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Research Article

MIDAZOLAM AS INTRANASAL SPRAY IN PAEDIATRIC SURGICAL PATIENTS

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ABSTRACT

Since introduction of intranasal midazolam, its use in pediatric population as premedication has expanded in scope and volume. This study proposes to test efficacy of intranasal midazolam spray as premedication in pediatric surgical patients. A prospective, randomized double blinded placebo controlled comparative study undertaken in 60 children aged 6 months to 6 years of ASA 1 & 2, undergoing surgery of duration <45 minutes for the first time with general anaesthesia, allocated equally into two groups, group M receiving midazolam intranasal spray (0.5% @ 0.2mg/kg) as premedication and group P receiving placebo with normal saline intranasal instillation. Efficacy was judged by child's emotional state during-parental separation, shifting to operating table, intravenous cannulation and application of face mask using emotion state scale and sedation by ramsay sedation score. Safety was assessed by occurrence of complications preoperatively and any significant adverse effects. Satisfactory sedation (Mean±SD=1.47±0.507) was obtained and comparison of child's emotion state between the groups during intravenous cannula insertion (1.77±0.430/3.47±0.730), patient shifting (1.47±0.507/1.47±0.507), face mask induction (1.30±0.466/3.27±0.944) were statistically significant. Induction time was significantly reduced in group m (25.17±9.513) to p (54.33±8.483). Induction of anesthesia was also easier and faster in them. No child suffered from any cardiorespiratory complications. Intranasal midazolam spray appears to be a near ideal premedicant having significant sedative and anxiolytic properties with no significant effect on hemodynamics and respiratory physiology. It also affects induction time thereby reducing the requirement of inhalational agents and is associated with no significant side effects.

Keywords: *Child, Premedication, General Anaesthesia, Anxiety, Intranasal, Midazolam*

INTRODUCTION

An apprehensive, crying and non cooperative child is a common sight in the operation theatre. Effective preanesthetic medication in children should allay apprehension regarding anesthesia and surgery, lessen trauma of parental separation, and facilitate the induction of general anesthesia without prolonging the post anesthetic recovery period.

In the current times midazolam has emerged as a near ideal premedicant, possessing sedative and anxiolytic properties with minimal respiratory depression.

The usual routes are oral, intravenous, intramuscular, subcutaneous, rectal, and sublingual over which till date oral route has been preferred in pediatric population. Intranasal administration of midazolam and sufentanil has been investigated advantages being rapid and virtually complete absorption due to high mucosal vascularity (Karl, 1992).

The purpose of the present study was to test the efficacy of intranasal midazolam as premedication in pediatric patients in the form of nasal spray, undergoing surgery for the first time assessing its effects on sedation, emotional state, hemodynamics, respiration and adverse effects if any.

MATERIALS AND METHODS

A prospective, randomized double blinded placebo controlled comparative study undertaken in 60 patients, with due approval of local ethical committee (Dean No/2009-10/800) after obtaining informed consent.

Children of both sex aged 6 months to 6 years of ASA 1 & 2, undergoing surgery for the first time of duration <45 minutes, receiving no anxiolytics or sedatives were included.

Children with neurological or psychiatric illness, upper respiratory tract infection, nasal obstruction (mass), epistaxis, nasal congestion, and sinusitis or with any history of benzodiazepine sensitivity were excluded.

These 60 children were then randomly allocated equally into two groups, one receiving midazolam intranasal spray 0.5% solution at doses 0.2mg/kg as premedication (group M) and other placebo with normal saline intranasal instillation administered randomly by personnel uninvolved in the study.

The containers was adequately covered and administered randomly by a personnel not involved in the study. Randomization was carried out by computer generated list of random numbers. After explaining fasting protocols, procedural hazards and obtaining child's actual body weight, a detailed preoperative assessment was done.

On the day of surgery routine monitoring like heart rate, pulse oximetry and respiratory rates were recorded with initial baseline readings. The drug or the placebo was administered, following which heart rate, oxygen saturation, respiratory rate, preoperative sedation assessed by Ramsay sedation score (Ramsay 1974) were recorded at 1 min and every 5 minutes till 30 minutes.

