

## ORIGINAL ARTICLE

### EVALUATION OF INTRANASAL MIDAZOLAM AS PREANAESTHETIC MEDICATION FOR BRIEF PAEDIATRIC SURGICAL PROCEDURES

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**ABSTRACT:** Intranasal midazolam has been used for premedication in children. To evaluate the efficacy of intranasal midazolam as premedication with regard to degree of sedation, ease of parental separation, response to venipuncture, response to induction, post anaesthesia recovery characteristics and side effects if any. 90 patients in the age group of 3-6 years of either sex belonging to ASA grade I and II posted for elective surgery under general anaesthesia were studied. The patients in group M<sub>1</sub> (midazolam) received 0.2 mg/kg of intranasal midazolam. The patients in group M<sub>2</sub> (midazolam) received 0.3 mg/kg of intranasal midazolam and patients in group NS (normal saline) received 0.04 ml/kg of normal saline. At 5 minutes after administration of the drug degree of sedation was assessed. The patients were followed up for 24 hours post operatively. In midazolam M<sub>1</sub> group, 24(80%) in M<sub>2</sub> group 22(65%) the children were satisfactorily sedated at 5 min after administration of the drug where as in normal saline group only 15(50%) were satisfactorily sedated. In midazolam M<sub>1</sub> group, at 10 minutes, parental separation in 27(90%) in M<sub>2</sub> group, parental separation in 25 (75%) children was much easier compared to 4 (13.3%) in NS group. Response to venipuncture was more satisfactory in both midazolam groups than normal saline. There was no undue prolongation of recovery time in all the groups. The study shows that intranasal midazolam 0.2 mg/kg administered 15 min prior to induction in Children of 3-6 years of age produces satisfactory level of sedation, ease of separation from parents, decreased discomfort associated with venipuncture with better mask acceptance.

**INTRODUCTION:** Surgery and Anaesthesia induce considerable emotional stress upon children.<sup>1</sup> The consequences of this stress remain in the child's psyche long after the hospital experience has passed.<sup>2,3</sup> Preoperative anxiety stimulates sympathetic, parasympathetic and endocrine system leading to an increase in heart rate, blood pressure and cardiac excitability. Children aged two to five years are especially vulnerable to this problem, since their understanding is limited.<sup>4</sup> Preoperative anxiety in unpremedicated children is twofold.<sup>5,6</sup> The premedicant should be pleasant, acceptable, rapid and reliable in onset with little adverse effects. Hence all pediatric patients need to be premedicated in order to decrease preoperative anxiety. Midazolam is a potent imdazobenzodiazepine which possesses typical benzodiazepine properties namely hypnotic, amnesic, anticonvulsant and anxiolytic activity. It is rapidly absorbed and short acting, having an elimination half-life of about 2 hours. Oral, rectal, intravenous, intramuscular and sublingual routes for premedication have been tried. Owing to its high mucosal vascularity, pre-anaesthetic medication administered nasally has rapid and reliable onset of action. Avoidance of painful injection, ease of administration has made it a convenient way to pre-medicate children. This study was designed to evaluate the efficacy of intranasal midazolam in children as pre-medication with two different doses in comparison with a placebo.

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**OBJECTIVES OF THE STUDY:** This study was designed to evaluate the following effects after intranasal midazolam.

1. Degree of sedation.
2. Ease of separation from parents.
3. Response to venipuncture.
4. Response to Induction/Mask placement.
5. Post anaesthesia recovery characteristics.
6. Side effects.

## **MATERIALS AND METHOD:**

### **Inclusion Criteria:**

- Patients aged between 3-6 years.
- Patients of either sex.
- Patients with ASA Grade I & II

Group NS: Children received 0.04 ml/kg of Normal Saline.

Group M1: Children received 0.2mg/kg of intranasal midazolam.

Group M2: Children received 0.3mg/kg of intranasal midazolam.

**METHOD OF PREMEDICATION:** All routine investigations were done. No sedative premedication ordered on the day prior to surgery. Parents were also instructed to keep the children fasting for 6-8 hours depending on the age. All the resuscitation and monitoring equipment were kept ready before administration of pre-medication, for management of any adverse reactions. On the morning of surgery, Children were shifted along with one of the parents to the Preop holding room. Baseline HR, RR, SpO<sub>2</sub>, BP was recorded. With the children sitting on the parent's lap, the Saline/ drug administered by the anaesthesiologist with the help of a atomizer avoiding wastage through anterior and posterior nostril. The concentration was 5mg/ml, INSED atomizer], 0.5 mg/metered dose, given equally in both nostrils.

