IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 18, Issue 3 Ser. 11 (March. 2019), PP 37-41
www.iosrjournals.org

Randomised Clinical Trial to Compare the Sedative Effects of Oral Triclofos with Oral Midazolam as Premedicants in Children

Dr Mytily, Dr. Sathya,
Assistant professors, Dept of anaesthesiology, Coimbatore medical college hospital, Coimbatore, Tamilnadu.
Corresponding Author: Dr Mytily

Abstract: *Background and Aims: Premedication in children is necessary to allay fear and anxiety before surgery and provide a smoother anaesthesia for the children. The search for a perfect premedicant has been on and continues. So we have done this study to find out a good premedication out of the ones widely used. Oral midazolam and Oral triclofos were compared as a premedicant in paediatric patients coming for daycare surgeries in our study. Methods: Double blinded randomised clinical trial was conducted.150 children of ASA class 1 were randomly allocated into 2 groups, one group received oral midazolam 0.5 mg/kg body weight and the other group received oral triclofos 75mg/kg body weight. Drug acceptance score, parent separation score and mask acceptance score were compared among the two groups. Sedation scores were recorded at various time intervals and after 45 minutes of drug administration in both the groups. Also the hemodynamic variables and adverse effects were recorded in both the groups. The collected data was analysed with SPSS 16.0 version. To find the significance difference between the bivariate samples in paired groups Wilcoxon signed rank test was used for skewed data and paired sample t-test for the normal data and for independent groups Mann-Whitney U test for skewed data and unpaired sample t-test for the normal data was used. For the multivariate analysis in the repeated measures the Friedman test was used. The probability value 0.05 is considered as significant level. Results: Triclofos being more palatable, was better accepted by the children, produced excellent sedation than midazolam after 45 minutes. The parent separation score was comparable between the two groups. The mask acceptance score was good with triclofos than midazolam. The postoperative recovery score was better with triclofos. Conclusion: Oral triclofos is better than oral midazolam as a sedative premedicant in paediatric patients.*

Keywords: *Sedation, midazolam, triclofos, children, premedication.*

Date of Submission: 28-02-2019 Date of acceptance:18-03-2019

I. Introduction

Surgery is always a stress to patients and causes anxiety and fear in the minds of patients. This is particularly significant in paediatric age group as they are separated from the parents causing fear that makes the child uncooperative and agitated. Surgery in paediatric age group is a great stress to both the parents and the children. The feeling of fear, anxiety and insecurity is mainly due to the separation of the child from the parent and also the encounter of strangers with mask and caps. Moreover children are also apprehensive of the needle prick and a face mask that puts them in a state of doom. So to calm down the child and to obtain their cooperation during parent separation, a premedicant is necessary. Premedication to sedate the children is a major part of anaesthetizing paediatric patients.

Various forms of premedicant drugs are available like oral formulations, nasal spray, sublingual preparations, intramuscular injections, rectal suppositories etc. Out of these, oral formulation is easier and simpler to administer in children. Children are more compliant with the oral formulations which are usually prepared as flavoured syrup making it acceptable by the children. Among the commonly used premedicant drugs, oral triclofos and oral midazolam are better sedatives and free of major adverse effects. These drugs leave the child sedated and withdrawn from surroundings which allows a calm child entering the theatre instead of a crying and agitated child. These drugs also have the advantage of short duration of action so that the child can be discharged on the same day. So these drugs are being used predominantly in day care surgeries.

Oral Triclofos has been used in the past as a sedative for various procedures like dental procedures, dressings, for the purpose of investigations like CT scan, MRI etc. With the upcome of Midazolam, the use of Triclofos has decreased to a great extent. Though Midazolam is short acting and has a rapid onset of action, the level of sedation produced is not as satisfying as with Triclofos. So this study was conducted to study the sedative effects of both these drugs; also the adverse effects and the anxiolytic effects were compared.