Emotion state of the child was recorded during administration by an Emotion State Scale, further during parental separation at 30 minutes, shifting the child to the operating table, insertion of intravenous cannula (one attempt before induction) and placement of face mask for inhalational induction with 60% nitrous oxide in oxygen and incremental halothane inhalation.

The child's acceptance to mask and induction time (time interval between face mask application and loss of eyelash reflex) and any signs of apnea were observed. Before administration, the containers were properly checked for the adequacy of function.

Airway was secured with LMA and child kept on spontaneous ventilation. Throughout, halothane concentration was maintained at minimum level which avoided light anesthesia.

Each child received intraoperatively intravenous Fentanyl 1 μgm/kg during induction and intravenous Paracetamol (10mg/kg) for postoperative analgesia. Halothane was stopped approximately 5 minutes before the end of surgery. Following completion of the surgery, LMA was removed after adequate suctioning.

The children were followed up for 1 hour from the point of stoppage of halothane. Any need for airway support, episodes of nausea and vomiting, complaints of any nasal irritation with its intensity were observed along with any other side effects.

Various parameters studied were compared using student's paired 't' test, for parametric variables and Chi-square test for non-parametric variables. The critical 'p' value was taken as <0.05 for comparison.

RESULTS AND DISCUSSION

Results

Both the groups were similar in age, sex, ASA grading, weight, duration of surgery (table 1).

Table 1: Distribution of age, sex, ASA grading, body weight, mean duration of surgery and their statistical significance

Patient parameters	Group M (midazolam intranasal spray-0.2mg/kg) n=30	Group P (normal saline intranasal instillation) n=30
Age (months) (Mean ±SD)	40.43±22.24	40.20±21.41
Sex (no. with %)	MALE: 17 (56.66) FEMALE: 13 (43.33)	MALE: 16 (53.33) FEMALE: 14 (46.66)
ASA Grading (no. with %)	I: 28 (93.3) II: 2 (6.7)	I:28 (93.3) II: 2 (6.7)
Body Weight (kg) (Mean±SD)	13.40±4.49	13.70±4.86
Mean Duration of Surgery (minutes) (Mean ±SD)	25.17±9.513	54.33±8.483

Table 2: Baseline heart rate, oxygen saturation and respiratory rate prior to administration of the drugs in the two groups and their statistical significance

Parameters	Group M (n=30)	Group P (n=30)	t-value	p-value
Baseline heart rate (per min)	119.63±23.404	120.17±20.060	0.095	0.925
Baseline Oxygen saturation (%)	98.80±1.031	98.60±0.855	0.818	0.417
Baseline Respiratory rate (per min)	29.03±6.688	28.00±6.571	0.604	0.548

The baseline values of heart rate, oxygen saturation, respiratory rates were also statistically comparable (table 2).

Table 3: Heart rate comparison between the two groups at different time intervals and their statistical significance

Time interval	Group M (n=30)	Group P (n=30)	t-value	p-value
0 min	119.63±23.404	120.17±20.060	0.095	0.925
1 min	121.93±23.792	121.53±19.814	0.071	0.944
5 min	120.13±24.030	120.53±20.584	0.069	0.945
10 min	118.80±24.132	120.63±20.711	0.316	0.753
15 min	117.10±24.567	120.73±20.003	0.628	0.532
20 min	116.80±24.212	120.37±19.572	0.627	0.533
25 min	116.13±23.196	120.40±19.665	0.768	0.445
30 min	116.50±23.434	120.17±19.789	0.655	0.515

The heart rates at different time intervals (table 3) show slight increase at 1 min just after drug administration in both the groups. Rest of the values were statistically insignificant ($p>0.05$). The comparison of mean oxygen saturation and respiratory rates between the two groups at different time intervals also show no statistical significance

Table 4: Comparison of mean value of Ramsay sedation score between the two group and their statistical significance

Time interval	Group M (n=30)	Group P (n=30)	t-value	p-value
0 min	1.60±0.498	1.67±0.479	0.528	0.599
1 min	1.53±0.507	1.40±0.498	1.027	0.309
5 min	1.90±0.305	1.40±0.498	4.687	0.000
10 min	2.00±0.263	1.53±0.507	4.474	0.000
15 min	2.60±0.498	1.60±0.498	7.773	0.000
20 min	2.93±0.450	1.67±0.479	10.553	0.000
25 min	3.33±0.547	1.73±0.450	12.379	0.000
30 min	3.67±0.479	1.80±0.407	16.260	0.000

