

COMPARISON OF EFFICACY OF ORAL MIDAZOLAM, KETAMINE AND TRICLOFOS SODIUM AS PREMEDICANTS IN CHILDREN

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ABSTRACT

BACKGROUND

In paediatric anaesthesia a good premedication is essential to reduce anxiety and agitation in children. Parental separation and strange operating room environment usually result in stormy induction while providing general anaesthesia. Sedative premedication is essential to make children calm and co-operative in the strange environment.

The aim of this study was to compare the efficacy of orally administered midazolam 0.5 mg/Kg, ketamine 5 mg/Kg and triclofos sodium 100 mg/Kg in children prior to induction of general anaesthesia for minor elective surgical procedures.

MATERIALS AND METHODS

A total of 180 children of both genders aged 1-8 years and American Society of Anesthesiologists (ASA) physical status I-II scheduled for minor elective surgical procedures under general anaesthesia were enrolled in this prospective randomized controlled trial. Patients were randomly allocated to receive oral midazolam (Group M, n=60), ketamine (Group K, n=60) and oral triclofos sodium (Group T, n=60). Group M children were premedicated with oral midazolam syrup 0.5 mg/Kg. 45 minutes prior to induction, Group K children were premedicated with oral ketamine syrup 5 mg/Kg and Group T children were premedicated with triclofos sodium syrup 100 mg/Kg 45 minutes prior to induction of anaesthesia. All children received oral atropine 0.04 mg/Kg 45 minutes before induction of anaesthesia. All children were evaluated for behaviour in the operating room environment during face mask placement for induction of general anaesthesia. The adverse effects related to each drug were recorded for 24 hour post operatively.

Setting and Design- Randomized controlled study.

Statistical Analysis- Pearson chi square test was used for qualitative data and Kruskal-Wallis test for qualitative or semi qualitative data. Kruskal-Wallis test was used to compare the behaviour of children in the operating room while placing the face mask for induction of general anaesthesia. Significance level was set at a p value of <0.001.

RESULTS

Children of all three groups were cooperative during induction of general anaesthesia. Cooperation score was assessed by acceptance of face mask by children before induction of anaesthesia. It was observed that 75% children were very cooperative with a score of 1 in oral ketamine group, 80% were very cooperative with a score of 1 in oral midazolam group and 90% were very cooperative with a score of 1 in oral triclofos sodium group (p=0.097). Even though we observed a difference between these groups clinically, during placement of mask before induction of anaesthesia the difference found was not statistically significant. The cooperation scores were comparable and satisfactory in all the three groups. No adverse effects were noted in children premedicated with oral midazolam and oral triclofos groups. But vomiting and abnormal movements were observed in two children premedicated with oral ketamine.

CONCLUSION

Oral midazolam, triclofos, and ketamine were effective in children before induction of general anaesthesia. Children accepted face mask and allowed smooth induction of general anaesthesia inside the operating room. All the three oral premedicants demonstrated comparable behaviour in the strange operation room environment. All the three premedicants are good and safe in paediatric anaesthesia.

KEYWORDS

Midazolam, Ketamine, Triclofos, Anaesthesia, Paediatrics, Premedication, Sedatives.

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BACKGROUND

The perioperative period is usually a traumatic experience for children undergoing surgery. Children are not cooperative in the strange environment, preoperative anxiety and stormy induction of anaesthesia may adversely affect the personality and behaviour in the post-operative period.¹ Premedication with sedative drugs reduce the adverse behavioural sequelae in the peri-operative period.²

Sedative premedication, parental presence during anaesthesia induction and behavioural preparation are some approaches adopted to make the children comfortable and cooperative. Sedative premedications are used widely to make children comfortable in the perioperative period. The ideal premedicant should have rapid and reliable onset of action, rapid recovery, simple route of administration, reliable pain relief and minimal side effects.^{3,4} Oral midazolam 0.5 mg/Kg is highly effective with adequate sedation and less side effects.⁵ Triclofos sodium a stabilized form of chloral hydrate is an oral sedative hypnotic used in the dose of 40-100 mg/Kg for paediatric sedation.⁶ Oral ketamine 3-10 mg/Kg is commonly used for paediatric sedation and it has analgesic properties and high first pass metabolism but the undesirable effects are salivation, vomiting, abnormal movement and delirium.⁷

The study was done to compare the clinical effects of orally administered midazolam, triclofos sodium, and ketamine in children administered forty five minutes prior to induction of anaesthesia. Reduction in anxiety will ensure smooth induction in children. Preoperative management of anxious and non-cooperative children is one of the great challenges in paediatric anaesthesia.

