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Comparative Study of Intravenous Midazolam and Intranasal Midazolam for Procedural Sedation in Children

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Abstract | **Original Research Article**

This study compared intranasal midazolam versus intravenous midazolam for procedural sedation in pediatric patients. It was a Prospective randomized study. Total 100 children between 1-12 years of age of either sex for various invasive and noninvasive procedures requiring sedation received either intravenous midazolam (0.2mg/kg) or intranasal midazolam (0.2mg/kg) with repeat dosing through same route (0.1mg/kg) if not sedated within 10 minutes. Time to sedation was significantly shorter in IVM group as compared to INM group [2.38 ± 0.96 min. vs 8.56 ± 1.75 min, p value <0.0001]. Duration of post procedure sedation, hypoxemia, respiratory depression, hypotension and vomiting had no statistical significance.

Keywords: Intravenous Midazolam, Intranasal Midazolam, Procedures, Sedation.

INTRODUCTION

Children frequently reveal significant distress during the invasive procedures even if effective analgesia and psychological support are provided, most of the times requiring effective sedation. It is in these circumstances that preprocedural sedation comes into play. 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 [1]. Benzodiazepines are commonly used for sedation and among them midazolam is the most commonly used drug. Midazolam can be administered through various routes such as oral, sublingual, per-rectal, intramuscular, intranasal and intravenous. Disadvantages of this route includes: The intramuscular and intravenous route are painful and children dislike the needle most. The rectal administration is associated with unpredictable absorption and discomfort to the child. Oral route has got low bioavailability due to high first pass metabolism and also bitter taste which is a limiting factor and it is a cause for rejection. In sublingual route, the drug must be held under the tongue for atleast thirty seconds**.** This requires co-operation and is difficult to achieve in children. Drugs administered to the nasal mucosa rapidly traverse through the cribriform plate into the central nervous system by three routes: (1) Directly by the olfactory neurons (2) Through supporting cells and the surrounding capillary bed and (3) Directly into the cerebrospinal fluid[2,3]. Along with avoidance of painful injection and ease of administration it is a convenient way to pre-medicate children. Therefore the current study was done to find out the efficacy of intranasal versus intravenous midazolam for the purpose of procedural sedation.

MATERIALS AND METHODS

Prospective, Single Blind, Randomized Controlled trial was conducted in Asian Institute of Medical Sciences, Faridabad, and Haryana from 1st August 2015 to 31st March 2017. Prior to procedure written informed consent was taken. Inclusion criteria were- all children between 1-12 years of age requiring sedation for procedures. Children who had rhinosinusitis, nasal polyp, past history of allergic reaction to midazolam, upper respiratory tract infection, hemodynamically unstable or unwilling for procedure under sedation were excluded from the study. Patients were divided in two groups of 50 children each. One group received intranasal midazolam at 0.2 mg/kg through nasal spray (dose divided equally and administered in each nostril) and second group received Intravenous midazolam at 0.2 mg/kg. If patient was not sedated within 10 minutes of administration of drug, repeat dose of 0.1 mg/kg was given by the same route. Time to sedation was noted from administration of the

first dose of drug till the patient was sedated. Ramsay Sedation Score (figure 1) was used and a score of 5 was taken as achievement of adequate sedation. Duration of post procedure sedation and any incidences of hypoxemia, respiratory depression, vomiting and hypotension were noted within 2 hours of procedure of till patient returned to baseline senosorium whichever was longer. Data collected was analyzed using unpaired t-test for quantitative variables and chi square test for qualitative variables.

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

Fig-1: Ramsay sedation score

RESULTS

The mean age in group Intranasal is 6.84 ± 3.28 years and in group intravenous is 5.84 ± 2.7. There were 46 children (46.00%) between 1-5 year age group, 42 children (42.00 %) between 6-10 year age group and 12 children (12.00%) between 10-12 year age group. P value was 0.157 -statistically insignificant. The sex distribution was 66 children (66.00%) were male and 34 (34.00%) female. P value was 0.091 -statistically insignificant. There were no significant differences found with regard to age and sex between the two groups.

Time to sedation in INM group was (8.56 ± 1.75) and in IVM group (2.38 ± 0.96). Time to sedation was shorter in IVM group (statistically significant - P value <0.0001) (Table 1). Duration of Post Procedure Sedation was 13.49 ± 1.15 in INM group and 13.73 ± 1.11in IVM group. P value 0.291(statistically not significant) (Table 2). No significant difference was observed in episodes of hypoxemia, respiratory depression, vomiting/nausea and hypotension (Table 3,4,5,6).

Table-1: Time to sedation in study groups

Time to sedation in minutes	**INM**	**IVM**	**P value**
Mean ± S.D.	8.56 ± 1.75	2.38 ± 0.96	<.0001

Time to sedation was significantly shorter in IVM group.