At 5 minutes after administration of the drug/ Saline the degree of sedation (Table no. 1), HR, RR, SpO<sub>2</sub>, NIBP were noted.

At 10 minutes, children were separated from the parents & shifted to the operation theatre. Reaction to separation from parents was assessed (Table no. 2). IV Cannulation attempted & reaction to venipuncture recorded.

At 15 minutes, general anaesthesia was induced using N<sub>2</sub>O, oxygen, halothane & response to mask placement assessed & recorded. Children shifted to PACU after confirmation of adequate clinical recovery. Closed observation on a ten point scale using the following parameters- colour, airway, respiration, level of consciousness and movement of all the 4 limbs was done for respiratory depression. Postoperative recovery score was assessed at 10, 20, 30 minute on a ten point scale using the following parameters- colour, airway, respiration, level of consciousness and movement of all the 4 limbs

Post operatively all the children were followed up for 24 hours for side effects & complication if any were noted.

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## Side Effects due to Intra-nasal Midazolam:

1. Watering of eyes.
2. Bad taste.
3. Nasal congestion/Nasopharyngeal irritation.
4. Blurred vision. (Older children who could explain).
5. Nausea.
6. Vomiting.

<b>Sedation scale</b>	<b>Criteria</b>	<b>Score</b>
Agitated	Patient clinging to parent and/or crying	1
Alert	Patients is aware but not clinging to parent, may whimper but not cry	2
Calm	Sitting or lying comfortably with spontaneous eye opening	3
Drowsy	Sitting or lying comfortably with eyes closed but responding to minor stimuli	4
Asleep	Eyes closed, arousable but does not respond to minor stimulation	5

Table 1: Grades of Sedation at 5 minutes

<b>Behaviour of the child during separation from parents</b>	<b>Criteria</b>	<b>Score</b>
Excellent	Patient unafraid, Cooperative or asleep	1
Good	Slight fear/crying, quite with reassurance	2
Fair	Moderate fear and crying not quiet with reassurance	3
Poor	Crying, need for restraint	4

Table 2: Parental separation score at 10 minutes

<b>Reaction to venipuncture</b>	<b>Criteria</b>
Satisfactory demeanour	If the child showed no response or winced or whimpered
Unsatisfactory demeanour	If the child cried or behaved in violent manner

Table 3: Response to venepuncture

<b>Behaviour of the child during mask placement</b>	<b>Criteria</b>	<b>Score</b>
Agitated	Refuses mask	1
Alert	Initially refuses mask, but accepts after persuasion	2

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Calm	Mask accepted with level 3 of sedation	3
Drowsy	Mask accepted with level 4 of sedation	4
Asleep	Mask accepted with level 5 of sedation	5

**Table 4: Mask placement/Induction score**

Recovery Score	Criteria	Score
Color	Cyanotic	0
	Pale, Dusky, Blotchy, others	1
	Pink	2
Airway	Total obstruction	0
	Partial obstruction	1
	No obstruction	2
Respiration	Apnoeic	0
	Dyspnea or limited breathing	1
	Able to breathe deeply and cough freely	2
Level of consciousness	Non responsive to stimuli	0
	Responsive to stimuli	1
	Awake	2
Movement	Able to move no extremities voluntarily or on command	0
	Able to move 2 extremities voluntarily or on command	1
	Able to move 4 extremities voluntarily or on command	2

