RESEARCH PAPER

Intranasal Clonidine *vs.* Midazolam as Premedication in Children: *A Randomized Controlled Trial*

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Objectives: To compare anxiolysis produced by intranasal clonidine with intranasal midazolam as premedication in children undergoing surgery.

Design: Double-blind randomized controlled study.

Setting: Tertiary-care hospital, July 2009 to June 2010.

Patients: 60 American Society of Anesthesiologists physical status I-II surgical patients aged 1-10 yr.

Intervention: Participants randomly allocated to receive either intranasal clonidine 4 mcg/kg (Group I) with atropine or intranasal midazolam 0.3 mg/kg (Group II).

Outcome measures: Primary: satisfactory anxiolysis at 30 min after drug administration. Secondary: satisfactory mask acceptance, times of onset of sedation and anxiolysis, drug acceptance, level of sedation, wake-up score and side effects.

Results: All children achieved satisfactory anxiolysis at 30 min. Group I fared significantly better than Group-II on mask acceptance (100% in Group I *vs*. 80% in Group II; *P*=0.024), drug acceptance (93% *vs*. 13%; *P*<0.001) and proportion of patients with satisfactory wake-up scores (100% *vs*. 53%; *P*<0.001). Group II patients had significantly faster onset of sedation (median 10 min *vs*. 15 min; *P*<0.05) but not that of anxiolysis compared to Group-I (median 10 min for both groups; *P*>0.05). Side effects were significantly more frequent in Group II.

Conclusions: Though intranasal midazolam produced faster sedation, both the drugs produced satisfactory anxiolysis at 30 min.

Keywords: *Anxiolysis, Clonidine, Efficacy, Midazolam*

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Induction of anesthesia is a stressful and anxiety-provoking experience for children undergoing surgery [1]. One of the main concerns of the pediatric anesthesiologist is the appropriate management of preoperative anxiety. This is because uncontrolled severe preoperative anxiety and distress may lead to prolonged induction of anesthesia and later negative postoperative behavioural sequelae [2]. Sedative premedication in general is considered to be an effective option for reduction of preoperative anxiety in children [3].

Midazolam is by far the most commonly used sedative premedicant [1,4], though it is far from ideal due to many shortcomings [5,6]. Clonidine is increasingly used in pediatric population as a sedative and analgesic because of its central α_2-adrenoceptor agonist action [7,8]. It has been successfully used orally, intravenously, intrathecally, epidurally and intramus-cularly in children in a dose range of 1-5 mcg/kg [5,7,8]. The published studies on intranasal clonidine as a premedicant in pediatric population have shown encouraging results [9-11].

Although clonidine has been compared with midazolam as premedication in children through the rectal [12] and oral [13] routes, no study directly compared intranasal clonidine and midazolam as a premedication in the pediatric population. Thus the present study was designed to compare the efficacy of intranasal midazolam and intranasal clonidine to produce satisfactory levels of anxiolysis as a premedicant for children undergoing surgery.

METHODS

The study was conducted from July 2009 to June 2010. Ethical approval for this study was provided by the Institutional Ethics Committee. Children of either sex, in age group of 1-10 yr, of American Society of Anesthesiologists (ASA) physical status I and II only, scheduled to undergo minor elective surgical procedures such as hydrocele repair, herniorrhaphy, circumcision or eye surgery were included in this prospective randomized parallel group (with 1:1 allocation ratio) double-blind study after obtaining written informed consent from the parents of these children and additional assent from children over 7 years. The exclusion criteria were: children with rhinopharyngitis or recent upper respiratory tract infection, known allergy or hypersensitivity to clonidine or midazolam, children requiring intravenous induction,

cardiac arrhythmias, congenital heart disease, prolonged PR interval, atrioventricular blocks, intrinsic bradycardia, prematurity, mental retardation, raised intracranial pressure, history of convulsions, liver and renal disease, and children refusing to take the whole dose of premedication.