II. Methods

150 ASA I patients (calculated with G* power 3.13 with reference to parent study) in the 2-9 years age and both sex undergoing day care surgeries under general anesthesia were randomly allocated into 2 groups by lots method, 75 children in midazolam group and 75 children in triclofos group. ASA PS1 cases were chosen so that there is no major side effect either by the drug or the co existing disease condition. The maximum weight allowed in the study was 20 kg to avoid giving large volume of drug as premedication thereby preventing aspiration.

Informed consent was obtained from the patient's parent or guardian. General physical examination and history taking were done. The child was shifted to the premedication room and oral midazolam 0.5mg/kg (iv drug containing 5mg/ml made into total volume of 0.5ml/kg mixed with flavoured paracetamol syrup) or oral triclofos 75mg/kg (each ml containing 100 mg made to a volume of 0.5 ml/kg was administered using a drug filler according to which group the child belongs to, by an assistant, who was not involved in the study. Drug compliance score was recorded in both the groups.

Drug Compliance Score:

1	good	Readily takes medicine
2	fair	Accepts medicine with persuasion
3	poor	Unwilling to take medicine or spits it out
4	Very poor	Refuses medicine

The children were observed for any side effects and hemodynamic variations were recorded at 5 minutes interval using multipara monitors. The level of sedation was assessed using the sedation score after 10, 20, 30 and 45 minutes of drug administration.

Ramsay Sedation Score

Level	Characteristics
1	Patient awake, anxious, agitated or restless
2	Patient awake, co-operative, oriented and tranquil
3	Patient drowsy, with response to commands
4	Patient asleep, brisk response to glabellar tap or loud auditory stimulus
5	Patient asleep, sluggish response to stimulus
6	Patient has no response to firm nail bed pressure or other noxious stimuli

The child was repeatedly assessed for the level of sedation and sent to operation theatre after 45 minutes of drug administration. Parent separation scoring was documented at this point. After shifting to operating table, basic parameters like blood pressure, heart rate and oxygen saturation were recorded.

Mask acceptance score was documented. Child was induced with sevoflurane 8% and O_2/N_2O mixture and atropine 0.02mgiv, in combination with fentanyl 1 to 2mcg/kg iv given. When the child was breathing smooth and regular, and when there was centrally fixed eye gaze, sevoflurane dial settings stepped down to 2%. Anesthesia was maintained with sevoflurane 2% and caudal block given using 0.25% of bupivacaine 1ml/kg. Anesthesia was maintained with sevoflurane, nitrous oxide and oxygen with Fio2 of 50%. Intra –operative heart rate, SPO2 and respiratory rate were recorded every 5 min for first 30 min and subsequently every 10 min intervals till the end of surgery. Bradycardia (HR < 60) persisting for > 2 min, is treated with Atropine 0.02 mg/kg IV boluses. Volatiles discontinued at the end of procedure. Ondansetron 0.2 mg/kg IV is given if post operative nausea vomiting present. Sedation score, heart rate, SPO2 and respiratory rate were observed for next 6 hours.

The datas collected from the study were statistically analysed. The collected data was analysed with SPSS 16.0 version. To describe about the data descriptive statistics frequency analysis, percentage analysis were used for categorical variables and for continuous variables the mean and standard deviation were used.

Triclofos was better in our study as a good sedative, with sedation score significantly better ($p=0.000$) with triclofos than midazolam .The drug acceptance was better with triclofos. The parent separation score was comparable between the two groups. The mask acceptance score was good with triclofos.

III. Discussion

Premedication is an essential part of anaesthesia in children. Midazolam is widely used in paediatric premedication. This study was done to compare the effectiveness of midazolam with the age old triclofos as sedative in paediatric premedication. A sample size of 142 was arrived accounting for any dropout from the study due to practical difficulties like spitting out of the drug, etc

ASA PS 1 cases were chosen so that there are no major side effects by the drug or the co existing diseases. The maximum weight allowed in the study was 20 kg to avoid large volume of premedicant drugs .