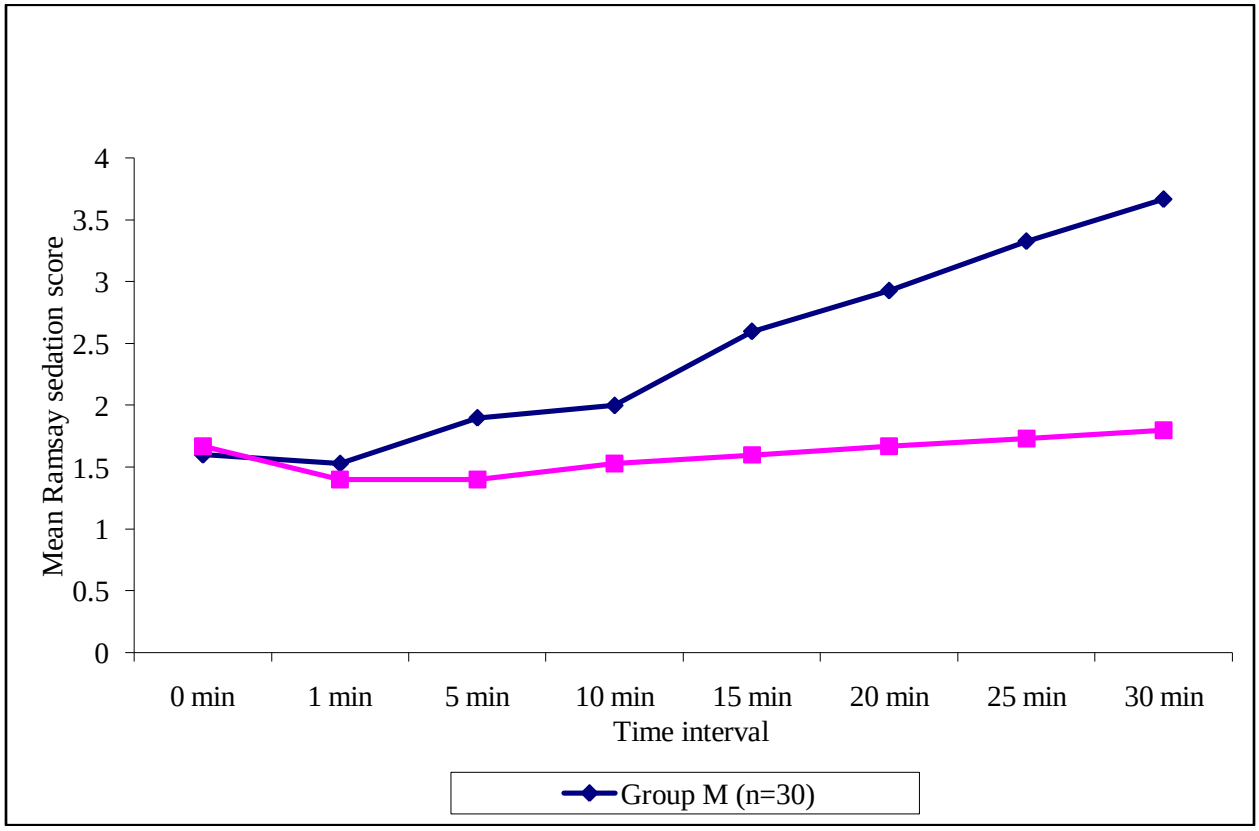

Figure 1: Comparison of mean value of Ramsay sedation score between the two groups and their statistical significance

Ramsay sedation score between the two groups show an initial agitation during the first minute reading immediately after drug administration. Compared readings of both the groups at 5 minutes 1.90±0.305/1.40±0.498), at 10 minutes (2.00±0.263/1.53±0.507), at 15 minutes (2.60±0.498/1.60±0.498), at 20 minutes (2.93±0.450/1.67±0.479), at 25 minutes (3.33±0.547/1.73±0.450) and at 30 minutes (3.67±0.479/1.80±0.407) respectively shows results to be statistically significant with $p<0.001$ (Table 4, figure 1).

