yrs). Each stratum consisted of permuted blocks of randomly varying sizes. Eligible subjects were randomly allocated in a 1:1 ratio into one of the two groups: Oral midazolam group & intravenous midazolam group. The random number table was generated using computer software. Concealment of allocation was ensured by placing the paper slips in opaque, serially numbered and sealed envelopes. One of the investigators generated the allocation sequence and assigned participants. As the patient gets enrolled, the envelope was opened and the intervention was executed.

INTERVENTION

All children fasted prior to the procedure, the fasting times being: 6 hours for solids, 4 hours for breastfeed and 2 hours clear fluids.[11] Eutectic mixture local analgesic (EMLA) patch for analgesia was applied topically in both the groups 45 minutes prior to the time of invasive procedures. Sedation was administered to all children by a pediatric resident under supervision of a pediatric intensivist in the procedure room of the pediatric ICU. Group I was given a mixture of undiluted preparation of midazolam (available for parenteral administration as 1 mg/1 ml in 10 ml vials) in the dose of 0.5 mg/kg and 5 ml of 33% sugar (sucrose) solution orally. Sugar solution was added to mask the bitter taste of midazolam. This solution was administered slowly into the child's mouth using a dropper. Group II was given the same drug IV in a dose of 0.15 mg/kg. [1] Dose of oral midazolam was repeated if the child spitted out immediately or vomited within 15 minutes of drug administration.The procedure was done 45 mins after the drug administration in the oral group and after 5 mins in the IV group. Resuscitation equipment, oxygen and suction were available during the sedation as well as recovery periods. The child was constantly monitored by the pediatric resident and a trained staff nurse and then he data was recorded in the proforma.Sedation score was recorded using the University of Michigan Sedation score (UMSS) in both the groups. [5] Scoring was as follows: 0=Awake and alert, 1=Minimally sedated, 2=Moderately sedated, 3= Deeply sedated,4=Unarousable.The ease of performance was scored during the procedure which was scored as follows: 1=Violent movement with or without hysterical crying that interrupt procedure, 2=Continuous movement with crying that makes procedure difficult, 3=Controllable movement with little crying that does not interfere with the procedure, 4=No movement, no crying. [12] The number of successfully completed procedures was noted.Routine behavior management techniques such as tender loving care and physical restraint (whenever required) were used to manage the children of both the groups during the procedure. The results of the level of sedation, ease of the procedure and the number of completed cases in both the groups were noted, tabulated and statistically analyzed. After the procedure, the child was monitored by the nursing staff until he was able to walk (if age appropriate), and gave age-appropriate responses to verbal commands [13]. If the sedation was not adequate in either of the groups, then the subject was deemed as a case of 'sedation failure'. The drugs used in such cases were propofol, ketamine or fentanyl as per the institution's policy. Propofol on combining with drugs like ketamine or midazolam helps instill better sedation and analgesic effect. [14]Adverse events were noted and defined as follows: 1) Hypoxemia-Any time during which a child's SpO2 was less than 90 %. Pulse oximetry was used for this purpose. [2] 2) Hypoventilation/ apnea: Poor breathing efforts or cessation of respiration for >20 seconds. [15] 3) Upper airway obstruction in the form of excessive secretions or spasm. 4) Hemodynamic changes: tachycardia, bradycardia or hypotension (systolic BP below the 5th percentile of normal for the patient's age.[15] 5) Hypersensitivity to the sedation

agent used. 6) Paradoxical agitation: Sustained severe irritability for ≥30 mins after procedure time [16]

OUTCOME MEASURES

Primary outcomes were level of sedation and ease of performing the procedure. Secondary outcomes were successful procedure completion rate and adverse effects