No child received any premedication before arrival in the operating room. Patients were randomized by computer generated random number list and randomly allocated to one of the two groups by using coded and sealed opaque envelopes for administration of study drug 30 minutes prior to surgery. The coded syringes were prepared by a person not involved in the study. The contents of the syringe were unknown to the person administering the drug and the anesthetist involved in the study. One person assessed the children during the study period. Another administered the nasal drug and noted the drug acceptance but was not involved in assessing anxiolysis, sedation or mask acceptance. Baseline heart rate, SpO_2 and respiratory rate was monitored before the administration of drug.

Group I patients received 4 mcg/kg intranasal clonidine (150 mcg/mL intravenous preparation; Clonidine hydrochloride, Neon Laboratories Limited, India) mixed with 20 mcg/kg of atropine. Atropine 0.6 mg/mL (Tropin, Neon Laboratories Limited, India) was given to prevent reduction in heart rate associated with clonidine. Group II patients received 0.3 mg/kg of midazolam (5mg/mL intravenous preparation; Mezolam, Neon Laboratories Limited, India) using a syringe whose needle was removed. The drugs were loaded in a graduated syringe, and instilled in separate nostrils in 0.2 mL aliquots, with the patient lying in semi-recumbent or supine position, till the total dose of drugs was administered. Heart rate, respiratory rate and SpO_2 was monitored every 5 minutes after administration of drug until transfer to operating room. Drug acceptance was recorded, defined as crying or complaints like nasal stinging and bitter taste after instillation of drug. The side effects of the study drugs, if any, were also noted during the study period.

Sedation score was assessed every 5 minutes from the administration of drug with the six-point Ramsay sedation score [14] for maximum of 60 minutes. Anxiety was similarly evaluated every 5 minutes by a four-point scale [15]. When an anxiolysis score of 4 or more was reached, the child was transferred to the operating room for induction and the time was noted. The time to reach point 4 on the anxiety scale was also noted. If no satisfactory anxiolysis level was achieved after 60 minutes, anesthesia induction was conducted. The primary outcome measure was proportions of patients in each group with satisfactory anxiolysis at 30 minutes after drug administration (scores 3-4 on the relevant scale). This primary outcome measure was selected *a priori,* because this was considered to be of foremost clinical relevance in the context of these drugs. Secondary outcome measures included times of onset of sedation and anxiolysis, and proportion of patients with acceptance of the drug (*i.e.*, not crying after drug administration), satisfactory mask acceptance (scores 3-4 on the relevant scale), satisfactory level of sedation (scores 4-6 on the sedation scale) and satisfactory waking up (scores 1-2 on the wake-up scale).

A standard technique for conduct of anesthesia was maintained for all the patients. Patients were transferred to the operating room accompanied by one parent. After placement of routine monitoring, anesthesia was initiated with 70% nitrous oxide in oxygen and sevoflurane via transparent face mask kept gently on face [15,16] and maintained with oxygen, nitrous oxide, sevoflurane and fentanyl 2mcg/kg. Behavior at awakening was evaluated with 4-point wake up score [17].

Statistical analysis: Fisher's Exact test was used to compare proportions. Onset time of sedation and anxiolysis was analyzed by Kaplan Meier survival curve and log rank test. Statistical significance was accepted if *P* value was less than 0.05. All data were analyzed using Statistical Package for Social Sciences (SPSS)15.0.

As there was no previous study directly comparing intranasal clonidine with intranasal midazolam, a pilot study was done using 10 patients in each group. Proportion of patients with satisfactory anxiolysis was 80% and 100%, respectively. Using this data, and setting alpha at 5% and power at 80%, we needed 35 patients in each group.

RESULTS

A total of 60 patients were enrolled, 30 in each group (23 males in group I and 27 in group II). The demographic profiles of the patients of two groups were similar with median (range) age of 2.5 (1-10) and 4 (1-10) years, respectively in group I and group II. The median (range) duration of surgery was 64 (35-90) and 62 (30-80) minutes in the two groups, respectively. The flow of patients in the study is shown in ***Fig.* 1**.

All the patients in both the groups developed acceptable levels of anxiolysis (anxiety score 3-4) after 30 minutes of drug administration. The secondary outcomes and adverse effects are shown in ***Table* I** and ***Figs.* 2 and 3**.