Table 5: Comparison of mean emotion state score at different points of observation in both the groups and their statistical significance

Time interval	Group M (n=30)	Group P (n=30)	t-value	p-value
ESS0	2.43±0.898	2.56±0.541	0.763	0.451
ESS – SEP	1.47±0.507	1.57±0.504	0.766	0.447
ESS – OT	1.47±0.507	2.77±0.626	8.836	0.000
ESS – VEN	1.77±0.430	3.47±0.730	10.986	0.000
ESS – Mask	1.30±0.466	3.27±0.944	10.228	0.000

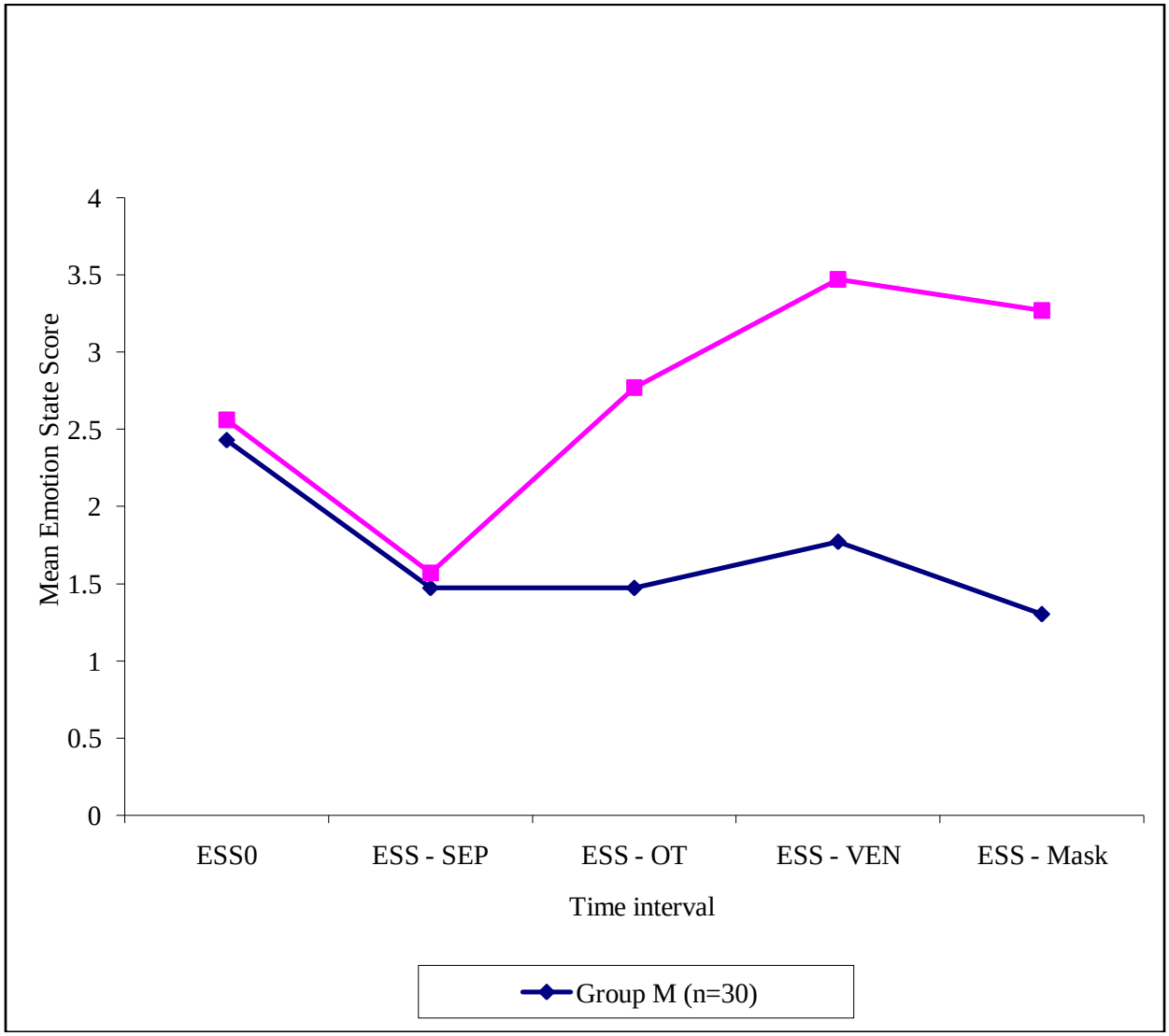

Figure 2: Comparison of mean emotion state score at different points of observation in both the groups and their statistical significance

The mean Emotion State Score at different points of observation in both the groups showed the children to be calmer in group M than P. The comparison of the emotion states of the children between Groups M and P during intravenous cannula insertion (1.77±0.430/3.47±0.730), during patient shifting (1.47±0.507/1.47±0.507), face mask induction (1.30±0.466/3.27±0.944) were statistically significant with p<0.001 (Table 5, figure 2).