MATERIALS AND METHODS

This study was conducted after approval from the Institutional Ethics Committee. A written and informed consent was obtained from the parents of all children. The study design was prospective, randomized and double blind trial. A total of 180 children of either gender (sixty in each group) participated in the study. Children scheduled for minor elective surgeries under general anaesthesia aged between one to eight years were included in the study. The study was conducted from December 2010 to September 2011 in the paediatric operating room of Govt. Medical College Kozhikode in a tertiary referral teaching hospital. All of them belonged to the Physical Status I or II as outlined by the American Society of Anesthesiologists (ASA).

Exclusion Criteria

1. Children less than one year and more than eight years of age.
2. Body weight more than 20 kg.
3. Children with difficult airway.
4. Central nervous system disorders.
5. Respiratory tract infection.
6. Patient on anticonvulsant and sedative medications.

Preoperative assessment was done by senior resident in anaesthesiology (Observer 1) who was blinded to the premedicant drug administered. Nil per oral orders were as per the standard protocol. All children were randomly allocated to group M (Midazolam group), group T (Triclofos sodium group) and group K (Ketamine) using random number draws.

Since ketamine syrup was not available, oral preparation of ketamine was made by the institutional pharmacist by mixing the specific drug (parenteral 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, syrup midazolam was given in the dose of 0.5 mg/Kg forty-five minutes prior to the anticipated time of induction of anaesthesia. In Group K ketamine was given in a dose of 5 mg/Kg forty-five minutes prior to the anticipated time of induction of anaesthesia. In Group T, syrup triclofos sodium was given in a dose of 100 mg/Kg forty-five minutes prior to the anticipated time of induction of anaesthesia. All children received oral Atropine 0.04 mg/Kg forty-five minutes before induction. The drug was administered by junior resident in anaesthesiology (Observer 2) in the preoperative holding area in the presence of the parent. Observer 2 was not involved in assessing the cooperation score in the study. Children who refused to take the drug were excluded from the study. On reaching the operating room a three-point score was used to assess the behaviour during face mask placement.

Behaviour during face mask placement was assessed by a three-point scale (cooperation score)⁸

1. Cooperative during mask placement for induction of anaesthesia.
2. Mildly resistant during mask placement for induction of anaesthesia.
3. Resist placement of mask during induction of anaesthesia.

Behaviour during mask placement was assessed by senior consultant in charge of the case (Observer 3) who was blinded to the premedication the child received. Routine monitors were connected before induction of anaesthesia. After preoperative assessment all children were subjected to inhalation induction with sevoflurane 8% in O₂- N₂O mixture. Variables monitored were oxygen saturation, electrocardiogram, heart rate and non-invasive blood pressure. After securing intravenous line, analgesia was provided with Fentanyl citrate (1-2 µg/kg). Endotracheal intubation was done under vecuronium bromide 0.1 mg/Kg. Anaesthesia maintained with sevoflurane, 66% N₂O in O₂ and vecuronium. Ventilation was done with Jackson Rees Circuit. All children received lactated Ringers solution at 6ml/kg/hour. Intra operative reduction of mean arterial blood pressure or heart rate by more than 30% of base line was defined as hypotension or bradycardia respectively, and they were treated with fluid bolus, ephedrine or atropine sulphate. Post-operative analgesia was provided with paracetamol suppository (20 mg/Kg). Residual neuromuscular blockade was antagonized with neostigmine (0.05 mg/Kg) and glycopyrrolate 0.01 mg/Kg). After extubation, the children were transferred to the post anaesthetic care unit for at least two hour or till complete recovery. Pulse rate, respiratory rate, and saturation were monitored continuously. The incidence of adverse effects such as nausea, vomiting, desaturation and abnormal movements were recorded.