Crying during drug administration, median duration of crying, complaints of nasal stinging and bitter taste were significantly higher in group II (***Table* I**). A higher

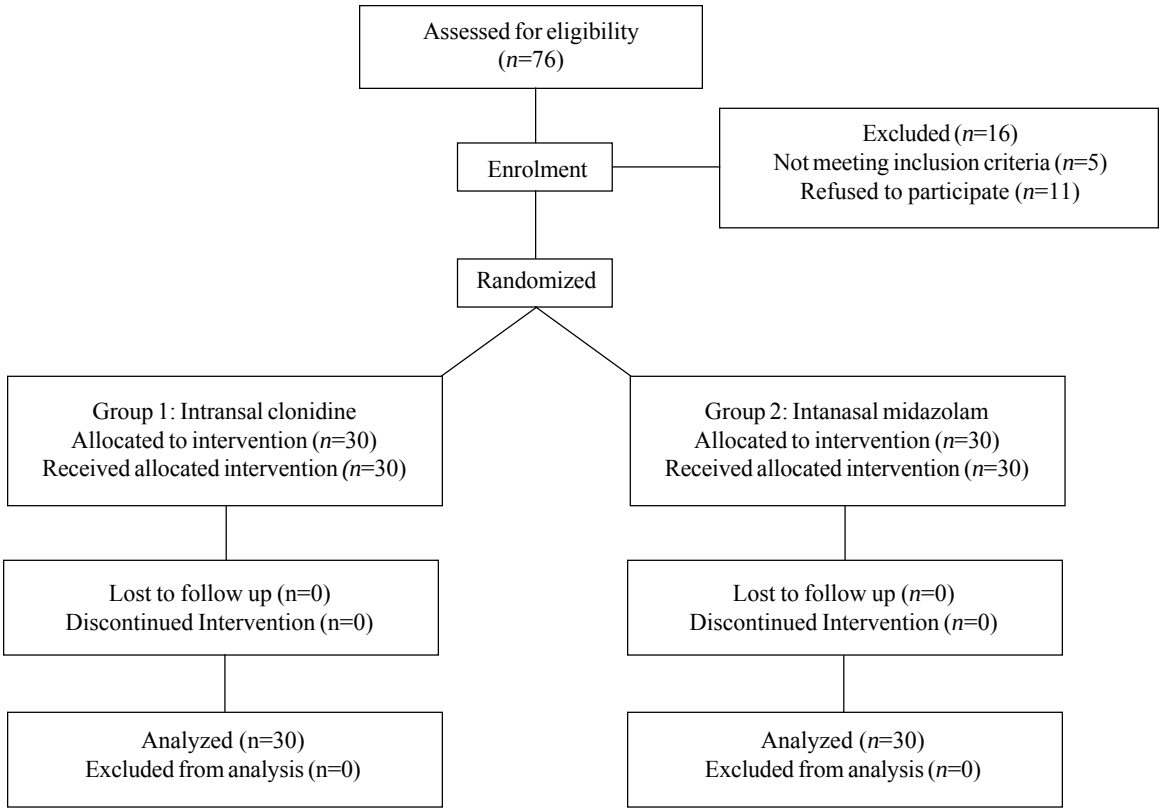

FIG.1 *Flow of patients in the study*

number of patients in Group I had a mask acceptance score 3-4.

Postoperatively, all the patients in Group I were either calm and cooperative or could be easily consoled (*i.e.*, wake-up scores 1-2) as compared to 53% of patients in Group II ($P < 0.001$).

DISCUSSION

This randomized controlled trial compared intranasal clonidine and intranasal midazolam as premedication in children undergoing elective surgery found satisfactory anxiety score in both groups. Mukherjee, *et al*. [16] found that the onset of anxiolysis after clonidine premedication was 15.8±2.6 minutes whereas Almenrader, *et al*. [9] reported 23.3±17.2 minutes for the onset of anxiolysis, that was longer than reported in our study. Kogan, *et al*. [15] found that the maximal anxiolysis was achieved at 20 minutes after intranasal midazolam administration. However, others have reported that intranasal midazolam provided maximal sedation and anxiolysis within 10 minutes after administration [18,19]. The results of our study are broadly in line with the previous studies, with the exception of one [9].

