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EFFECT OF MIDAZOLAM AS ORAL PREMEDICATION IN CHILDREN

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ABSTRACT

Background and Aims: The perioperative behavioural studies demonstrate that children are at greater risk of experiencing turbulent anaesthetic induction and adverse behavioural sequelae. We aimed to compare the efficacy of midazolam 0.5 mg/kg with triclofos sodium 100 mg/kg as oral premedication in children undergoing elective surgery. **Methods:** In this prospective, randomised and double-blind study, sixty children posted for elective lower abdominal surgery were enrolled. The patients were randomly divided into midazolam group (Group M) and triclofos sodium group (Group T) of thirty each. Group M received oral midazolam 0.5 mg/kg 30 min before induction, and Group T received oral triclofos sodium 100 mg/kg 60 min before induction. All children were evaluated for level of sedation after premedication, behaviour at the time of separation from parents and at the time of mask placement for induction of anaesthesia. Mann–Whitney U-test was used for comparing the grade of sedation, ease of separation and acceptance of face mask. **Results:** Oral midazolam produced adequate sedation in children after premedication in comparison to oral triclofos (P = 0.002). Both drugs produced successful separation from parents, and the children were very cooperative during induction. No adverse effects attributable to the premedicants were seen. **Conclusions**: Oral midazolam is superior to triclofos sodium as a sedative anxiolytic in paediatric population.

Key words: Anaesthesia, hypnotics and sedatives, midazolam, paediatrics, premedication, Triclofos

INTRODUCTION

The perioperative behavioural studies demonstrate that children are at greater risk of experiencing turbulent anaesthetic induction and adverse behavioural sequelae.[1] Furthermore, children admitted to hospitals are displaced from their comfort zone of home and family.[2] Proper pre-operative planning is necessary to minimize adverse psychological effects in children during the entire perioperative experience.[3] The ideal premedicant should have a rapid and reliable onset, minimal side effects, rapid recovery and should facilitate smooth induction of anaesthesia.

Oral midazolam fulfils many of the criteria required for an ideal premedicant. [4] Midazolam is currently commercially available as oral preparation, but the intravenous formulation by the oral route has been found to be more reliable and effective. A dose of 0.25–0.5 mg/kg of midazolam orally has proven to be efficacious in children with fewer side-effects.[5]

A stabilised form of chloral hydrate, triclofos sodium is an older nonopiate, nonbenzodiazepine oral sedative-hypnotic drug used for paediatric sedation in a dosage of 40–100 mg/kg for years.[6] It is more palatable than chloral hydrate. The oral solution is well-absorbed and produces hypnosis for 6–8 h.

The study was designed to compare the effects of midazolam and triclofos sodium when given as oral premedication in children. The primary objective was the sedative effect after premedication, and the secondary objectives were the anxiolytic effect at the time of separation of children from parents and at the time of mask application during induction of anaesthesia.

MATERIAL & METHODS

The study commenced after obtaining approval from the Institutional Ethics Committee. A written and informed consent was obtained from the parents of all children after explaining the nature of the study. In this prospective, randomised and double-blind study, sixty children of either gender participated in the study. Each group had thirty children each. All of them belonged to American Society of Anesthesiologists physical status I or II. Children <1 year of age and with a body weight more than 20 kg, children with difficult airway, mental retardation, central nervous system disorders, on anticonvulsant, or sedative medications and those who required additional sedation were excluded from the study. Children who participated in the study belonged to the age group of 1–8 years and underwent elective lower abdominal surgery from July 2016 to March 2017.

Pre-operative assessment was performed by a senior resident in anaesthesiology (Observer 1) who was blinded to the drug administered. Nil per oral orders were as per the standard protocol. Patients were randomly allocated to midazolam group (Group M) and triclofos sodium group (Group T) using random number draws. Oral premedication was made by the institutional pharmacist by mixing the specific drug to a fixed volume of fruit juice without pulp (orange juice) to mask the bitter taste and also to maintain the double-blind nature of the study. In Group M, placebo was given at 60 min before and preservative-free injection form of midazolam was given in the dose of 0.5 mg/kg 30 min before the anticipated time of induction of anaesthesia. In Group T, syrup triclofos sodium was administered in a dose of 100 mg/kg 60 min prior to and placebo 30 min prior to the anticipated time of induction of anaesthesia. The drug was administered by junior resident in anaesthesiology (Observer 2) and was not involved in assessing sedation score in the study. After administration of oral premedication, the children were made to relax along with their parents in an undisturbed area where there were some colourful toys. Here respiratory rate, oxygen saturation and pulse rate were monitored and recorded.