Luz Maria et al[19], have accepted ASA 1 and 2 patients for their study on evaluating the efficacy of oral midazolam with acetaminophen for premedication. Wilson et al[16], selected ASA 1 patients for their study on the effectiveness of oral midazolam for sedation in orthodontic procedures.

The dose of drug was chosen as Midazolam 0.5 mg/kg based on the study, "Premedication of children with midazolam " by Mc Millan et al[21],which concluded that oral midazolam given at a dose of 0.5 mg/kg was effective at causing sedation without any side effects. Fazi et al[11], in a study to compare oral midazolam and clonidine for sedation of paediatric tonsillectomy patients used midazolam as 0.5 mg/kg. Shabbir et al[33], in their study for comparison of conscious sedation between oral midazolam and triclofos used midazolam 0.5 mg/kg orally.

The dose of triclofos was 75 mg/kg based on the studies of Aruna Parameswari et al[2] and Sujata Chaudhry et al[35], where the doses of 75 mg/kg proved effective in both the studies. R.K.gupta et al[29], in their study on oral premedication in children had used oral triclofos in the dose of 75 mg/kg. Bhatnagar et al[4], in their study on comparison of oral midazolam, triclofos and zolpidem for sedation of paediatric dental patients used triclofos in the dose of 70mg/kg.

The use of intravenous preparation of midazolam given orally mixed with a vehicle in our study to make it palatable and the fact that it is more reliable and effective than the commercially available formulation is supported by the study of Brosius KK et al[5], where the study proved that the iv preparation mixed with a vehicle produced a more reliable sedation and higher plasma level of the drug compared to the equivalent dose of the commercially available preparation. The drugs were given 45 minutes prior to induction time to match the peak effect of both the drugs in common[2].

The age distribution was comparable in our study, with the mean age being 4 years in both the groups and insignificant difference was noted (p=0.442) between the two groups. The gender difference between the midazolam and triclofos group was not significant (p=0.547) and the weight in kilograms of the children in both the groups was on an average 13.7 kg without any significant difference (p=0.741). This is in favour that any difference between the two groups in demographic profiles would be purely by chance.

The aim of our study was to compare the sedative effects of oral midazolam and oral ticlofos. Triclofos was better in our study as a good sedative, with the sedation score significantly better (p=0.000) with triclofos than midazolam which is in concordance with Aruna Parameswari et al[2] study where they concluded triclofos as a better sedative anxiolytic than midazolam.

The drug acceptance was better with triclofos shown by a statistically significant difference (p=0.032) in contrary to the study by Sujata Chaudhry et al[35] in which greater percentage of children were compliant with midazolam than triclofos but with a statistically insignificant difference. Aruna Parameswari et al[2], in the study for comparison of sedative effects of triclofos and midazolam had 80% of the patients in midazolam group accepted the drug whereas 20% resisted the dug, but in triclofos group 75% accepted the drug and 25% resisted the drug but the difference between the two groups was not statistically significant.

Sedation scores at 10 minutes and 20 minutes showed no significant difference between the two drugs. Whereas the sedation scores at 30 minutes of drug intake showed 40% of children in score5 in triclofos group, but the midazolam group had only 13% in score5, which means there is a statistically significant difference (p=0.004).

The preoperative sedation score showed a highly significant difference (p=0.000) at 45 minutes of drug administration with the triclofos group having 34% of the children in score 6 against midazolam group which had only 12% of children in score 6. So it was evident from the preoperative sedation scores, that triclofos produces better sedation than midazolam which is similar to the results of the study of Aruna Parameswari et al[2], where only 5% of patients in midazolam group after 30 minutes were asleep as compared to 65% after 90 minutes in the triclofos group, showing a significant difference. Bhatnagar et al[4], in comparing oral midazolam with triclofos and two other drugs, triclofos had better sedation score when compared to midazolam.