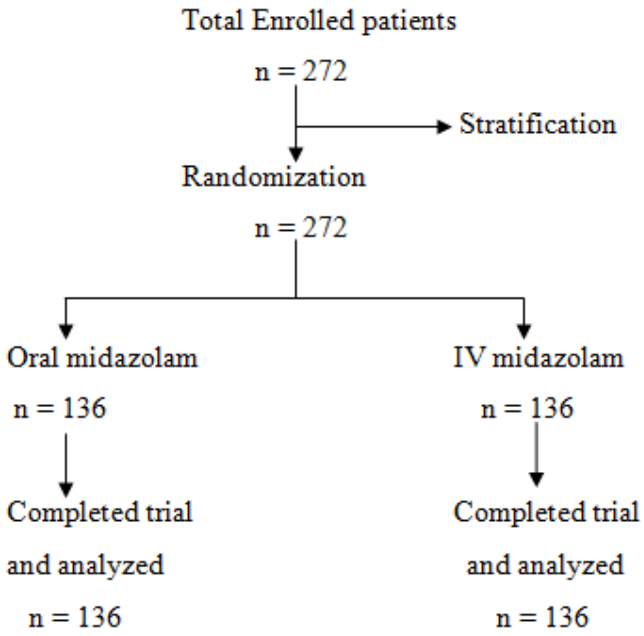
STATISTICAL ANALYSIS

The baseline variables were described by descriptive statistics. Mean age was compared between the two groups using Student's't' test. The comparison of procedures between two groups was done by Chi-square test. In case of groups with dichotomous variables, the difference was tested by Fisher's Exact Test. Ordinal data obtained with the scoring scales were analyzed using the non parametric Mann Whitney U Test at the 95% significance level, to compare the effectiveness of the groups. P value <0.05 was taken as significant. Data was analyzed using the computer software, Statistical Package for Social Sciences (SPSS) version 17 and Microsoft Excel 2007.

RESULTS

In total, 272 children were enrolled in the study and included in the randomization. Of these, 191 (70.2%) children were in the age strata of 6 mo-6yrs and 81 (29.8%) in the >6yrs-12yrs. 150 (55%) were males and 122 (45%) were females. Among the procedures, 115 (42.5%) were invasive and 157 (57.5%) were non invasive. The two groups were balanced in terms of baseline characteristics at presentation.

TRIAL PROFILE



CHARACTERISTICS OF STUDY SUBJECTS

Baseline Data	Oral midazolam n=136	I.V. midazolam n=136
Mean age in yrs (range)	4.5(1.1–7.9)	5.1(1.2–9.0)
Male	69(50.7%)	81(59.6%)
Female	67(49.3%)	55(40.4%)
Invasive procedures	56(41.2%)	59(43.4%)
Non invasive procedures	80(58.8%)	77(56.6%)
Procedures:		
LP	41(31.1%)	47(34.6%)
BM	7(5.1%)	6(4.4%)
Central line	5(3.7%)	4(2.9%)
ICD	3(2.2%)	2(1.5%)
CT	47(34.6%)	37(27.2%)
MRI	33(24.3%)	40(29.4%)

COMPARISON OF SEDATION SCORE: INVASIVE PROCEDURES

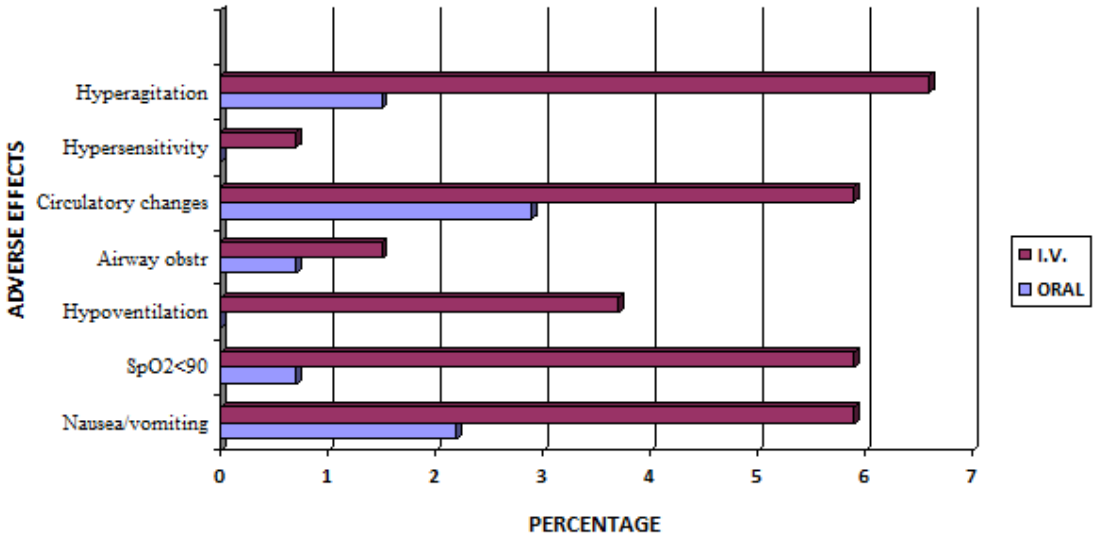
SEDATION SCORE [5]	ORAL n=56	I.V. n=59	p VALUE
0=Awake and alert	4(7.1%)	1(1.7%)	
1=Minimally sedated	12(21.5%)	12(20.3%)	
2=Moderately sedated	22(39.3%)	30(50.8%)	>0.05
3=Deeply sedated	14(25%)	13(22%)	
4=Unarousable	4(7.1%)	3(5%)	