Findings on various drug effect related parameters have varied markedly across various studies. This variation might be due to several factors such as drug dose, preparation, exact mode of administration (single, repeated, patient position, etc.), observer-related factors, patient-related factors, state of nasal mucosa, preoperative information and experience, and even cultural and environmental differences in experiencing and reporting some outcomes. There is a practical limit to the total volume of the drug that can be instilled through the nasal route. Inadvertent swallowing of the drug and subsequent gastric absorption are other potential drawbacks. It has been shown that direct transport of clonidine from the nasal mucosa to systemic circulation can be erratic and unpredictable [11]. Further, atropine was co-administered intranasally in the clonidine group. Nasal atropine has been shown to reduce nasal secretions and mucociliary clearance [20,21], which might have favored nasal clonidine absorption in our study.

As regards the secondary outcome measures, drug acceptance was better in clonidine group than midazolam. Midazolam, either directly or because of its acidic pH, may be responsible for nasal mucosal irritation, thus causing low acceptance [6,15].

TABLE I COMPARISON OF SECONDARY OUTCOMES AND ADVERSE EFFECTS IN THE TWO GROUPS

	Group-I (Clonidine)N=30 (%)	*Group-II (Midazolam)N=30 (%)*	*P value*
Drug acceptance (No crying)	28 (93.3)	4 (13.3)	<0.001
†Duration of crying (s)	0 (0-60)	50 (0 – 120)	<0.001
Nasal stinging	0	28 (93.3)	<0.001
Bitter taste	0	15 (50.0)	<0.001
Mask acceptance score*			
1	0	3 (10.0)	
2	0	3 (10.0)	
3	11 (36.7)	14 (46.7)	
4	19 (63.3)	10 (33.3)	
Satisfactory level (3-4)	30 (100)	24 (80.0)	0.024
Sedation score at 30 min#			
1	0	0	
2	0	0	
3	0	5 (16.7)	
4	7 (23.3)	15 (50.0)	
5	13 (43.3)	5 (16.7)	
6	10 (33.3)	5 (16.7)	
Acceptable level (4-6)	30 (100)	25 (83.4)	0.052
Wake-up score$			
1	10 (33.3)	1 (3.3)	
2	20 (66.7)	15 (50.0)	
3	0	13 (43.3)	
4	0	1 (3.3)	
Acceptable level (1-2)	30 (100)	16 (53.3)	<0.001

*****As per reference 23; #As per ref. 22, $As per ref. 24; †median (range).*

Significantly more patients in the clonidine group than in the midazolam group accepted mask satisfactorily. Mask acceptance can be an important composite marker signifying a combination of anxiolysis, lack of fear, drug tolerability and the resultant cooperativeness. Steal induction could be performed in four (13.3%) of the patients in clonidine group as compared to three (10%) in midazolam group. Almenrader, *et al*. [9] found that steal induction was possible in 60% of the patients whereas Mukherjee, *et al*. could perform it in 20% of the patients [16]. Although patients were well-sedated, steal-induction could not be performed as patients were waking up during transfer. It is possible that Almenrader, *et al*. achieved steal induction in 60% cases because they induced children in the parents' arms in a dimmed and quiet operating room [9].

The onset of sedation was significantly faster in midazolam group as compared to clonidine group in this study but both the groups achieved acceptable sedation levels at 30 min. The onset of sedation after clonidine premedication in our study is consistent with their findings [9,16] but faster compared to few other reports [18,19,22,23]. In contrast, a recent publication compared two dose strengths of an aerosol preparation of nasal clonidine with placebo in a double-blind randomized trial and found that only 55% of the children receiving the higher dose (7-8 μg/kg) were adequately sedated at 30 min after administration of the aerosol [24]. The variations in these study results might be because of several factors mentioned above. It is an interesting and important area for future research.