The parameters assessed were level of sedation post premedication, ease of separation from parents and the behaviour during mask acceptance. The assessment was made by anaesthesia consultant in charge of the case (Observer 3) who was blinded to the premedication the child received.

The level of sedation was graded by 5 point score [7] (1 = asleep not readily arousable, 2 = asleep responds slowly to gentle stimulation, 3 = drowsy readily responds, 4 = awake calm and quiet, 5 = awake active).

The behaviour at the time of separation from parents was assessed when the child was separated from parents to shift to operating room using the separation score [7] (1 = excellent-happily separated, 2 = good-separated without crying, 3 = fair-separated with crying, 4 = poor need for restraint). Score of ≤2 were considered successful while score >2 were considered unsuccessful. Ketamine 3 mg/kg IM with glycopyrrolate (10 μg/kg) was to be given if the

separation was difficult. In the operation theatre, sedation score, respiratory rate and oxygen saturation and heart rate were noted before induction of anaesthesia.

Inhalational induction with 33% oxygen in nitrous oxide and sevoflurane was done. Behaviour during face mask placement was assessed by cooperation score [7] (1 = cooperative, 2 = mildly resistant, 3 = resists placement of mask). Pulse rate, blood pressure and oxygen saturation were monitored. Once the child was asleep an intravenous line was set up. Endotracheal intubation was facilitated with vecuronium bromide 0.1 mg/kg. Anaesthesia was maintained with O2 (33%)-N2O-isoflurane and vecuronium. Analgesia was provided with intravenous fentanyl (1–2 μg/kg) and paracetamol suppository (20 mg/kg). The patients were transferred to postoperative recovery room and monitored.

Side-effects of oral premedicants such as nausea, vomiting, hiccups, airway obstruction, restlessness, or slurring of speech were noted after the drug administration and in the recovery period. A previous study by Saarnivaara et al. compared chloral hydrate and midazolam premedication in children. [8] A sample size of 30 per group was arrived by assuming 30% difference in sedation score, at two-sided Type 1 error of 0.05 and power of 90%. Statistical analysis was performed using the SPSS 16.0 (Statistical Package for the Social Science for windows; Version 16.0, SPSS Inc., Chicago, USA). Results were analysed using Student's t-test for parametric data and Mann–Whitney U-test for nonparametric data. Significance level was set at $P < 0.05$.

RESULTS

The age and weight were comparable in both the groups. There was a female predominance in the triclofos group. After premedication, 93.33% of children of midazolam group were adequately sedated (sedation score 4) compared to 60% in the triclofos group. The differences in sedation between the two groups were found to be statistically significant with a P = 0.002 [Table 1]. None of the children had oxygen saturation below 97%.

Table 1: Comparison of sedation scores postpremedication

Sedation score	Group M (*n*=30)	Triclofos sodium group (*n*=30)	*P*
1	0	0	0.002
2	1	12	
3	1	0	
4	28	18	
5	0	0	

n = number of cases

On comparison of separation score, both groups had an equal number of children with successful separation (score 1 and 2 clubbed together as successful).

At the time of mask application 80% of children belonging to the midazolam group were cooperative compared to 90% in the triclofos group [Figure 3]. The difference found between the two groups was statistically not significant with a P = 0.282 [Table 2]. No adverse effects attributable to premedicants were seen in both groups.

Table 2: Comparison of co-operation score (face mask acceptance by the child)

Score	Midazolam group (*n*=30)	Triclofos sodium group (*n*=30	P
1	24	27	0.282
2	6	3	
3	0	0	

n = number of cases

DISCUSSION

In paediatric day care anaesthesia, a good premedicant is required to minimize the psychological stress and to control a distressed child. It should make the child calm and quiet during induction of anaesthesia and should have no adverse cardiovascular or pulmonary ventilatory effects. It should be reliable in the onset of action with minimal side effects, should provide rapid recovery and return to alertness postoperatively permitting easy discharge from recovery room. To reduce anxiety in the subsequent visits amnesia during transport to the operation theatre and a smooth induction is desired.[9] Oral premedications in children are widely used as it is readily acceptable to children

Oral route is the route of choice for children as it is acceptable and least threatening to children.[10] Triclofos sodium is commonly used drug for sedation in children preoperatively, and also for diagnostic, dental and other potentially uncomfortable procedures.[11]

This study was undertaken to examine the efficacy of midazolam as the oral premedicant and also to compare the efficacy with triclofos sodium which is commonly used sedative-hypnotic in any setup.