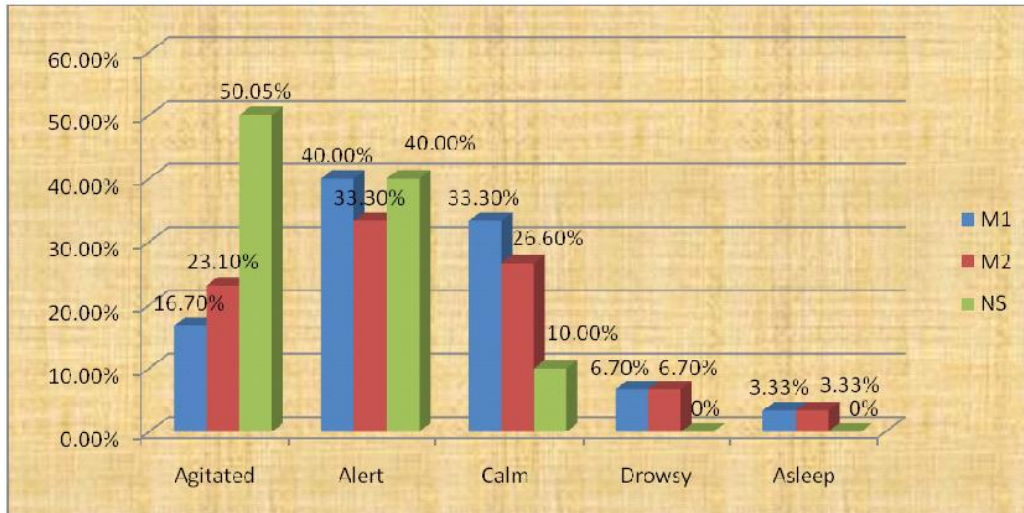
**Table 5: Post Anaesthesia recovery characteristics**

### RESULTS AND OBSERVATIONS:

**Study Design:** The study was undertaken to evaluate the efficacy of intranasal midazolam as premedication.

Group	No of patients	Drug administered
M1	30	received 0.2mg/kg of intranasal midazolam
M2	30	received 0.3mg/kg of intranasal midazolam
NS	30	received 0.04 ml/kg of Normal Saline

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**SEDATION LEVEL AT 5 MIN AFTER PREMEDICATION**

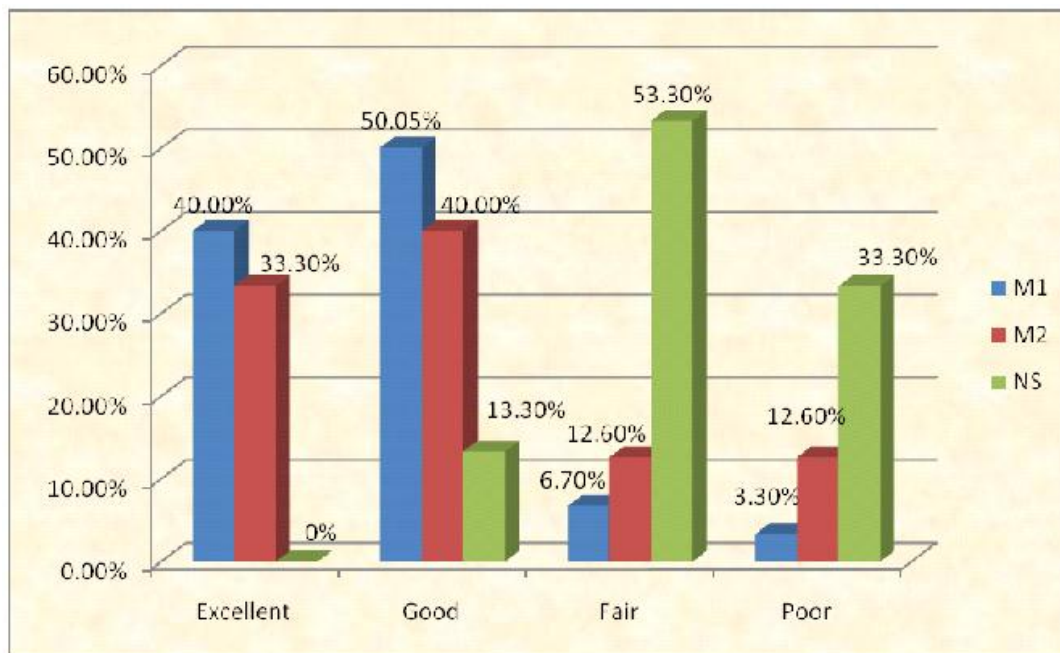
Comparing the Sedation Score in M1 group, majority 25 (83.3%) of the children were adequately sedated (ie. alert, calm, drowsy, asleep) in M2 group, majority 21 (70%) of the children were adequately sedated. Normal Saline group, majority 15 (50%) of the children remain agitated.

