International Journal of Science and Research (IJSR)
ISSN (Online): 2319-7064
Index Copernicus Value (2016): 79.57 | Impact Factor (2015): 6.391

Comparison of Midazolam and Triclofos Sodium as Oral Premedication in Pediatric Patients Undergoing Elective Surgery

Dr. Raksha Vyas[1], Dr. Bhavna Sojitra[2], Dr. Pragna Vachhrajani[3]

[1]Third Year Resident, Department of Anaesthesiology, Surat Municipal Institute of Medical Education and Research, Surat, Gujarat

[2]M.D, Anaesthesia Assistant Professor, Department of Anaesthesiology, Surat Municipal Institute of Medical Education and Research, Surat, Gujarat

[3]M.D D.A PGDHHM, Professor and Head Anaesthesia, Department of Anaesthesiology, Surat Municipal Institute of Medical Education and Research, Surat, Gujarat

Abstract: ***Aims and objectives: 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. Materials and Methods: In this prospective 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. Expected 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.***

Keywords: Anaesthesia, Hypnotics and sedatives, Midazolam, Premedication, Triclofos sodium

1. Introduction

- The perioperative behavioural studies demonstrate that children are at greater risk of experiencing turbulent anaesthetic induction and adverse behavioural sequelae.[1]
- The emotional and psychological trauma in children due to unfamiliar hospital environment,fear of operation ,injections and separation from parents prior to anaesthesia is well known. 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 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 hours when given as oral premedication in children.
- The primary objective was to compare the sedative effect after premedication, and the secondary objective was to compare the anxiolytic effect at the time of separation of children from parents and at the time of mask application during induction of anaesthesia.

2. Materials and Methods

The study started 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 April 2017 to August 2017. All eligible pediatric patients undergoing elective infraumbilical surgery during the study period were included.According to the current admission rate in the institute , 3 pediatric patients were posted for lower abdominal surgery per week. So,the

sample size came to be 60,divided in two groups,receiving 30 patients each.

Power=90%
Level of significance=99%
N=30 in each group(total=60 patients).

Pre-operative assessment was performed by a 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) . 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**.**

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.

Group T:syrup triclofos sodium was administered in a dose of 100 mg/kg 60 min prior to andplacebo 30 min prior to the anticipated time of induction of anaesthesia. The drug was administered by another 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 O_2(33%)-N_2O-isoflurane and vecuronium or regional anaethesia like caudal block depending upon surgery and choice of anaesthetist.

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.

3. Statistical Analysis

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 $P < 0.05$.

4. Observations and 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 [Figure 1]. 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%.

On comparison of separation score, both groups had an equal number of children [Figure 2] 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.

Sedation score	Group M (n=30)	Group T (n=30)	P value
1	0	0	0.002
2	1	12	0.002
3	1	0	0.002
4	28	18	0.002

Values expressed as number (percentage). *n*=Number of cases

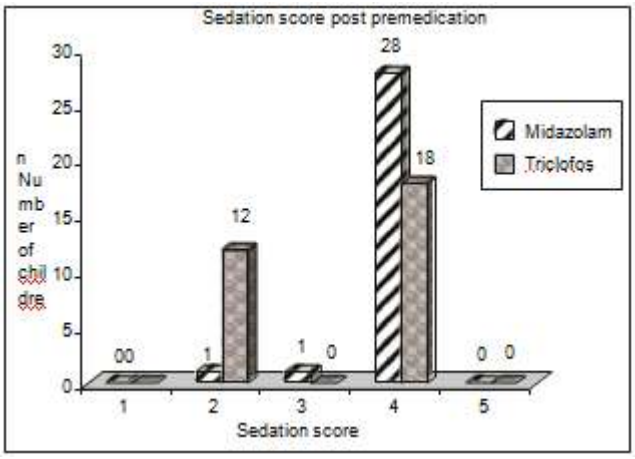

Figure 1: Level of sedation after premedication (assessed after 30 min in midazolam group and after 60 min in triclofos group) 1 = asleep not readily arousable, 2 = asleep responds slowly to gentle stimulation, 3 = drowsy readily responds, 4 = awake calm and quiet, 5 = awake active

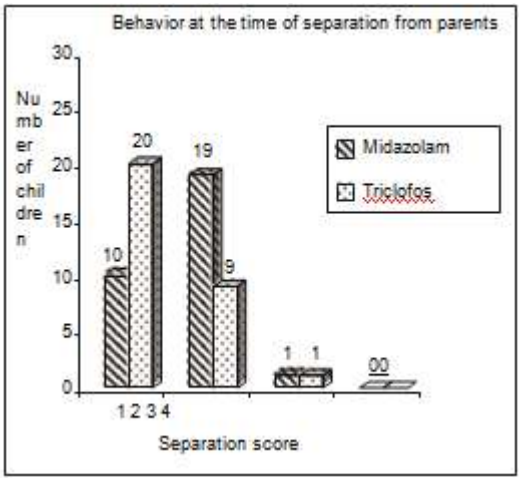

Figure 2: Separation score (at the time of separation from parents) 1 = excellent-happily separated, 2 = good-separated without crying, 3 = fair-separated with crying, 4 = poor-need for restraint.