Statistical Analysis

Data was analysed using SPSS 16.0 (Statistical package for the Social Science for windows; Version 16.0 SPSS Inc Chicago, USA). Results were analysed using Pearson chi square test for qualitative data and Kruskal-Wallis test for qualitative or semi quantitative data. Significance value was set at a P value of ≤ 0.001 .

RESULTS

The age and weight were comparable in all the three groups (Table I). There was a female predominance in the ketamine group but this was neglected since the sex characteristics do not affect the pharmacokinetics of drugs used in the study. ASA Grade was also comparable. (Table 2).

Co-operation Score (Face mask acceptance by the child)

After separation from the parents the behaviour at the time of face mask application was noted in the operating room and was compared between the three groups. At the time of face mask application 75% of children belonged to the ketamine group, 80% of children in the midazolam group and 90% children in the triclofos group were very cooperative and accepted the face mask without any resistance. Clinically higher proportion of patients in the triclofos group were very cooperative compared to oral midazolam group and oral ketamine group (Figure 1). The difference noted between triclofos group, midazolam group and ketamine group were statistically not significant with a P value of 0.097 (Table 3).

Parameters	Group M (n=60)	Group T (n=60)	Group K (n=60)	p-Value
Age (Years) Mean (SD)	4.72 (2.5)	4.22 (2.27)	4.26 (2.1)	0.437 (NS)
Weight (Kg) Mean (SD)	14.58 (4.8)	13.52 (4.25)	14.03 (4.40)	0.44 (NS)
Gender Male/Female	44/16	46/14	38/22	

Table 1. Comparison of Demographic Data

Kruskal Wallis test for age and sex, n= number of cases, SD – Standard Deviation. NS-Not significant.

ASA Grade	Group M (n=60)	Group T (n=60)	Group K (n=60)
I	58	58	58
II	2	2	2
Total	60	60	60

Table 2. ASA Grade

ASA- American Society of Anaesthesiologist.

Co-operation Score	Group M (n=60)	Group T (n=60)	Group K (n=60)	Total	p-Value
1	48 (80%)	54 (90%)	45 (75%)	147	0.097 NS
2	12 (20%)	6 (10%)	15 (25%)	33	
3	0	0	0	0	

Table 3. Comparison of Co-Operation Score (Face Mask Acceptance by The Child)

Kruskal-Wallis Test.

NS: Not Statistically significant,

n=Number of cases,

Values expressed as number (percentage)

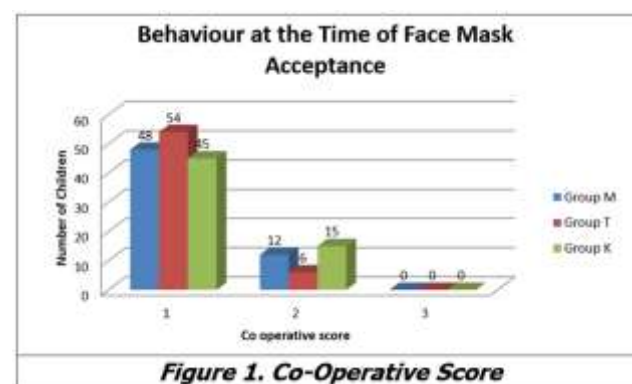


Figure 1. Co-Operative Score

1 = Co-operative.

2 = Mildly Resistant

3 = Resist placement of mask.

Adverse Effects

No adverse effects attributable to oral midazolam and oral triclofos were seen. But two patients (3.33%) had vomiting and two patients (3.33%) had abnormal movements in the ketamine group.

DISCUSSION

Perioperative period is usually a traumatic experience for children undergoing surgery. In children, premedication is used to ensure a calm co-operative child without producing deep sedation and respiratory depression. Anxiolysis or sedation is the aim of modern premedication to obtain a calm and co-operative child. There are various routes for premedication administration but oral route remains the route of choice for children because it is easy to administer and least threatening to children.⁹ Therefore in this study all drugs were given orally as the sole agent. The time interval between premedication and separation from parents should provide adequate sedation and anxiolysis at the time of separation from parents and at the time of face mask placement for induction of anaesthesia in the operating room.