P value obtained was;

M1 – NS 0.019 ( $< 0.05$ ); found to be statistically highly significant.

M2 – NS 0.045 ( $P < 0.05$ ); found to be statistically significant.

M1 - M2 0.9551 ( $P > 0.05$ ); found to be statistically not significant.



**RESPONSE TO SEPARATION FROM PARENTS AT 10 MINUTES**



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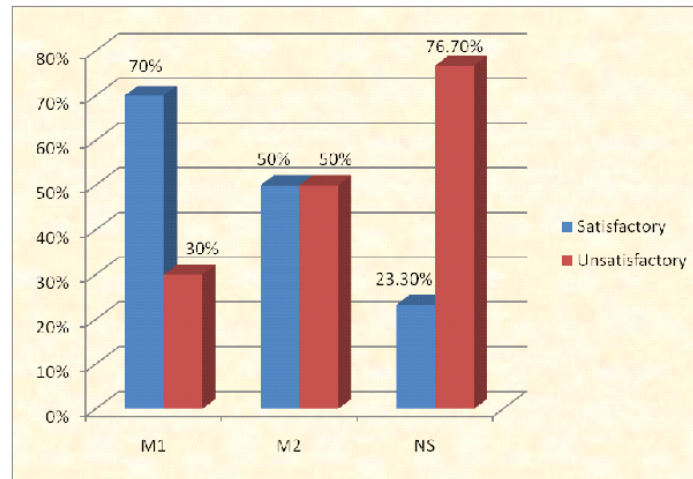
The M1 27(90%) & M2 22(73.33%) Children were separated easily from Parents (grading being excellent & good) whereas in Normal Saline group, 26(86.6%) children separation was not satisfactory (grading being fair & poor).

P value obtained was;

M1 – NS < 0.001 (P < 0.05); found to be statistically very highly significant.

M2 – NS 0.001 (P < 0.05); found to be statistically very highly significant.

M1 - M2 0.3943 (P > 0.05); found to be statistically not significant.



**Response to Venepuncture**

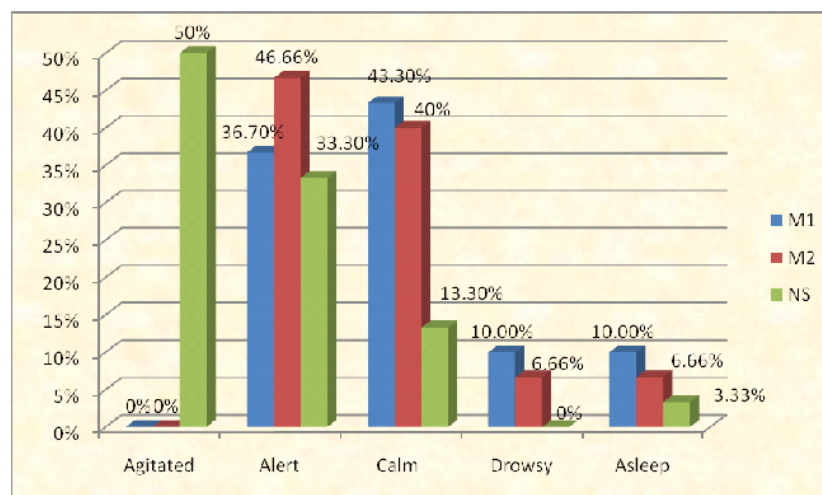
The M1 group, 21(70%), M2 group 15 (50%) and Normal Saline group, only 7(23.3%) children responded satisfactorily. In M1 group, only 9(30%), M2 group 15 (50%) and Normal Saline 23(76.7%) children response was unsatisfactory.

P value obtained was;

M1 – NS < 0.001 (<0.05); found to be statistically very highly significant.

M2 – NS 0.032 (P > 0.05); found to be statistically significant.

M1 - M2 0.1138 (P > 0.05); found to be statistically not significant.



**Response to Mask placement at 15 minutes**

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In both Midazolam groups, there was a favourable response to mask placement in 30 (100%) of the children (grading being alert, calm, drowsy, asleep) & none of them were agitated. In Normal Saline group, only 15 (50%) of them showed a favourable response & the remaining 15 (50%) were agitated.