COMPARISON OF SEDATION SCORE: NON-INVASIVE PROCEDURES

SEDATION SCORE [5]	ORAL n=80	I.V. n=77	p VALUE
0=Awake and alert	1(1.3%)	7(9.1%)	
1=Minimally sedated	16(20%)	21(27.3%)	
2=Moderately sedated	28(35%)	23(29.9%)	**<0.05**
3=Deeply sedated	26(32.5%)	21(27.3%)	
4=Unarousable	9(11.2%)	5(6.5%)	

In our study, for invasive procedures, 22 subjects in the oral midazolam group had ease of procedure score of ≤ 2 and 34 had scores of >2. In the IV group, 28 had scores ≤ 2 and 31 >2. For non invasive procedures, 18 subjects in the oral midazolam group had ease of procedure score of ≤ 2 and 62 had scores of >2. In the IV group, 37 had scores ≤ 2 and 40 >2. In subjects who underwent lumbar puncture, 37 out of the 41 underwent the procedure successfully subjects in the oral midazolam group and 37 out of 47 in the IV group. For CT and MRI, the rate was 93.6 and 93.9% in oral group and 86.5 and 82.5% in the IV group.

COMPARISON OF ADVERSE EFFECT PROFILE



DISCUSSION

In our study, we divided the children into two strata as it was assumed that mechanism of response of the body to disease differs with age, and so is the effect of the drug. We enrolled 272 children in our study, 191(70.2%) in the 6 months–6 year group and 81(29.8%) in the > 6yrs-12 yrs. Charles J. Cote *et al* [17] in their prospective randomized study included children from 6 months–16 yrs. Of the 272 children in our study, 136 each were randomized to oral and IV midazolam group respectively.Of the 272 subjects, invasive procedures were performed on 115(42%) children, with 56 (41.2%) receiving oral and 59(43.4 %) receiving IV midazolam. 157(57.7%) children underwent noninvasive procedures, with 80(58.8%) in oral and 77(56.5%) in IV midazolam group. Majority of the trials on procedural sedation were done on individual procedures like CT scan [18], LP and others. We have included most of the commonly performed pediatric procedures. Non invasive procedures require the child to be 'just' immobile, whereas invasive procedures are traumatic and require higher sedation and amnesia. Hence we thought it was wiser to evaluate invasive and non invasive procedures separately. The distribution of invasive (LP, BM, central line, ICD) and non-invasive procedures (CT, MRI) were almost equal in oral and IV groups.

LEVEL OF SEDATION ASSESSED BY SEDATION SCORE [5]

Since this was one of the primary objectives of our study, a detailed literature search and critical review of all the possible major studies evaluating the efficacy of midazolam as a procedural sedative was done. There are hardly any previous trials comparing oral and IV midazolam in procedural sedation.In our trial, for invasive procedures, there was no statistically significant difference in sedation scores between oral and IV midazolam. On the other hand, we observed that, for non-invasive procedures, children in oral midazolam group were better sedated than those in the IV, which was significant. On studying the same in two age strata, we observed that for invasive procedures, age had no relation to the difference in the sedation score between oral and IV patients. For non invasive procedures, oral midazolam was a better sedative with statistically significant results in the age strata >6 years to12 years. Daniel Haas et al [19] in their randomized controlled trial comparing oral midazolam and chloral hydrate in pediatric dental sedation observed that, age had no correlation with the difference in the overall behavior. F.C Davies et al [8] in their two stage trial observed that oral midazolam was effective in 76% of children as measured by anxiety score. Hence, our study is at par with major studies favoring oral midazolam as a sedative for pediatric procedures.