Table-2: Duration of Post procedure Sedation (Recovery time) in study groups

Duration Of Post Procedure Sedation in minutes	INM	IVM	P Value
Mean ± S.D	13.49 ± 1.15	13.73 ± 1.11	0.291

There was no significant difference in duration of post procedure sedation between two groups.

Table-3: Episodes of Hypoxemia in study groups

		Type of intervention		**Total**	**P value**
		INM	**IVM**		
Any episode of hypoxemia during procedure	NO	50 (100.00%)	49 (98.00%)	99 (99.00%)	1.00
	YES	0 (0.00%)	1 (2.00%)	1 (1.00%)	
Total		50 (100.00%)	50 (100.00%)	100 (100.00%)	

Table-4: Episodes of Respiratory Depression in study groups

		Type of intervention		Total	P value
		INM	IVM		
Any episodes of respiratory depression during procedure	NO	50 (100.00%)	49 (98.00%)	99 (99.00%)	1.000
	YES	0 (0.00%)	1 (2.00%)	1 (1.00%)	
Total		50 (100.00%)	50 (100.00%)	100 (100.00%)	

Table 5: Incidence of Nausea/Vomiting in Study groups

		Type of intervention		Total	P value
		INM	IVM		
Nausea/Vomiting after procedure up to 2 hours	NO	49 (98.00%)	48 (96.00%)	97 (97.00%)	1.000
	YES	1 (2.00%)	2 (4.00%)	3 (3.00%)	
Total		50 (100.00%)	50 (100.00%)	100 (100.00%)	

Table-6: Incidence of Hypotension in Study groups

		Type of intervention		Total
		INM	IVM	
Any episode of hypotension during procedure	NO	50 (100.00%)	50 (100.00%)	100 (100.00%)
Total		50 (100.00%)	50 (100.00%)	100 (100.00%)

DISCUSSION

Midazolam is a water soluble benzodiazepine with a more rapid onset and shorter duration of action. This drug is closer to the ideal than all others. The various modes of administration are intranasal, oral, per rectal, intravenous or intramuscular route. Oral route has high first pass metabolism, rectal route has erratic absorption, intramuscular injections and placement of intravenous cannula for intravenous route are painful. So the current study was undertaken to study the efficacy of Intranasal Midazolam versus Intravenous Midazolam for Procedural Sedation in Pediatric Patients.

A total of 100 patients aged between 1 year to 12 years of either sex were selected randomly and prospective study was done by dividing them into 2 groups. One group received intravenous midazolam and the second group received intranasal midazolam. The demographic parameters of the children in this study were comparable. There was no statistical difference ($p>0.05$) among the groups as regards age and sex.

Our study demonstrated that the time to sedation was longer with INM as compared to IVM. With intranasal midazolam time to sedation was 8.56 ± 1.75 and with intravenous midazolam was 2.38± 0.96 minutes with p value <.0001. Alex *et al.* [4] compared the efficacy of intranasal and oral Midazolam as a premedication in pediatric patients and found the mean time for onset of sedation was 8.63 ± 1.5 min for the intranasal midazolam group.

Trivedi *et al.* [5] who compared the effects of Intranasal Midazolam versus Sublingual Midazolam in pediatric patients undergoing MRI and found that the mean time for onset of sedation was 7.3 ± 0.8 min for the intranasal group.

Singh *et al.* [6] who in their prospective clinical trial evaluated the efficacy and adverse effects of IV midazolam as a sole agent for sedation in children for computed tomography (CT) imaging found mean time for onset of sedation was 4.75 ± 1.75 minutes.

Duration of post procedure sedation (Recovery time) was approximately the same in both groups. The difference was statistically insignificant. Trivedi *et al.* [5] showed no difference in the recovery score between those receiving intranasal midazolam and sublingual midazolam.

Respiratory Depression, Hypoxemia and Hypotension did not occur in any child in INM group in our study and is consistent with study done by Abhishek R *et al.* [7] who compared intranasal midazolam spray and oral midazolam syrup as premedication in pediatric patients and did not find any adverse events in their study.

In our study in IVM group hypotension did not occur in any child who is in accordance with the study done by Sievers TD *et al.* [8] who evaluated IV midazolam for conscious sedation during pediatric oncology procedures: safety and recovery parameters. In their study respiratory depression did not occur in any case and hypoxemia occured in 13% (n=9) as compared to 2% (n=1) in our study.

Nausea/Vomiting occured in 1 child in INM group and 2 in IVM group

In study done by Raval *et al.* [9] who compared oral and transnasal midazolam as a sedative pre-medication in pediatric patients no incidence of post-operative vomiting was observed in either group.

CONCLUSION

Midazolam through intranasal route provides safe, convenient and effective noninvasive method for procedural sedation in children; however time to achieve sedation was significantly faster through intravenous route.

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