P value obtained was;

M1 – NS <0.001 (P <0.05); found to be statistically very highly significant.

M2 – NS <0.001 (P <0.05); found to be statistically very highly significant.

M1 - M2 0.7754 (P >0.05); found to be statistically not significant.

Group	Scores				
	6	7	8	9	10
M1	0	16	12	2	0
M2	0	12	10	4	0
NS	0	5	22	3	0

Post anaesthesia recovery score at 10 minutes

Group	Scores				
	6	7	8	9	10
M1	0	0	10	12	8
M2	0	0	11	11	8
NS	0	0	0	12	18

Post anaesthesia recovery score at 20 mins

Group	Scores				
	6	7	8	9	10
M1	0	0	0	0	30
M2	0	0	0	0	30
NS	0	0	0	0	30

Post anaesthesia recovery score at 30 mins

**DISCUSSION:** Premedication in addition to allaying the anxieties of surgery, parental separation, and pain allow smoother and safer induction of anaesthesia. Midazolam is a water soluble benzodiazepine with a more rapid onset and shorter duration of action.

The present study is a randomized prospective study in 90 patients belonging to the age group of 3 to 6 years of either sex and of ASA grade I and II who were scheduled to undergo elective surgical procedures.

Group M1 children received 0.2 mg/kg preservative free midazolam intranasally.

Group M2 children received 0.3 mg/kg preservative free midazolam intranasally.

Group NS children received 0.04 ml/kg of normal saline intranasally.

Children received either of this drug, 15 minutes prior to surgery. Results of the present study are discussed under the following headings.

1. Sedation.
2. Ease of separation from the parents.
3. Response to venepuncture.
4. Ease of induction/mask placement.
5. Post anaesthesia recovery characteristics.

**SEDATION:** At the end of 5 minutes after premedication, Groups M1 and M2 majority of children 25(83.3%) and 21(70%) respectively had satisfactory higher level of sedation (Sedation level 2, 3, 4, 5) and only 5(16.7%) in M1 and 9(30%) in M2 were agitated whereas in NS group 15 (50%) were agitated, and the remaining 15(50%) had lower level of sedation (sedation level 2,3,4,5) with p value being 0.019 between M1 and NS; 0.045 between M2 and NS which are statistically significant.

Manjushree Roy et al. compared 2 doses of intranasal Midazolam with that of NS and concluded that majority of the children in Midazolam group had significant level sedation at 5 minutes with 0.2mg/kg and delayed onset of sedation at 10 minutes with 0.3mg/kg.<sup>8</sup>

Weber et al. studied the effect of Midazolam in 3 groups of patients. One group received 0.2mg/kg of Intranasal Midazolam and other two groups received 0.2mg/kg Midazolam with 2 different doses of Ketamine. The sedation score improved at 5 minutes after premedication in Midazolam group with p value 0.03.<sup>9</sup>

Wilton et al. administered 2 doses of Midazolam 0.2mg/kg and 0.3mg/kg and compared with the placebo and he concluded that the significant level of sedation occurred in the lower dose Midazolam group from 5minutes after administration. And in the high dose 0.3 mg/kg from 10 minutes after administration. 60 % of the children were agitated in the NS as compared to only 3% in the Midazolam group.<sup>10</sup>

From the present study it is observed that intranasal Midazolam 0.2 mg/kg produces significant level of sedation at 5 minutes after administration.

**Ease of Parental Separation:** At 10 minutes after administration of the drug, M1 27(90%) & M2 22(73.33%) Children were separated easily from Parents. M1 3(10%), in M2 8(26.6%) patients it was poor to fair. Whereas in the NS group only 4 (13.3%) children were good and the rest 26 (86.6%) were poor to fair with p value <0.001 which is very highly significant.