ASSESSMENT BY EASE OF THE PROCEDURE [12]

In our study, we observed that for invasive procedures, children with violent(score 1) and continuous(score 2) movements were more in the IV group(18.6% and 28.8%) as compared to oral(14.3% and 25%). Children with controllable (score 3) movement and with no movement were more in the oral group (42.9% and 17.9%) than IV (39% and 13.6%). For non invasive procedures, we found that subjects with violent and continuous movement were more in IV(15.6% and 32.5%) than oral midazolam group(5% and 17.5%). Subjects with controllable and nil movement were significantly higher in the oral group(40% and 37.5%) in comparison to IV(33.8% and 18.2%). We noted that, for non-invasive procedures, oral midazolam has a statistically significant ease of the procedure score than IV midazolam with better sedation in the >6yrs-12yrs strata (p=0.001). On the contrary, there was no significant difference between the same for invasive procedures.For invasive procedures, sedation score was almost equal for oral and IV but the ease of the procedure was better for the former than the latter. It is noted that there is no apparent direct relation between sedation score and the ease of the procedure score probably due to a wide age range and variations in the temperament of children.

ASSESSMENT OF SUCCESSFUL PROCEDURE COMPLETION RATE

For invasive procedures, successful procedure completion rate was 73.2% for subjects in the oral group in comparison to 72.9% for those in IV (p value >0.05). For non-

invasive procedures, the rate was 93.8% for subjects in the oral whereas 84.4% for those in the IV group (p value > 0.05). Thereby we inferred that for invasive procedures, there was no significant difference in the procedure completion rate between oral and IV midazolam. On the other hand, oral midazolam was more suitable for non-invasive procedures. Among individual procedures, successful procedure completion rate was better for oral than IV midazolam for lumbar puncture, CT scan and MRI scan. Age had no relation to the same. Kapur et al [20] in their study on oral midazolam in pediatric dentistry inferred that successful completion of procedures were more in the case group compared to the placebo group.

COMPARISON OF SIDE EFFECT PROFILE

We observed that oral midazolam was well tolerated by most of the children. Nausea or vomiting was present in 3 subjects in oral group and 8 in IV. Upper airway obstruction was seen in 1 subject in oral group and 2 in the IV. Circulatory changes in oral and IV group were seen in 4 and 8 subjects respectively. There was one case of hypersensitivity to IV midazolam. Desaturation, hypoventilation and paradoxical hyperagitation were more with IV(8, 5 and 9 subjects, respectively) than oral(1, 0 and 2 subjects) midazolam, which was statistically significant (p value <0.05). F C Davies *et al* [8] in their study found that there were no adverse side effects except paradoxical hyperagitation in 3(6%) children receiving oral midazolam, which did not require any specific treatment. This was at par with studies by Charles J. Cote et al [17] and K.E. Wilson et al [21] where no significant side effects of oral midazolam were reported.

CONCLUSION

We concluded that the safety profile for oral midazolam is better than IV and hence it can be safely used as a procedural sedative in children. It provides reasonable sedation and/or amnesia for the majority of children with lesser adverse effects which is of immense importance, especially in peripheral pediatric practice where limited infrastructure is available for IV sedation.STRENGTHS OF OUR STUDY: It was a pioneering study in the field of use of oral midazolam as a procedural sedative in children. The randomization, stratification and a good sample size adds strength to our study design.

LIMITATIONS

Our study had a few limitations, but every effort was made to minimize their effects on the study outcome. We did not objectively measure the depth of sedation. Some researchers suggest the utility of bispectral index in PSA. Although early evidence is supportive, there is insufficient evidence to advocate its routine use in procedural sedation. [22] We could not 'blind' the intervention. Due to different routes of drug administration in both the groups, in practice, staff could simply observe the wide variability of response of subjects to midazolam.

IMPLICATIONS FOR RESEARCH

If we were to perform this study again, 1) we would explore the impact of oral midazolam on additional variables such as time to sedation and time to recovery. 2) We would use the oral midazolam syrup preparation. At the time of study oral preparation was not available commercially. We used the IV preparation, orally in this study.

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