Mohamed et al[23], found that oral midazolam with ketamine provided high sedation levels after 30 minutes of administration when compared to dexmedetomidine in their study. Wilson et al[16] in studying the effectiveness of oral midazolam sedation for paediatric orthodontic procedures, found that the mean level of sedation to be greater for midazolam when compared to nitrous oxide. Singh et al[34], found midazolam to be the best sedative among the three drugs (midazolam, triclofos, promethazine) for conscious sedation in paediatric dentistry.

The parent separation score was comparable between the two groups in the present study (p=0.3). Sujata Chaudhary et al[35], in their study also showed comparable parent separation score with both midazolam and ticlofos. Luz Maria et al[19], in their study on efficacy of oral midazolam combined with acetaminophen showed that 86% of children were quiet at parent separation.

The mask acceptance score was good with triclofos as compared to midazolam (p=0.00) in our study. In contrary, Aruna Parameswari et al[2], have depicted a better mask acceptance with midazolam in their study comparing 40 children with 20 in each group. Whereas Sujata Chaudhary et al[35], had no difference in both the

groups when comparing 20 children in the midazolam group with 20 in the triclofos group for mask acceptance. Nicole Almanrader et al[25], found no statistical difference between clonidine and midazolam for mask acceptance with 86% satisfactory mask induction in midazolam group and 83% in clonidine group. Mohamed et al[23], study demonstrated better facemask acceptance at induction in the midazolam ketamine group when compared to dexmedetomidine group.

The postoperative sedation scores at 2 hours postoperative showed significant difference between the triclofos and midazolam (p=0.015), with midazolam showing greater percentage of the children in higher sedation levels but the post operative sedation scores at 1, 3 ,4, 5 and 6 hours showed no significant difference between the two groups. Sujata Chaudhary et al[35], found no significant difference in the post operative recovery characteristics in the midazolam and triclofos group in their study. There was no significant difference in the recovery profile between the butorphanol and midazolam group in the study by Singh et al[34]. No significant difference noted by Saarnivaara et al[18] in the recovery scores between chloral hydrateand midazolam in children.

The intraoperative variables in the two groups did not show a significant variation (p>0.05) from the pre operative values. The adverse effects occurred were minimal and were statistically insignificant (p=0.412). Laryngospasm occurred in 2 children in the midazolam group, treated with 100% 0_2; vomiting occurred in 1 child in both the groups , Inj ondansetron given iv. One child in triclofos group had shivering.

IV. Limitations

Peak onset of action of both the drugs was not similar but the difference was only 10-15 minutes. As the study included only day care procedures, most of the children were males presenting with phimosis, hernia and hydrocele for surgery. The volume of drug in both the groups could not be kept constant as drug was administered on weight basis and the two drugs are available as different per millilitre doses.

Bibliography

[1]. Arathi Papineni, Liege Lourenic O.Matharu & Paul F.Shley Safety of oral midazolam sedation use in paediatric dentistry: a review International journal of Paediatric dentistry 2014, 24, 2-14.

[2]. Aruna Parameswari, Gudapati Maheedar, Mahesh Vakamudi. Sedative and anxiolytic effects of midazolam and triclofos oral premedication in children undergoing elective surgery, A comparison; Journal of anaesthesiology clinical pharmacology 2010, 26(3):340-344.

[3]. Ashu Mathai, Marilynn Nazareth, Rinu Susan Raju, Preanesthetic sedation of preschool children: Comparison of intranasal midazolam versus oral promethazine, Anaesthesia: Essays and researches January-June 2011, 5(1), 67-71.

[4]. Bhatnagar S, Das UM, Bhatnagar G, Comparison of oral midazolam with oral tramadol, triclofos and zolpidem in the sedation of pediatric dental patients: An in vivo study Journal of Indian society of Pedodontics and preventive dentistry, April-June 2012, Issue 2, Vol 30, 109-114.

[5]. Brosius KK, Bannister CF, Midazolam premedication in children: A comparison of two oral dosage formulations on sedation score and plasma midazolam levels. Anesth Analg 2003; 96: 392-5

[6]. C.Abdallah anf R.Hannallah, Premedication of the child undergoing surgery, M.E.J. Anesth 21(2), 2011, 168-176.