Karl et al. Administered midazolam (0.2mg/kg) in 2 different routes (sublingual and intranasal) in 93 patient aged 0.5to 10 years. Children in intranasal group showed decreased anxiety in response to the stress of separation, compared to sublingual group (p 0.01) at 11 minutes.<sup>11</sup>

Wilton et al. in 1998, administered 2 doses of intranasal midazolam 0.2 and 0.3mg/kg and compared with the placebo (saline). It was observed that parental separation was easy in both the doses of intranasal midazolam at 10 minutes after administration of the premedication.<sup>10</sup>

**Response to Venepuncture:** In M1 group 21 (70%) showed satisfactory response to venepuncture and the remaining 9(30%) showed unsatisfactory response. In M2 group 15 (50%) children responded satisfactorily to venepuncture and the remaining 15(50%) children showed



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unsatisfactory response. In NS group 7(23.3%) children showed satisfactory response, the remaining 23(76.7%) showed unsatisfactory response, with p value of 0.001, which is statistically, very highly significant between M1- NS groups. P value of 0.032, which is statistically, significant between M2- NS groups.

Asif Pervez kazerni Ct al. conducted a study on 130 children (2-5years) and compared intranasal Midazolam 0.2mg/kg Ketamine 5mg/kg, with NS as a placebo, the response of the child to intravenous canulation was good in both Midazolam and Ketamine group.

J. M. Malinovsky Ct al in 1995 observed higher mean plasma midazolam concentration (146 nanogm I ml) measured at 11.8 minutes following intranasal midazolam administration, in a dose of 0.2mg/kg compared to oral and rectal route. This has been explained as the reason for satisfactory demeanour during venepuncture.<sup>12</sup>

**Ease of Induction:** At 15minutes after premedication, the ease of induction in terms of mask acceptance was observed. In both midazolam groups all the 60 (100%) children had satisfactory response to mask placement whereas in NS group 15 (50%) were agitated and the remaining 15 (50%) showed satisfactory response to mask placement. The p value was <0.001 which is statistically very highly significant.

Davis et al. compared 2 doses of intranasal midazolam (0.2 & 0.3 mg/kg) with saline as placebo in 88 patients and concluded that the patients receiving midazolam had better induction scores than the patients who received NS.<sup>13</sup>

Wilton et al. also compared 2 doses of intranasal midazolam (0.2 & 0.3 mg/ kg) with saline (0.2ml/5kg) in 45children (18 months to 5 years). 60% of the patients who received NS were agitated during induction whereas only 3% of those receiving midazolam.<sup>10</sup>

Manju Shree Roy et al. compared 2 doses (0.2 and 0.3 mg/kg) of intranasal midazolam with NS and observed that majority of the patients had accepted the mask in midazolam groups. One patient in the dose of 0.2 mg/kg was found to be in grade 5of sedation i.e., asleep.<sup>8</sup>

**Post anesthesia recovery characteristics:** Children were considered fit for discharge from PACU, at a score of 10; that is When the children were conscious, colour pink, no obstruction in the airway, able to breathe deeply and cough freely, able to move 4 limbs freely, SpO<sub>2</sub>> 98% on room air.

At 30 minutes all the children in both the groups had a score of 10 and were fit for discharge to the wards.

No significant changes were observed in NIBP, Heart rate during this period.

All the children were followed up for a period of 24 hours.

Wilton et al. concluded that there was no difference in the recovery room score between those patients receiving normal saline and those receiving midazolam.<sup>10</sup>

Manjushree Roy et al found that there was no evidence of delayed recovery in two doses of midazolam. Post-operative recovery room score was comparable in normal saline and 2 doses of midazolam.<sup>8</sup>

**Side Effects:** In the present study in M1 group only 3 had developed side effects, in M2 group 8 had developed side effects. No side effects were observed in the saline group. The side effects observed in midazolam group are:

1. Nasal congestion.
2. Nasopharyngeal irritation
3. Bad taste.
4. Daniel P. Wermeling observed eyes watering, dizziness, bad taste, nasal congestion, nasopharyngeal irritation in the intranasal route.<sup>14</sup>

**CONCLUSION:** Administration of preservative free intranasal midazolam in the dose of 0.2 mg/kg as premedication in paediatric patients produces satisfactory sedation.

**Advantages are;**

1. Better sedation and rapid onset of action.
2. Ease of separation from parents.
3. Decreased discomfort associated with IV cannulation.
4. Better mask acceptance.
5. Recovery time not prolonged
6. Minimal side effects.

After considering all the parameters from this study it is concluded that intranasal midazolam 0.2 mg/kg as premedication provides effective sedation in paediatric patients of 3 -6 yrs without any untoward side effects. No nausea and vomiting as seen in the oral group.

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