Original Article

Is midazolam superior to triclofos and hydroxyzine as premedicant in children?

Sujata Chaudhary, Reena Jindal, Gautam Girotra, Rashmi Salhotra, Rajesh Singh Rautela, Ashok Kumar Sethi

Department of Anaesthesiology and Critical Care, University College of Medical Sciences & Guru Teg Bahadur Hospital, Dilshad Garden, New Delhi, India

Abstract

Background: Search for an ideal premedicant drug for children is still on. A prospective, randomized trial was conducted to compare the efficacy of midazolam, triclofos and hydroxyzine as premedication in children undergoing lower abdominal surgeries.
Materials and Methods: Sixty American Society of Anesthesiologists I or II patients 2-8 years of age, scheduled for elective lower abdominal surgery were included. The patients were randomly divided into three groups M, T and H of 20 children each who received midazolam 0.5 mg/kg, triclofos 75 mg/kg and hydroxyzine 0.5 mg/kg respectively, orally 60 min before surgery. The acceptability of drugs, level of sedation, anxiety during separation and on mask application was assessed.
Results: The acceptability of midazolam and hydroxyzine was better than triclofos. Hydroxyzine was found to have lesser sedative effect as compared to both midazolam and triclofos. No major adverse effects were observed.
Conclusion: Midazolam was found to be a better premedicant in terms of sedation, anxiolysis and safety.

Key words: Children, hydroxyzine, midazolam, premedication, triclofos

Introduction

The emotional and psychological trauma in children due to unfamiliar hospital environment, fear of operation, injections and separation from parents prior to anesthesia is well-known.[1] To achieve a state of psychological and physical normalcy, various methods ranging from physical presence of parents in operation theatre to pharmacological methods have been tried by various workers. Premedicating the pediatric patients has always been a challenge to the anesthesiologist because of their lack of co-operation, preferred non-traumatic route of administration and susceptibility to respiratory depression. No drug or combination of drugs has been found to be ideal for premedication. Hence the quest for ideal drug for this purpose continues. Among the various routes of administration, oral route is best preferred in children.[2]

Benzodiazepines are routinely used in children and adults for their anxiolytic and hypnotic properties. Midazolam has the advantage of a rapid onset and relatively short duration of action. Though the oral preparation of midazolam is commercially available now, the parenteral preparation is still being used by the oral route after mixing it in a vehicle to make it more palatable.[3,4] Moreover, the IV formulation by the oral route has been found to be more reliable and effective as compared to the commercially available oral formulation.[4] A dose of 0.25-0.5 mg/kg of midazolam orally has proven to be efficacious in children with fewer side-effects.[5]

Oral triclofos, a stabilized form of chloral hydrate is an older sedative-hypnotic drug. It is more palatable than chloral hydrate.[6] Triclofos has been used as a sedative for short procedures, but has not been widely studied as a premedicant. The oral solution is well-absorbed, proves effective within 30-40 min and produces hypnosis for 6-8 h in doses of 25-75 mg/kg.[7]

Hydroxyzine is an antihistaminic tranquilizer, which produces anxiolytic, analgesic, antihistaminic, antiemetic, bronchodilatory and anticholinergic effects and is available

Address for correspondence: Dr. Rashmi Salhotra,
A/2, 268, Second Floor, Paschim Vihar, New Delhi- 110063, India.
E-mail: rashmichabra@yahoo.com

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in the form of syrup for pediatric use. Therapeutic doses of 0.5 mg/kg of hydroxyzine produce peak action in 30 min.

The aim of this study was to compare and evaluate the effects of midazolam, triclofos and hydroxyzine when given orally as premedicants in children. The primary objective was sedation and secondary objectives were anxiolysis, ease of parental separation and face mask acceptability during induction and clinical recovery.

We hypothesized that all three drugs would have the same sedative, anxiolytic and hypnotic effect when used as premedicants in children.

Materials and Methods

After attaining institutional review board approval, this prospective randomized observer blind study was conducted in 60 American Society of Anesthesiologists physical status I and II children, in the age group of 2-8 years posted for elective lower abdominal surgical procedures. The children requiring emergency surgeries, history of central nervous system disorder, severe respiratory or cardiac disorder, hypersensitivity to any of the study drug or refusal to take premedication were excluded from the study.