[7]. Chandni Sinha , Manpreet Kaur, Ajeet kumar, Anand Kulkarni, Bareesha M, Madhusudan Upadaya, Comparative evaluation of midazolam and butarphanol as oral premedication in paediatric patients, Journal of anaesthesiology clinical pharmacology, January-March 2012/ Vol 28/ Issue 1, 32-35.

[8]. Cote, Charles J, Cohen, Ira T, Suresh, Santhanam, Rabb, Mary, Rose, John B, Weldon, B.Craig, Davis, Peter J, Bikhazi, George B, Karl, Helen W, Hummer, Hannallah, Raafat S,Khoo, Ko Chin MS, Collins, Patrice, A Comparison of three doses of a commercially pepared oral midazolam syrup in children, Anaesthesia & Analgesia : January 2002-volume 94-Issue 1-pp 37-43.

[9]. Elliot Krane, Guidelines for the Paediatic preoperative anaesthetic evaluation.

[10]. Etsuro K. Motoyama, Peter J. Davis, Smith's Anaesthesia for infants and children, seventh edition, 265-268.

[11]. Fazi l, Jantzen EC, Rose JB, Kuth CD, Watcha MF, A comparison of oral clonidine and oral midazolam as preanesthetic medications in the pediatric tonsillectomy patient, Anesthesia Analagesia, 2001 Jan; 92(1): 56-61.

[12]. Jackson EA, Rabbette PS, Dezateux C, Hatch DJ, Stocks J. The effect of triclofos sodium sedation on respiratory rate, oxygen saturation , and heart rate in infants and young children. Pediatric Pulmonology 1991; 10:40-5.

[13]. Juliet D.Boyd and Margaret L. M. Manford, Premedication in children, A Controlled Clinical trial of oral triclofos and diazepam, British journal of anaesthesia, 1973, 45:501-506.

[14]. Kain ZN, Hofstadter MB et al. Midazolam: Effects on amnesia and anxiety in children. Anesthesiology 2000; 93(3): 676-684.

[15]. Kazak Z, Sezer GB, Yilmaz AA, Ates Y. Premedication with oral midazolam with or without parental presence. Eur J Anaesthesiology 2010; 27: 347-52.

[16]. K.E. Wilson, R.R.Welbury and N.M. Girdler, A study of the effectiveness of oral midazolam sedation for orthodontic extraction of permanent teeth in children: a prospective, randomised, controlled, crossover trial, British dental journal, April 2002, volume 192, no 8, 457-462.

[17]. Lindgren L. The effects of oral triclofos premedication in children. Anesthesia Analgesia 1986; 65: 963-974.

[18]. L.Saarnivaara, L. Lindgren and U.M.Klemola, Comparison of chloral hydrate and midazolam by mouth as premedicants in children undergoing otolaryngological surgery. British journal of anaesthesia 1988(61) 390-396.

[19]. Luz Maria Gomez B, Federico Ocampo A, Jaime Andres Orozco A, Juliana Caicedo S, Efficacy of anaesthetic premedication in pediatric patients using oral midazolam and acetaminophen. Observational study Colombian journal of anaesthesiology 2013, 41(1) 4-9.

[20]. Mary Ellen McCann, MD.FAAP, and Zeev N Kain, The management of preoperative anxiety in children: An Update, Anesthesia Analgesia review article 99 2001; 93:98-105.

[21]. Mc Millan CO, Sphar-Schoeffr IA, Sikich N et al . Premedication of children with oral midazolam. Can J Anaesth 1992; 39(6): 545-550.

