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A Comparative Study On The Efficacy Of Intranasal Midazolam And Oral Midazolam As Premedicants In Preschool Children Undergoing Day Care Surgeries

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Abstract:
Background: *The goal of premedication is to make the child calm and cooperative. Midazolam has an important place in premedicants due to short duration of action, powerful anterograde amnesic effect.*
Aim*: We undertook this study to compare the efficacy of intranasal midazolam and oral midazolam in children as premedicant.*
Settings and Design: *The study was conducted in prospective, double blind manner.*
Materials and Methods: *Sixty patients belonging to ASA physical status I and II within the age group of 6 months to 6 years, scheduled for day care surgeries were randomly divided into intranasal and oral groups with 30 patients in each group. Patients in intranasal group received nasal Midazolam 0.3 mg/kg, oral placebo and in oral group received oral Midazolam 0.5 mg/kg, nasal placebo 30 minutes before parental separation. Both the groups were observed and compared for Wilton's five point sedation score, four point separation score, ease application of face mask, Mean time of onset of satisfactory sedation.*
Results: *In age and weight both the groups were comparable. Mean sedation, separation scores at 5min, 10min, and 15min, were highly significant in intranasal group than oral group with the P value of 0.000. Mean time of onset of satisfactory sedation for intranasal group was (9.675 min) highly significant in comparison to oral group (17.283min) as the P value was 0.000(P<0.05).*
Conclusion: *From our study, we conclude that intranasal route is superior to oral route for midazolam administration in paediatric day care surgeries because of early onset of action without any complications.*
Keywords: *Premedication, Midazolam, Intranasal, Oral, Sedation and separation score.*

I. Introduction

Surgery and anaesthesia induce considerable emotional stress, especially in children. Preoperative anxiety stimulates sympathetic, parasympathetic and endocrine system leading to an increase in heart rate, blood pressure and cardiac excitability [1]. Preoperative anxiety in children can lead to postoperative maladaptive behaviors in the form of eating problems, bad dreams, enuresis, temper tantrums, increased fear of doctors and hospitals[2]. Hence, all pediatric patients need to be pre-medicated in order to decrease preoperative anxiety.

The preoperative interventions directed towards reduction of anxiety are grouped into non-pharmacological and pharmacological methods. Non-pharmacological means in the form of friendly visit by the anesthesiologist to establish rapport with the child helps to minimize the child's anxiety. Even parenteral presence inside the operation theatre may not be fully effective [2]. However, the reliability of these is unknown. Sedative premedication are more effective in this regard.

Numerous premedicants have been advocated to facilitate the separation of children from their parents and to reduce the anxiety associated with unfamiliar persons and the strange operating room environment. However, an ideal premedicant should serve all the goals of premedication like allay anxiety, provide analgesia, amnesia, sedation, good parent and patient acceptance, with predictable results, easy to administer, ensure smooth induction, with minimal or no side effects[3].

Many drugs have been tried for premedication in children. Opioid premedication can result in unpleasant dysphoria and increased incidence of preoperative and post operative vomiting. They also produce significant respiratory depression [4]. Nausea, vomiting and pruritus limit the usefulness of Fentanyl as preoperative sedation [5]. Hypoxemia and decreased chest wall compliance are the complications with sufentanil. Ketamine is most likely to prolong recovery and delay discharge from post anaesthesia room. Dexmeditomidine time of onset is high. Some children may become distressed with Dexmeditomidine when they were aroused because of the property of conscious sedation and easy arousability.

Benzodiazepines are the most commonly used sedative – hypnotic drugs and also they have anxiolytic, anticonvulsant and anaesthetic properties. Among Benzodiazepines, Midazolam, a short acting drug has

occupied an important place in anaesthetic practice due to certain unique advantages like high water solubility and high lipophilic nature at physiological pH, short duration of action, powerful anterograde amnesic effect, anxiolytic effect and reduction of adrenergic response to surgical stress. Midazolam is 2 – 3 times more potent than Diazepam.

The aim of this study is to evaluate and compare the efficacy of Midazolam by two different routes – Oral and Intra nasal as premedicants in preschool children in alleviating anxiety and fear and to produce sedation while undergoing day care surgeries.

II. Materials And Methods

This is a prospective, randomized, double blinded study undertaken in GSL Medical College, Rajahmundry after obtaining the Institutional Ethical Committee approval. Informed parent consent was taken. Sixty pediatric patients belonging to ASA (American Society of Anaesthesiologists) physical status I and II within the age group of 6 months to 6 years, scheduled for day care surgeries were included in the study. The randomization list was generated by an independent statistician who was not involved in data collection or analysis

The exclusion criteria were age more than 6 years, known allergy to midazolam or upper respiratory tract infection, patients with a history of developmental delay, hepatic and renal disease. Disorders of gastrointestinal system that affect the drug absorption, otorhinolaryngeal diseases such as nasal polyp, rhinitis, nasal pathology or nasal trauma and patients taking cytochromeP-450 3A4 inhibitors or inducers were excluded from the study.