After pre-anesthetic assessment, the procedure was explained to the parents and informed consent taken. Clear fluids were permitted up to 6 h prior to the procedure. Children were randomly assigned to three groups of 20 each using a computer generated random number table. Children in Group M were given midazolam 0.5 mg/kg orally constituted by using sweetened syrup (Frooti), Group T were given oral triclofos 75 mg/kg available as market preparation (Pedichloryl 500 mg/5 ml) and Group H were administered oral hydroxyzine 0.5 mg/kg commercially available as syrup (Atarax 10 mg/5 ml).

The anesthesiologist gave the pre-calculated dose of the test drug to the parent who in turn administered it to the child orally 60 min prior to surgery. Acceptance of the drug was assessed by this independent observer using the compliance score (1 = Good – readily takes medicine, 2 = Fair – accepts medicine with persuasion, 3 = Poor –unwilling to take medicine or spits it out, 4 = Refuses medicine).[8]

The children were made to relax in a quiet, undisturbed area along with the parent. Monitoring was instituted and pulse rate, systolic arterial pressure, respiratory rates and oxygen saturation were monitored and recorded. Level of sedation was assessed on five point sedation score (1 = Child awake and oriented, 2 = Drowsy, 3 = Eyes closed but rousable to command, 4 = Eyes closed, but rousable to mild physical stimulation, 5 = Eyes closed, but unarousable to mild physical stimulation).[9]

Ease of separation was noted at 60 min and graded on a four point separation score when the child was being taken for surgery (1 = Calm and sleepy, 2 = Apprehensive but withdrawn from surroundings, 3 = Crying, 4 = Agitated but difficult to control).[10] In the operating room, sedation score, heart rate (HR), respiratory rate and oxygen saturation were noted before induction of anesthesia.

Anesthesia was induced by a standard technique of inhalational induction with 33% oxygen in nitrous oxide and sevoflurane via face mask. Quality of anesthetic induction in terms of acceptance of face mask was graded on four point score (1 = Poor – afraid, combative, crying, 2 = Fair – moderate fear of mask, not easily calmed, 3 = Good – slight fear of mask, easily calmed, 4 = Excellent – unafraid, cooperative, accepts mask easily).[8] An intravenous infusion line was set up after the child was asleep. Endotracheal intubation was done after giving injection vecuronium (0.1 mg/kg) and anesthesia was maintained with nitrous oxide in 33% oxygen and sevoflurane with supplemental doses of vecuronium (0.025 mg/kg) as and when required for controlled ventilation. Monitoring included pulse rate, systolic blood pressure (SBP) and oxygen saturation. Intraoperative analgesia was provided with intravenous fentanyl (1-2 mcg/kg) and caudal block was given with 0.25% bupivacaine for post-operative analgesia before extubation. Side-effects such as nausea, vomiting, hiccups, airway obstruction, restlessness or slurring of speech, if any, were noted after the drug administration and in the recovery period. Post-operative recovery of child from anesthesia was assessed using the simplified scoring system given by Steward.[11]

The various parameters and scores used in the study were: compliance score, sedation score, separation score, quality of induction score and clinical recovery score.

Statistical analysis

The demographic profile was analyzed using one way ANOVA, HR, SBP, diastolic blood pressure (DBP) were compared using repeated measures of ANOVA and intergroup comparisons by Fisher's exact test. The compliance score, quality of induction score and sedation scores were analyzed by using the Chi-square test. All data was expressed as mean ± SD and $P < 0.05$ was considered as statistically significant.

Post-hoc power of the study was calculated for sedation at 60 min after the premedication for patients who achieved

excellent sedation scores and it came out to be 94% at 5% type I (alpha) error.

Results

The three groups were statistically similar in relation to age, sex, weight and duration of surgery and premedication to induction of anesthesia interval [Table 1].

Greater percentage (95%) of children were compliant and accepted midazolam and hydroxyzine (Group M and H) as compared to triclofos (65%) [Figure 1]. However, there was statistically insignificant difference between the three groups ($P = 0.16$).

Maximum percentage of patients achieving excellent sedation scores at 60 min were seen in the midazolam group (Group M). In triclofos group (Group T), 30% children achieved excellent level of sedation by 30 min, which increased to 50% at 60 min whereas only 5% children attained excellent score at 60 min in hydroxyzine group (Group H). Hydroxyzine was found to have mild sedative effect as compared to both midazolam and triclofos [Figure 2]. This difference was found to be statistically highly significant ($P = 0.001$). Most of the children, in midazolam and triclofos group (95% each) remained calm and sleepy whereas there were lesser number of children in hydroxyzine group who were calm (65%) and 5% children in this group were crying at the time of separation [Figure 3].