[22]. Michael F.Hasty, DDS, MS William F .Vann, Jr, DMD, MS, PhD Diane C.Dilley, D Jay A.Anderson, DDS, Conscious sedation of pediatric dental patients: an investigation of chloral hydrate, hydroxyzine pamoate, and meperidine vs chloral hydrate and hydroxyzine pamoate Pediatric dentistry: January/February, 1991-volume 13, numbe 1, 10-19.
[23]. Mohamed A Daabiss and Mohamed Hashish, Dexmedetomidine versus Ketamine combined with midazolam: a comparison of anxiolytic and sedative pemedication, British journal of medical practitioners December 2011, volume 4, number 4.
[24]. M.R.J.Sury, Paediatric sedation, Oxford journals, BJA CEACCP, volume4, Issue 4:118-122.
[25]. Nicole Almenrader, Maurizio Passariello, Bruno Coccetti, Robeta Haiberger and Paolo Pietropaoli, Premedication in children: a comparison of oral midazolam and oral clonidine, Pediatric Anesthesia 2007, 17:1143-1149.
[26]. Payne K, Mattheyse FJ, Liebenberg D, Dawes T. The pharmacokinetics of midazolam in paediatric patients. Eur J Clin Pharmacology 1989; 37: 267-72.
[27]. Razieh Fallah, Mohammad Hosein Ataee Nakhaei , Shekofah Behdad, eza Nafisi Moghaddam and Ali, Oral chloral hydrate vs Intrasal Midazolam for sedation during computerized tomography, Indian Paediatrics, 2013, 50, 233-235.
[28]. Reves JG, Kissin I, Smith LR, The effective dose of midazolam. Anesthesiology 1981;55:82.
[29]. R.K.Gupta, H.R.Blades, D.J.Hatch, Oral premedication in children, Anaesthesia vol 27, no 1 January 1972, 32-36.
[30]. Robert K Stoelting, Simon C Hillier, Pharmacology & Physiology in Anaesthetic practice, fourth edition, 140-146.
[31]. Ronald S Litman, Jennifer A Kottra, Dot,Karen A Verga, DDSS, Robert J Berkowitz, DDSS and Denham S Ward, MD, PhD, Chloral hydrate sedation: The additive sedative and respiratoy depressant effects of nitrous oxide, Anaesthesia Analgesia 1998; 86: 724-8.
[32]. Saad A Sheta and Maha Al Sarheed, Oral midazolam premedication for children undergoing general anaesthesia for dental care, International Journal of Pediatrics, volume 2009, Article ID 274380, 7pages.
[33]. Shabbir A, Bhat SS, Sundeep Hegde K, Salman M, Comparison of oral midazolam and triclofos for conscious sedation of uncooperative children, in the journal of clinical paediatric dentistry 2011, volume 36, number 2, 189-196.
[34]. Singh N, Pandey RK, Saksena AK, Jaiswal JN, A comparative evaluation of oral midazolam with other sedatives as premedication in pediatic dentistry, J CIi Pediatr Dent. 2002 Winter; 26(2):161-4.
[35]. Sujata Chaudhary, Reena Jindal, Gautam Girotra, Rashmi Salhotra, Rajesh Singh Rautela, Ashok kumar Sethi. Is midazolam superior to triclofos and hydroxyzine as premedicant in children? , Journal of anaesthesiology clinical pharmacology, January-March 2014, volume 30, Issue1: 53-58.
[36]. Suresh C, Kulshetra S, Jain A, Kohli P. Oral premedication for pediatric anaesthesia –Comparison of midazolam and ketamine. Indian J Anaesth 2000; 44:41-6.
[37]. Thomas Vetter, A comparison of midazolam, diazepam and placebo as oral anesthetic premedicants in younger children, Journal of clinical anaesthesia, January-february 1993, volume 5, issue 1, 58-61.
[38]. Weldon BC, Watha MF, White PF. Effects of oral midazolam in children. Anesthesia Analgesia 1992; 75: 51-55.

Mytily. "Randomised Clinical Trial to Compare the Sedative Effects of Oral Triclofos with Oral Midazolam as Premedicants in Children." OSR Journal of Dental and Medical Sciences (IOSR-JDMS), vol. 18, no. 3, 2019, pp 37-41.