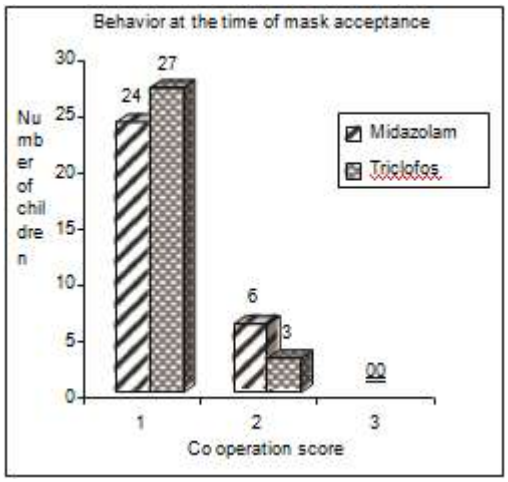

Figure 3: Co-operation score (behavior during face mask placement at the time of induction) 1 = co-operative, 2 = mildly resistant, 3 = resists placement of mask

5. 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 triclofospremedicated 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, in15% patients in midazolam and triclofosgroup.[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.

6. Conclusion

- Children premedicated with oral midazolam were adequately sedated in comparison to oral triclofos sodium.
- Quality of induction of anaesthesia and behaviour during separation from parents was similar to that of triclofos sodium.
- Oral midazolam is superior to oral triclofos sodium as sedative anxiolytic in pediatric patients.

References

[1] Cote CJ, Welzel RC. Paediatricanaesthesia. PaediatrClin North Am 1994;41:31-58.
[2] Steward DJ. Experiences with an outpatient anesthesia service for children. AnesthAnalg 1973;52:877-80.
[3] Vas L. Preanaesthetic evaluation and premedication in paediatrics. Indian J Anaesth 2004;48:347-54.
[4] Feld LH, Negus JB, White PF. Oral midazolam preanesthetic medication in pediatric outpatients. Anesthesiology 1990;73:831-4.
[5] Kazak Z, Sezer GB, Yilmaz AA, Ates Y. Premedication with oral midazolam with or without parental presence. Eur J Anaesthesiol 2010;27:347-52.
[6] Razieh F, Sharam J, Motahhareh G, Sedighah AK, Mohammad-Hosein J. Efficacy of chloral hydrate and promethazine for sedation during electroencephalography in children; a randomised clinical trial. Iran J Pediatr 2013;23:27-31.
[7] Pandit UA, Collier PJ, Malviya S, Voepel-Lewis T, Wagner D, Siewert MJ. Oral transmucosal midazolam premedication for preschool children. Can J Anaesth 2001;48:191-5.
[8] Saarnivaara L, Lindgren L, Klemola UM. Comparison of chloral hydrate and midazolam by mouth as premedicants in children undergoing otolaryngological surgery. Br J Anaesth 1988;61:390-6.
[9] Griffith N, Howell S, Mason DG. Intranasal midazolam for premedication of children undergoing day-case anaesthesia: Comparison of two delivery systems with assessment of intra-observer variability. Br J Anaesth 1998;81:865-9.
[10] Nicolson SC, Betts EK, Jobes DR Chriastianson LA, Walters JW, Mayes KR, Korevaar WC. Comparison of oral and intramuscular premedication for pediatric inpatient surgery. Anaesthesiology 1989;71:8-10.
[11] Millichap JG. Electroencephalographic evaluation of triclofos sodium sedation in children. Am J Dis Child 1972;124:526-7.
[12] McMillan CO, Spahr-Schopfer IA, Sikich N, Hartley E, Lerman J. Premedication of children with oral midazolam. Can J Anaesth 1992;39:545-50.
[13] Brosius KK, Bannister CF. Midazolam premedication in children: A comparison of two oral dosage formulations on sedation score and plasma midazolam levels. AnesthAnalg 2003;96:392-5.
[14] Kaplan RF, Yaster M, Stafford MA, Cote CJ. Pediatric sedation for diagnostic and therapeutic procedures

outside the operating room. In: Cote CJ, Ryan JS, Todres ID, Goudsouzian NG, editors. Anesthesia for Infants and Children. 3rd ed. Philadelphia: WB Saunders Company; 1994. p. 598-600.
[15] Anderson BJ, Exarchos H, Lee K, Brown TC. Oral premedication in children: A comparison of chloral hydrate, diazepam, alprazolam, midazolam and placebo for day surgery. Anaesth Intensive Care 1990;18:185-93.
[16] Mitchell V, Grange C, Black A, Train J. A comparison of midazolam with trimeprazine as an oral premedicant for children. Anaesthesia 1997;52:416-21.
[17] Parameswari A, Maheedar G, Vakamudi M. Sedative and anxiolytic effects of midazolam and triclofos oral premedication in children undergoing elective surgery: A comparison. J AnaesthClinPharmacol 2010;26:340-4.
[18] Chaudhary S, Jindal R, Girotra G, Salhotra R, Rautela RS, Sethi AK. Is midazolam superior to triclofos and hydroxyzine as premedicant in children? J AnaesthesiolClinPharmacol 2014;30:53-8.
[19] Singh N, Pandey RK, Saksena AK, Jaiswal JN. A comparative evaluation of oral midazolam with other sedatives as premedication in pediatric dentistry. J ClinPediatr Dent 2002;26:161-4.
[20] Connors K, Terndrup TE. Nasal versus oral midazolam for sedation of anxious children undergoing laceration repair. Ann Emerg Med 1994;24:1074-9.