Table 6: Comparison of induction time in both the groups

Group	Min.	Max.	Time (sec) (Mean ± SD)	't' value	'p' value
Group M (n=30)	10	50	25.17±9.513	12.534	<0.001
Group P (n=30)	35	70	54.33±8.483		

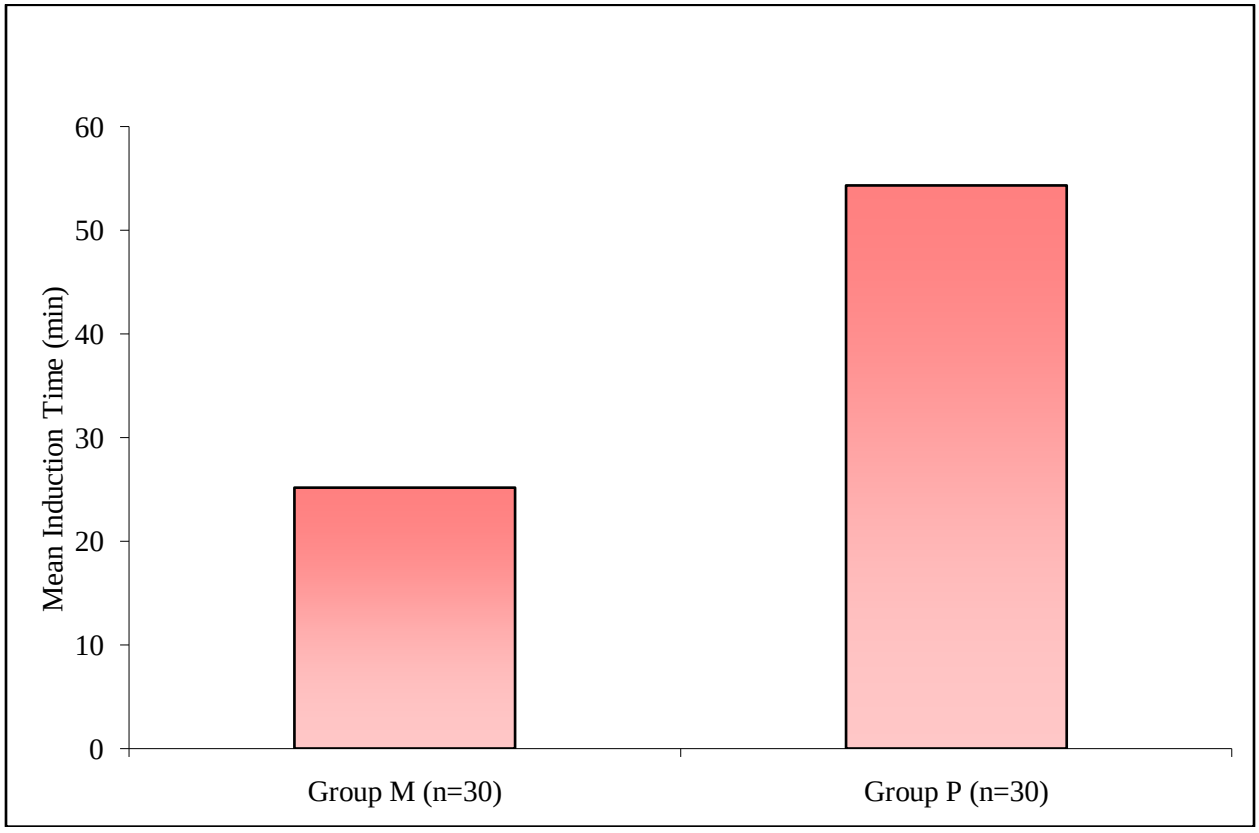

Figure 3: Comparison of induction time in both the groups

Induction time was significantly reduced in Group M (25.17±9.513) as compared to P (54.33±8.483) with $p<0.001$ (Table 6, figure 3). Any episode of nasal irritation was assessed in children >4 years. There were 21 children (70%) of age <4 years and 9 (30%) children who were >4 years in both the groups. All children (100%) who were >4 years from both the groups showed reactions at the time of administration of the formulation. No child showed nausea, vomiting, signs of apnea nor required any airway support in the pre-induction or one hour postoperative follow up period.