Intra nasal group Patients received intranasal Midazolam 0.3 mg/kg, 10ml of sugar syrup 30 minutes before parental separation. Oral group Patients received oral Midazolam 0.5 mg/kg mixed in sugar syrup made to 10ml, nasal saline spray 30 minutes before parental separation. Drugs were administered by an independent anaesthesiologist not involved in the study. Anesthesiologist making the observations was blinded

All children are allowed to take clear fluids up to 2 hours before surgery.

In both the groups, the following data was recorded and compared

1. Sedation score – Wilton's five point sedation score.
2. Ease of separation from parents – four point separation score.
3. Ease of application of facemask – four point score.
4. Time of onset satisfactory sedation .Time at which sedation score $\geq$3 and separation score < 3 was achieved is considered as time of onset of satisfactory sedation.

Sedation score and separation scores were noted before administration of midazolam (baseline), 5min, 10min, 15min, 20min, 30min and were compared between two groups. Baseline measurements of Heart rate, respiratory rate and SpO_2 were taken and monitored from the time of administration of drug to general anaesthesia every 5 min.

Table no 1 Wilton's five – point sedation scale

Score	Sedation level	Child untouched
1	Agitated	Child clinging to parents and / or crying.
2	Alert	Child is awake may whimper, not crying
3	Calm	Child is sitting / lying comfortably eyes open
4	Drowsy	Child is lying comfortably with eyes closed, responds to minor stimulus
5	Asleep	Eyes closed, no response to minor stimulus

Table no:-2 Four point Separation Scale

Score	Findings during separation	
1	Patient unafraid, cooperative, asleep	Excellent
2	Slight fear or crying, quite with reassurance	Good
3	Moderate fear, crying not quite with reassurance	Fair
4	Crying, need for restraint	Poor

Table no:-3 Four point scale to assess mask acceptance

Score	Mask acceptance level
4	Very good, immediate acceptance
3	Good, slight resistance
2	Moderate, struggle against mask
1	Difficult ,moderate physical restrain necessary

After receiving the patient at pre-anaesthesia room, the patients were induced using the technique described above. Patients were induced with oxygen (O_2) (50%), nitrous oxide (N_2O) (50%) and Sevoflurane (8%) by facemask and intravenous line was secured. Response to mask placement was assessed by using four point scale. Sevoflurane was then discontinued.

Statistical analysis was done using SPSS (Statistical package for the social sciences) 21 software. Data was presented as either mean and standard deviation or numbers. Student T-test was used to compare the study groups. Chi-square test was used to analyze the categorical data and for testing the association between the variables. The p value of<0.05 was considered statistically significant.

III. Results

A total of 60 patients, 30 patients randomly assigned to each group, were included in the study. The mean age for the intranasal group was 3.26 years and for the oral group was 3.17 years (p value 0.818). There was equal distribution of male and females in both groups including 19 males and 11 females (p value 1). The mean weight in intranasal group was 11.03 kilograms and oral group was 9.96 kilograms (p value 0.327).

Table no:-4 Mean ages (yrs) in both groups

Group	N	Mean	Std.Deviation	P Value
Intranasal	30	3.263	1.5917	
Oral	30	3.173	1.4234	0.818

Table no:-5 Mean weight (kilograms) in both groups

Group	N	Mean	Std.Deviation	P Value
Intra nasal	30	11.033	4.3429	
Oral	30	9.967	4.0020	0.327

In nasal midazolam group 26 children were in ASA I and 4 children were ASA II. In oral midazolam group 25 children were ASA I and 5 children were in ASA II. In both the groups surgeries such as herniotomy, circumcision, high ligation, L.N. biopsy, lip & palate repair, laceration repair were done in nearly equal number. The above parameters compared and evaluated and were found to be non-significant statistically based on their p value.

The sedation scores were measured at baseline, 5 min, 10 min, 15 min, 20 min and 30 min. The mean scores in the intranasal group were 1.13, 2.23, 2.96, 4.13, 4.63 and 4.56 respectively, while in the oral group were 1.13, 1.2, 1.46, 2.4, 3.93 and 4.53 respectively. The values in both the groups were compared and the values at 5 min, 10 min, 15 min and 20 min showed significant difference in intranasal compared to oral group (p<0.05). The values at baseline and at 30 min post administration of the drug were not significant.