None of the children in the midazolam group were combative or crying at the time of application of mask during induction of anesthesia. Twenty percent children in hydroxyzine group were combative and crying at the time of mask application in comparison to 5% children of triclofos group [Figure 4]. The difference in three groups was statistically insignificant ($P = 0.30$).

There was a uniform trend of decrease in HR in all three groups as compared to the baseline value, which was statistically highly significant ($P < 0.001$). The intergroup comparison revealed that the decrease in blood pressure in the midazolam group was significantly more in comparison to triclofos and hydroxyzine groups ($P = 0.000$).

The SBP and DBP were not found to be statistically significant when analyzed using repeated measures ANOVA test.

Post-operative recovery was assessed in terms of consciousness, patency and ability to maintain airway and limb activity after 30 and 90 min of recovery from anesthesia. There was no

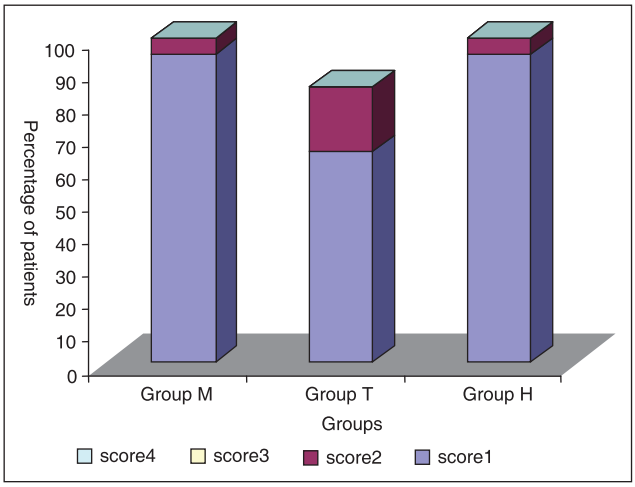

Figure 1: Compliance score (at time of drug administration) (1 = Good – readily takes medicine, 2 = Fair – accepts medicine with persuasion, 3 = Poor – unwilling to take medicine or spits it out, 4 = Refuses medicine)

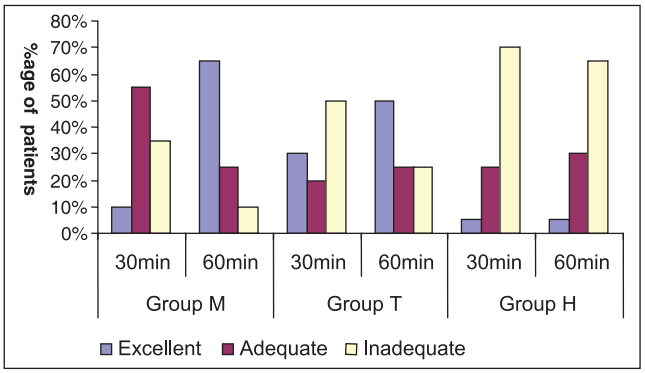

Figure 2: Sedation score (assessed at 30 and 60 min after premedication) (Excellent = Child awake and oriented (1)/Drowsy (2), Adequate = Eyes closed, but rousable to command (3)/Eyes closed but rousable to mild physical stimulation (4), Inadequate = Eyes closed but unarousable to mild physical stimulation (5))

Table 1: Patient characteristics

Characteristic	Group M	Group T	Group H	Total
Number	20	20	20	60
Gender ratio M/F	16/4	16/4	19:1	51/9
Age* (year)	4.90±2.05	4.85±1.98	4.90±1.97	4.89±1.97
Weight* (kg)	15.75±5.38	13.95±4.21	16.80±5.62	15.5±5.16
Basal HR* (bpm)	102.85±18.65	106.50±20.45	98.37±21.91	102.64±20.28
Basal SBP* (mmHg)	99.25±8.71	106.85±11.21	109.11±12.56	105.0±11.54
PI interval (min)	56.75±8.47	56.00±9.95	57.25±10.93	
Duration of surgery (min)	66.50±23.90	64.75±20.23	68.00±24.41	