Conclusion

Pediatric anesthesia always presents with major challenge as it deals with psychobiologically vulnerable age group. Despite reassurance by parents, surgeons and anesthetist, a large number of children still remain anxious preoperatively and an equal number of children suffer from postoperative maladaptive behavior (Kain, 1999). Prime objective of the anesthesiologist should be aimed at ensuring and thereby reducing occurrence of postoperative negative psychological and behavioral changes.

Separation from parents, application of face masks during induction of anesthesia or attempts at intravenous cannulation are major factors that contribute significantly to emotional trauma in children. Several sedative drugs administered via different routes have been studied (McCann, 2001; Anderson, 1990) and used as premedicant successfully with minimal risk of adverse effects.

An ideal premedicant for children should be easily available, palatable, have both rapid onset and short duration of action, be able to reduce anesthetic and analgesic requirements and possess minimal side effects without significant delay in recovery period. As none of the premedicants meet all the criteria for an ideal agent, several studies have been performed to recognize and define the near ideal sedative premedicant.

Midazolam has been used via the intranasal route as nasal drops for premedication in children. Bhakta *et al.,* (2007) concluded that 0.2 mg/kg midazolam nasal drops effectively produced anxiolysis and sedation in paediatric patients (Dallman, 2001), showed intranasal midazolam with atomizer on pediatric dental procedures to be safe. Recently available midazolam intranasal spray is both convenient with easy dose calculation making it a reliable, unique formulation**.**

Wermeling *et al.,* (Wermeling, 2006) in a 3 way cross over study compared intranasal, intramuscular and intravenous formulations of midazolam and concluded that intranasal routes (5 mg single dose via 100 µl unit dose spray) had better absorption and shorter median time to attain maximum concentration. Zedie *et al.,* (1996) in a comparative study of intranasal midazolam and sufentanil premedication in pediatric outpatients stated that both intranasal midazolam and sufentanil provide rapid, safe and effective sedation.

This study aimed to establish the efficacy and safety of intranasal midazolam, while comparing it with a placebo for premedication in children undergoing elective surgical procedures at Sir Sunderlal Hospital, BHU, Varanasi. The intranasal midazolam used was a metered dose atomizer (Insed) manufactured by Samarth Pharma Pvt Ltd. containing 50 metered doses of 100 µl, each delivering 0.5 mg of the drug.

Children of age 6 months to 6 years were chosen for the study as this is the most vulnerable group for stress response. Kogan *et al.,* (2002) showed that intranasal midazolam (0.3 mg/kg) premedication in young children achieved maximum sedation and anxiolysis at 20 minutes. Hence we set parental separation time to be exactly 30 min after premedication. During parental separation, children were evaluated for sedation and emotion state based on Ramsay Sedation Score and Emotional State Scale respectively. Children were reassessed after being shifted to the operating table, during intravenous cannula insertion, application of face mask, ease of induction of general anesthesia based on the same scoring system as mentioned above.

Both the study groups were comparable with respect to age, weight, ASA grading, sex, parent child separation time and duration of surgery. In our study, the Emotion State Score at the time of separation from parent, during shifting to the operating table and intravenous cannula insertion were significantly less in children who were premedicated with intranasal midazolam as compared to the placebo group. Induction of anesthesia was also easier in these children as they accepted the mask readily and time required for induction was comparatively less in the midazolam group (Mean±SD=25.17±9.513) than the placebo group (Mean±SD=54.33±8.483). Kogan *et al.,* (2002) also supported that majority of children showed better acceptance to face mask (>75 %).Moreover sedation score of >3 was achieved in both the groups within 10 minutes of drug administration.