Finally, patients in clonidine group had significantly better wake up score than midazolam group. Previous reports [9,16] also found that the majority of the patients were either calm and cooperative, or could be easily consoled postoperatively when clonidine was used as premedicant. Other authors also report that clonidine produces more effective early postoperative analgesia,

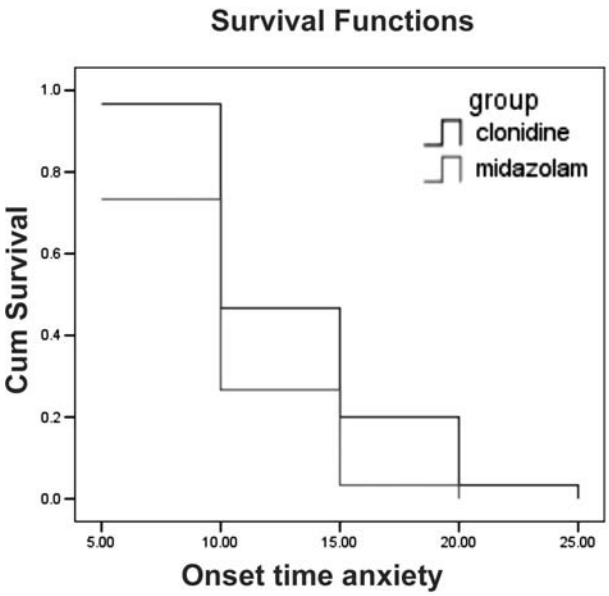

FIG. 2 *Kaplan-Meier survival curve showing onset of anxiolysis in the two groups. p = 0.7261 (Log rank test).*

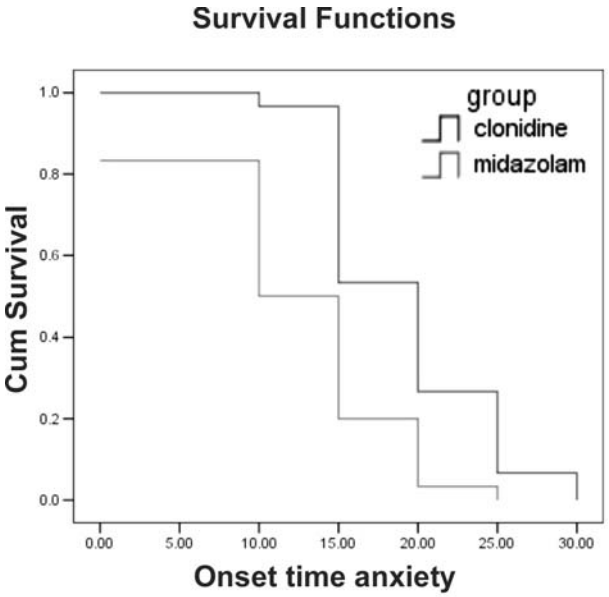

FIG. 3 *Kaplan-Meier survival curve showing onset of sedation in the two groups. p = 0.0208 (Log rank test).*

reduces the incidence of postoperative nausea vomiting and shivering, and causes attenuation of postoperative delirium when compared to midazolam and thus produces better wake up score [5,8]. This is consistent with the results obtained in our study. Further, midazolam, a benzodiazepine, causes anterograde and retrograde amnesia, and this has been suggested to be a potential mechanism for causing poorer wake-up score and early postoperative agitation in the midazolam group [5].

We did not study the cognitive functions of the children before and after receiving the drugs. This may be considered a limitation of the study, though our primary focus was on efficacy. Other limitations include a sub-optimal sample size lack of a placebo control group and lack of generalizability of the findings in children undergoing emergency surgery. Further, preoperative anxiety was measured by a previously used scale [15] but not compared with other validated scales [25]. However, these limitations should not invalidate the main conclusions from this study.

In conclusion, intranasal clonidine has been shown to produce comparable level of sedation and effective anxiolysis as nasal midazolam after 30 minutes, but with a better mask acceptance and recovery profile.

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