**Mean±SD. bpm=Beats per minute, HR=Heart rate, SBP=Systolic blood pressure, PI=Premedication to induction, Intergroup comparison P>0.05*

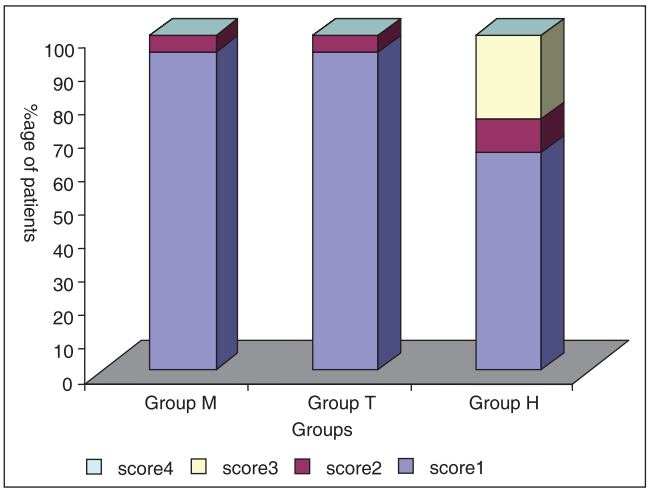

Figure 3: Separation score (at time of separation from parents) (1 = Calm and sleepy, 2 = Apprehensive, but withdrawn from surroundings, 3 = Crying, 4 = Agitated, but difficult to control)

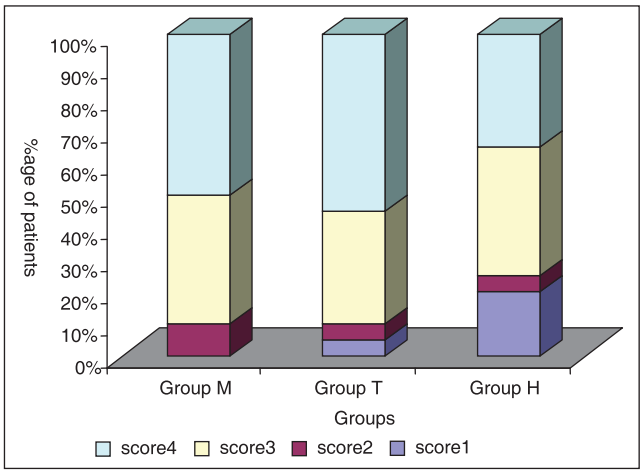

Figure 4: Quality of induction score (at time of induction) (1 = Poor – afraid, combative, crying, 2 = Fair – moderate fear of mask, not easily calmed, 3 = Good – slight fear of mask, easily calmed, 4 = Excellent – unafraid, cooperative, accepts mask easily)

statistically significant difference in the recovery characteristics in the three groups ($P = 626$ and $P = 0.509$ at 30 min and 90 min respectively.).

Side-effects were compared using the Fischer's exact test. Restlessness was the most frequent side-effect seen in both midazolam and triclofos pre-medicated children (15% each). However, the incidence was not significant ($P = 0.680$). 10% children developed ventricular ectopics after laryngoscopy and intubation in the triclofos group, which were transient in nature and statistically insignificant ($P = 0.322$). One child (5%) in hydroxyzine group (Group H) complained of dry mouth, which was again statistically insignificant ($P = 1.00$).

Discussion

Oral formulation of midazolam has recently been marketed in India. At the time of inception of this study, it was not available and hence midazolam meant for parenteral use has been used by mixing it in a palatable vehicle as has also been carried out in previous studies.[4,12] In the present study, the sweetened vehicle (mango Frooti) was used to constitute midazolam suitable for oral consumption. Although midazolam has a bitter taste, but when formulated in mango flavored syrup, it was well-accepted as shown by high level of compliance. Midazolam and hydroxyzine had better acceptability probably due to better taste as compared with triclofos. It was observed that two aliquots of triclofos were needed in 55% children where the calculated dose according to the weight resulted in relatively larger volumes. Most of them (40%) accepted the medication in single aliquot. However, 15% of the children had to be persuaded again to accept the medication as the volume had to be divided in two aliquots.