Satisfactory sedation (Ramsay Sedation Score of 3 or 4) were observed in most of the children after premedication in the midazolam group (Mean±SD=1.47±0.507) with $p<0.001$ (highly significant) whereas with placebo it was not significant ($p>0.05$). Hollenhorst *et al.,* (Hollenhorst, 2001) in their comparative study between intranasal midazolam with a placebo, found that patients receiving midazolam spray were more sedated and less anxious just prior to MRI. They also reported of better quality of MRI image in midazolam group. Another study by Roelofse *et al.,* (Roelofse, 2004) stated that intranasal administration of drugs for sedation and analgesia has promising features in preschool children undergoing multiple dental extractions.

All children were monitored for heart rate, oxygen saturation, respiratory rate at the stated time intervals. None of the children suffered from any respiratory or cardiovascular complications before separation from the parents.

The mean baseline values of cardiovascular and respiratory parameters, when compared to those obtained at subsequent intervals were found to be statistically insignificant. There was also not much significant difference ($p>0.05$) in values obtained from both the groups. Audenaert (1995) in his study compared the cardiorespiratory effect of premedication for children by different routes and stated that intranasal midazolam (0.2 mg/kg) produced no significant cardiorespiratory effects. A study by Samuelson et al (Samuelson 1981) on healthy subjects and patient with ischemic and valvular heart disease, reported minimum hypotensive effects and proved safety and efficacy even in patients with

severe aortic stenosis. In another prospective randomized study Imtiaz *et al.,* (2004) tested the efficacy of midazolam given by nasal and sublingual route. They concluded that no statistically significant variation in heart rate, respiratory rate and oxygen saturation was found from baseline in both groups ($p > 0.05$).

Though in our study the children from both the groups showed reaction to both formulations, it was not possible to ascertain whether it was due to the irritant effect of midazolam or simply fear of the child. The main reason was difficulty in communication with children of this age group and unreliability of the information obtained. Although it was not possible in this setup, various authors have however reported the irritant nature of intranasal midazolam. Daniel *et al.,* (2006) in a 3 way cross over study compared intranasal, intramuscular and intravenous formulations of midazolam and concluded that the adverse effects were minimum in all routes except nasopharyngeal irritation, watering eyes and bad taste which were reported after intranasal route. Kogan *et al.,* (Kogan, 2002) also stated that intranasal midazolam caused significant nasal irritation, in a comparative study of different routes of administration. McCormick *et al.,* (2008) compared midazolam by intranasal and nebulized routes and inferred that midazolam caused more discomfort in intranasal group but lower dose were needed to produce adequate response. However in one study in adult population Primosch *et al.,* (2005) concluded that spray administration of midazolam produced significantly less aversive behavior than administered drops in 2-3 years old dental patients of similar behavioral characteristics. Knoester *et al.,* (2002) found that in healthy adult volunteers, a concentrated midazolam nasal spray (single dose of 5mg midazolam intranasally) was easily administered and well tolerated. In our study the children did not have any complications like any episodes of apnea, respiratory distress, any requirement of airway support, nausea, vomiting in both the study groups during preinduction and within one hour of postoperative period.

Although intranasal midazolam can be appropriate alternatives as premedicants in terms of efficacy and safety, it is not routinely recommended for use in every child. Griffith *et al.,* (1998) in his study did not recommend the use of intranasal midazolam as a method of routine premedication of young children. However in our study, children who were at increased risk of preoperative anxiety and fear have shown benefit with minimum risk of unwanted effects. This was supported by Saile *et al.,* (1988) who stated that children between 6 months and 4 years have been reported to experience the greatest negative postoperative behavior changes.

In an effort to find a near ideal sedative premedicant in our context, better drug formulation with proper delivery system that could reduce the irritant property of midazolam is warranted. These when added on to the efficacy and safety profile of the drug, would most probably give a near ideal premedicant for children.

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REFERENCES

Anderson PJ *et al.,* (1990). Oral premedication in children: a comparison of chloral hydrate, diazepam, alprazolam, midazolam and placebo for day surgery. *Anesthesia & Intensive Care* **18** 185-193.

Audenaert SM, Wagner Y, Montgomery CL, Lock Richard L, Colclough George, Kuhn Robert J, Johnson Gregory L and Pedigo Norman W Jr (1995). Cardiorespiratory Effects of Premedication for Children. *Anesthesia Analgesia* **80** 506-10.