In a clinical study, excellent anxiolysis was obtained in 80–90% of the children at the time of separation when oral midazolam 0.5 mg/kg was used 30 min before induction of anaesthesia.[12] Furthermore, midazolam in doses >0.5 mg/kg did not provide additional sedation or anxiolysis but caused side effects such as loss of balance and head control as well as dysphoria and blurred vision. The authors concluded that oral midazolam 0.5 mg/kg is a safe and effective premedication and its use as early as half an hour is acceptable. In another randomised, double-blind, placebo-controlled study of 124 children, an oral dose of 0.5 mg/kg midazolam was required to produce adequate sedation.[4] They also found that there was no prolongation of time to discharge and no likelihood of overnight admission. Effective and significant sedation occurred at 30 min. Hence, in our study, we selected oral midazolam 0.5 mg/kg 30 min before the induction of anaesthesia.

Intravenous preparation of midazolam was used by mixing it in a palatable vehicle and used orally.[13] The parenteral preparation mixed with fruit juice without pulp (orange juice) to make it palatable so that each millilitre contained 1 mg of midazolam hydrochloride. The intravenous formulation by the oral route has been found to be more reliable and effective when compared to the oral formulation.[13] One of the limitations of our study was the alteration in drug absorption based on pH changes induced by the diluent orange juice which was not addressed.

To assess sedation and anxiety at their peak effects of drugs, we compared the sedation score at fixed time after each premedication.[12,14] We selected 30 min for midazolam and 60 min for triclofos sodium. We also compared the behaviour of the children during separation from parents (separation anxiety) and co-operation inside the theatre while placing the face mask during induction. Some investigators have found that anxiety scores and behaviour at induction were not different in children receiving placebo or oral midazolam (0.3 mg/kg) 83 ± 38 min before induction of anaesthesia, but addition of chloral hydrate produced more calm and asleep patients at induction of anaesthesia.[15]

In a similar clinical study where both midazolam and chloral hydrate administered 65 ± 12 min before induction found good anxiolysis in chloral hydrate group compared to midazolam group.[8] They attributed the effect to the same time of administration of both the drugs. In our study majority of children were adequately sedated (awake, calm and quiet) in the midazolam group compared to triclofos sodium group which was found to be statistically significant. This observation was similar to a study where majority of children were awake, calm and quiet (25/27) in the midazolam group compared with trimeprazine (12/28). [16]

The mean duration from the administration of midazolam to separation was 33.83 ± 1.42 min in this study. We found that most of the children who received oral midazolam were awake calm and quiet, easily separable and readily accepted the mask in the operation theatre. The time interval between drug administration to separation was limited to 30– 40

min which was similar to another study.[12] In this study, the mean duration from the administration of triclofos sodium to separation was 64.16 ± 1.80 min.

The children were asleep, calm and quiet and easily separable from parents and cooperative in the operation theatre. Thus, we found that both drugs are good agents for premedication in children, and an absolute silence was maintained in the pre-operative room.

On comparing the separation scores, we found that there were equal numbers of children with successful separation in both groups (96.66%) Only one child in each group had unsuccessful separation (3.33%). Furthermore, the co-operation scores were also comparable between the two groups. Oral midazolam provided rapid anxiolysis, little sedation and easy separation within 30 min. Because of the short half-life oral midazolam, it is an ideal drug for children coming for short procedures and day stay anaesthesia where excessive sedation has to be avoided. One study found that oral triclofos provided better sedation as compared to midazolam and midazolam premedicated children accepted the face mask better as compared to triclofos premedicated children.[17] Another study found midazolam and triclofos as equally effective in producing anxiolysis at the time of separation from parents.[18] This is also in concordance with a study which found that midazolam premedication is better when compared to triclofos or promethazine for providing sedation and anxiolysis.[19]

Even though midazolam and triclofos are considered as safe premedicants, two studies have described restlessness, in 15% patients in midazolam and triclofos group.[8,16] Ataxia, drowsiness and grogginess have also been previously reported.[20] We found no side effects attributable to oral midazolam and triclofos in the present study.

The advantage of oral midazolam was that the children were adequately sedated, but it also reduced separation anxiety and improved the quality of induction of anaesthesia in the theatre. In addition, no adverse effects were seen in the group, and the premedicant was safe in children.

CONCLUSION

Children premedicated with oral midazolam were adequately sedated in comparison to oral triclofos sodium. This adds to the safety margin after premedication with oral midazolam. Quality of induction of anaesthesia was similar to that of triclofos sodium. Oral midazolam is superior to oral triclofos sodium as sedative anxiolytic in paediatric population.

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