Saarnivaara *et al.* in a comparative study of midazolam and chloral hydrate as oral premedicants, observed that acceptance of chloral hydrate was always inferior to that of midazolam.[13] Data published by Millichap indicate that triclofos was palatable in a significantly greater proportion of patients than was chloral hydrate.[6] In independent studies, Wallace and Mindlin and Franssen *et al.* have shown that hydroxyzine is less palatable as compared to lorazepam[14] or alprazolam[15] respectively. In the present study, the acceptability of midazolam and hydroxyzine was superior to that of triclofos. The time taken from administration of premedicant drugs to the start of induction by application of mask was comparable in three groups.

Payne *et al.* observed that the peak serum levels of midazolam are achieved at 60 min following oral administration of 0.5 mg/kg.[16] Millichap found mean times of sleep onset with triclofos as 37.3 ± 12.1 min.[6] Singh *et al.* found that oral midazolam was a better drug amongst triclofos and promethazine to produce conscious sedation in children.[17] Midazolam was also found to be more effective than hydroxyzine as a sedative agent in young pediatric dental patients.[18] The results of our study are also comparable to the studies carried out by other workers, where it was found that greater percentage of children achieved excellent sedation score with midazolam as compared to triclofos or hydroxyzine. Sixty five percent of children pre-medicated with hydroxyzine were calm but awake during separation and 95% of children pre-medicated with midazolam and triclofos were calm and sleepy at time of separation from their parents. Only 5% achieved excellent sedation level with hydroxyzine at the end of 60 min.

Saarnivaara *et al.* found that the largest dose of chloral hydrate, i.e., 75 mg/kg, provided good anxiolysis, whereas midazolam in the dose of 0.4-0.6 mg/kg produced fair anxiolysis in

children younger than 5 years and good anxiolysis in children above 5 years.[13] Kazak *et al*. in a recent study have shown that 0.5 mg/kg midazolam is a good sedative-anxiolytic for children and with parental presence the dose can be reduced to 0.25 mg/kg.[5] In our study also, 0.5 mg/kg of midazolam produced satisfactory anxiolysis after 60 min of administration. Haselhuhn compared hydroxyzine with other premedicants and found 90% children to be calm and alert, rarely dozing after hydroxyzine.[19] In our study, midazolam and triclofos were found to be more effective in providing anxiolysis at time of separation from parents as compared with hydroxyzine. This is also in concordance with the study by Singh *et al*. who found that midazolam premedication is better when compared to triclofos or promethazine for providing sedation and anxiolysis.[17] However, our results are in contrast with the study conducted by Parameswari *et al*. who found that oral triclofos provided better sedation as compared to midazolam.[20]

Kazak *et al*. have shown that midazolam in doses of 0.25 mg/kg with parental presence or 0.5 mg/kg without parental presence produced good anxiolysis as rated on the anxiety scale and sedation at the University of Michigan Sedation Scale at the time of entrance to the operating room and for tolerance to the face mask when compared to a group where no premedication was given and only parental presence was ensured.[5] In the current study, none of the children in midazolam group were combative or crying at the time of application of mask during the induction of anesthesia as compared to 20% and 5% in hydroxyzine and triclofos group respectively. This is congruous with the study by Parameswari *et al*. wherein it was found that midazolam pre-medicated children accepted the face mask better as compared to triclofos pre-medicated children.[20]

The occurrence of adverse events was consistent with known safety profile of midazolam, triclofos and hydroxyzine. Restlessness, which was seen in 15% patients in midazolam and triclofos group has been described in many studies.[8,13] Side-effects such as ataxia, drowsiness and grogginess have also been previously reported.[6] In the present study, two children in the triclofos group developed ventricular ectopics after laryngoscopy and intubation. These changes were transient in nature and resolved spontaneously. Very low incidence of severe side-effects has been reported with hydroxyzine. In our study also, minor side-effects like dry mouth were observed in 5% of patients given hydroxyzine.

Various studies have shown that midazolam, triclofos and hydroxyzine produce slight decrease in HR and blood pressure and the same effect has been noted in our study.[21,22]

The limitations of the study are that the carbohydrate content in each of the syrups could not be quantified and it may have an added sedative effect. The volume of the study drugs could not be kept constant as the drug was administered on weight basis and was not made up to a similar volume to avoid increasing the total volume given.

To conclude, midazolam was found to be better premedicant in terms of sedation, anxiolysis and safety when compared to triclofos or hydroxyzine. Triclofos also proved to be an acceptable alternative. However, hydroxyzine did not prove to be as good a premedicant.

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