Bhakta P, Ghosh BR, Roy M and Mukherjee G (2007). Intranasal sedation for paediatric patients. *Indian Journal of Anesthesia* **51**(2) 111 –116.

Dallman JA, Ignelzi MA Jr and Briskie DM (2001). Comparing the safety, efficacy and recovery of intranasal midazolam vs. oral chloral hydrate and promethazine. *Pediatriatric Dentistry* **23**(5) 424-430.

Griffith N *et al.,* (1998). Intranasal midazolam for premedication of children undergoing day – case anaesthesia: Comparison of two delivery systems with assessment of intraobserver variability. *British Journal Anaesthesia* **81** 865-869.

Hollenhorst J, Münte S, Friedrich L, Heine J, Leuwer M, Becker H and Piepenbrock S (No Date). Using intranasal midazolam spray to prevent claustrophobia induced by MR Imaging. *American Journal of Roentgenology* **176** 865–868

Imtiaz WN, Zargar J and Farooqi A (2004). Midazolam Premedication in Children: Comparison of Nasal and Sublingual Routes. *Journal of Anaesthesia and Clinical Pharmacology* **20**(2) 141-145.

Kain ZN, Mayes L, Wang S and Hofstadter MB (1999). Postoperative behavioral outcomes in children: effects of sedative premedication. *Anesthesiology* **90**(3) 758-765.

Karl HW, Keifer AT, Rosenberger JL, Larach MG and Ruffle JM (1992). Comparison of the safety and efficacy of intranasal midazolam or sufentanil for preinduction of anesthesia in pediatric patients. *Anesthesiology* **76**(2) 209-215.

Knoester PD, Jonker DM, Van der Hoeven RTM, Vermeij TAC, Edelbroek PM, Brekelmans GJ and De Haan GJ (2002). Pharmacokinetics and pharmacodynamics of midazolam administered as a concentrated intranasal spray, A study in healthy volunteers. *British Journal of Clinical Pharmacology* **53** 501–507.

Kogan A, Katz J, Efrat R and Eidelman LA (2002). Premedication with midazolam in young children: a comparison of four routes of administration. *Paediatric Anaesthesia* **12**(8) 685-689.

McCann ME and Kain ZN (2001). The management of preoperative anxiety in children: An update. *Anesthesia Analgesia* **93**(1) 98–105.

McCormick ASM, Thomas VL, Berry D and Thomas PW (2008). Plasma concentrations and sedation scores after nebulized and intranasal midazolam in healthy volunteers. *British Journal of Anaesthesia* **100**(5) 631–636.

Primosch RE and Guelmann M (2005). Comparison of Drops Versus Spray Administration of Intranasal Midazolam in Two- and Three-year-old Children for Dental Sedation. *Pediatric Dentistry* **27**(5) 401-408.

Ramsay MA, Savege TM, Simpson BR and Goodwin RB **(1974).** Controlled sedation with alphaxalone-alphadolone. *British Medical Journal* **2**(5920) 656-659.

Roelofse JA, Shipton EA, Harpe de la CJ and Blignaut RJ (No Date). Intranasal sufentanil/midazolam versus ketamine/ midazolam for analgesia/ sedation in the pediatric population prior to undergoing multiple dental extractions under general anesthesia: A prospective, double-blind, randomized comparison. *Anesthesia Progress* **51**(4) 114-121.

Saile H, Burgmeier R and Schmidt LR (1988). A meta-analysis of studies on psychological preparation of children facing medical procedures. *Psychology and Health* **2** 107-132.

Samuelson PN, Reves JG, Kouchoukos NT *et al.*, (1981). Hemodynamic responses to anesthetic induction with midazolam or diazepam in patients with ischemic heart disease. *Anesthesia Analgesia* **60** 802-809.

Wermeling Daniel P *et al.*, (2006). Pharmacokinetics and pharmacodynamics of a new intranasal midazolam formulation in healthy volunteers. *Anesthesia Analgesia* **103** 344 –349.

Zedie N, Amory DW, Wagner BK and O'Hara DA (1996). Comparison of intranasal midazolam and sufentanil premedication in pediatric outpatients. *Clinical Pharmacology and Therapeutics* **59**(3) 341-348.