Table no:-6 Mean sedation score in both the groups

Sedation score	Group	Mean	Std. Deviation	P value
Base line	Intra nasal	1.133	0.3457	
	oral	1.133	0.3457	1.00
5 min	Intra nasal	2.233	0.7739	0.000
	oral	1.200	0.4068	
10 min	Intra nasal	2.967	0.7649	0.000
	oral	1.467	0.5074	
15 min	Intra nasal	4.133	0.6288	0.000
	oral	2.400	0.6215	
20 min	Intra nasal	4.633	0.4901	0.000
	oral	3.933	0.7849	
30 min	Intra nasal	4.567	0.5683	0.811
	oral	4.533	0.5074	

The mean separation scores in the intranasal groups were 3.86, 3.36, 2.33, 1.66, 1.23, 1.3 and the mean separation scores in the oral group were 3.9, 3.87, 3.63, 3.23, 1.66 and 1.36 at 5 min, 10 min, 15 min, 20 min and 30 min respectively. Mean separation score at baseline and 30 min shows no significant difference between intranasal and oral group. Mean separation score at 5 min, 10 min, 15 min and 20 min shows significant difference in intranasal compared to oral group as the P value is 0.000 (P<0.05).

Table no:-7 Mean separation score in both the groups

Separation score	Group	Mean	Std.Deviation	P value
baseline	Intra nasal	3.867	0.3457	0.694
	oral	3.900	0.3051	
5min	Intranasal	3.367	0.4901	0.000
	oral	3.867	0.3457	
10min	Intranasal	2.333	0.4795	0.000
	oral	3.633	0.4901	
15min	Intranasal	1.667	0.4795	0.000
	oral	3.233	0.6261	
20min	Intranasal	1.233	0.4302	0.001
	oral	1.667	0.4795	

30min	Intranasal oral	1.300 1.367	0.4661 0.4901	0.591

Mean time of onset of satisfactory sedation in intra nasal group (9.67 min), was highly significant compared to oral group (17.28 min) as the P value was 0.000(P<0.05). Mask acceptance score for intranasal group (3.633), was not statistically significant compared to oral group (3.6) as the P value was 0.827. Mean heart rate, mean respiratory rate, mean SpO_2 at the time of separation were not showing any significant difference as the P values were >0.05.

Table no:-8 Mean time of onset of satisfactory sedation.

Group	N	Mean	Std.Deviation	P Value
Intranasal	30	9.6750	1.17655	
Oral	30	17.2833	1.43649	0.000

Table no:-9 Mean mask acceptance score

Group	N	Mean	Std.Deviation	P Value
Intra nasal	30	3.633	0.5561	
Oral	30	3.600	0.6215	0.827

IV. Discussion

The outcome of any anesthetic is determined by how well prepared the anaesthesiologist is to handle that particular patient. Preoperative anxiety is operationally defined as subjective feeling of tension, apprehension, nervousness, worry and vigilance associated with increased autonomic nervous system activity. Younger children are more concerned about separation from parents and older children are more anxious about the anesthetic and surgical process. Children are threatened by anticipated parental separation, pain or discomfort. All these factors are likely to prolong the induction of anaesthesia. Therefore premedication in addition to allaying the anxieties of surgery, parental separation and pain, allow smoother and safer induction of anaesthesia.

The commonly used premedicants are benzodiazepines, Ketamine, Dexmeditomidine and Fentanyl. Because of the disadvantages with other premedicants, benzodiazepines are commonly used. Midazolam is a water soluble benzodiazepine with a more rapid onset and shorter duration of action. This drug is closer to the ideal than others. The various modes of administration are intranasal, oral, rectal, intravenous and intramuscular route. Intranasal route appears to be better because of high vascularity and offers rapid and complete absorption into the systemic circulation. Previous studies have shown that intranasal administration is an effective way to administer premedication and sedation [6-8]. The early onset of sedation and better sedation, separation scores in intra nasal group were due to rapid and near complete absorption of the drug owing to rich blood supply of the nasal mucosa and nose brain pathway through the olfactory mucosa into the CSF. As midazolam has high hepatic clearance, and transnasal route avoids fist pass hepatic metabolism, a greater systemic bioavailability can be achieved [9].

V. Conclusion

Both the routes were equally effective when compared at 30min after drug administration. But onset of action was faster in intra nasal group. Better sedation and separation scores were achieved faster with intra nasal route than with oral route from our study we conclude that Intra nasal route is superior to oral route for midazolam administration in paediatric day care surgeries because of early onset of action without any complications.

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