Triclofos sodium is the commonly used drug in our set up for oral premedication in children. Oral midazolam syrup is also freely available for premedication. Since ketamine syrup was not available, oral preparation of ketamine was made by the institutional pharmacist by mixing the specific

drug (parenteral 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. The present study was done to examine the efficacy of oral midazolam, triclofos sodium and ketamine as premedicants in children undergoing minor elective surgical procedures.

In paediatric day care anaesthesia, a good premedicant is required to minimize the psychological stress and preoperative anxiety. The premedication should make the child calm and quiet during induction of anaesthesia. It should be acceptable, rapid and reliable in onset of action with minimal side effects, should provide rapid recovery and return to alertness post operatively permitting easy discharge from post anaesthesia care unit.

This present study showed that oral triclofos syrup provided very good co-operation in 90% of the children and they accepted the face mask without any resistance and the remaining 10% were mildly resistant during face mask placement. Oral midazolam provided very good co-operation in 80% of the children, and the remaining 20% were mildly resistant during face mask placement. Only 75% were very co-operative in ketamine group and they accepted the face mask without any resistance and the remaining 25% were mildly resistant to face mask placement. The aim of premedication is to reduce anxiety and to make the children calm and undergo smooth induction of anaesthesia. Oral premedications are easy to administer and this route is less threatening for children. The present study showed that all the three premedicants reduced the anxiety and made the children very co-operative for a smooth induction. In our previous study we observed that the behaviour of children at the time of mask placement was comparable between orally administered midazolam 0.5mg/Kg administered 30 minutes prior to induction of anaesthesia and oral triclofos sodium 100mg/ kg administered 60 minutes prior to induction of anaesthesia. To assess the clinical effect of these drugs at peak plasma level 30 minute was chosen for midazolam and 60 minutes was chosen for triclofos group in the previous study.¹⁰ In the present study we assessed the clinical effects of all the three drugs which were administered 45 minutes prior to induction of anaesthesia. We found that co-operation scores were not statistically significant and the behaviour at the time of mask placement were comparable between oral midazolam, oral triclofos sodium and oral ketamine administered 45 minutes prior to induction of anaesthesia.

Parameswari A et al compared efficacy of oral midazolam 0.5 mg/Kg and oral triclofos sodium 75 mg/Kg as premedicant in children aged 1-10 years undergoing elective surgery. They observed that children who received oral midazolam accepted the face mask better than the children who received triclofos sodium.¹¹ In the present study acceptance of face mask was comparable between midazolam and triclofos group. This difference could be attributed to the use of lower dose of triclofos sodium 75 mg/ kg in their study compared to higher dose of triclofos sodium 100 mg/Kg in the present study.

In this study all premedicants provided very good cooperation and peaceful induction of anaesthesia similar to that obtained in a study by Lindgren et al¹² Authors have mentioned various routes for premedicant administration like intramuscular, rectal, intranasal, and trans mucosal routes but oral route is least threatening to children.^{13,14,15} In a study authors found that administration of 0.5 mg/ kg oral midazolam thirty minutes prior to induction of anaesthesia reduced anxiety and children were co-operative in 80-90% children, and in our study 80% of children were found to be cooperative prior to induction of anaesthesia¹⁵ Investigators have found that oral midazolam in a dose of 0.5 mg/Kg is superior to oral clonidine four microgram/kg as an anxiolytic in children.¹⁶ Newer drug like dexmedetomidine produced equally effective preoperative sedation and better recovery from anaesthesia in children in comparison to oral midazolam.¹⁷

Investigators have found that behaviour at induction were not different in children who received placebo or oral midazolam (0.3 mg/ kg) 83 ± 38 minutes before induction of anaesthesia.¹⁸ The reason for similar behaviour in both groups could be due to administration of midazolam at 83 ± 38 minutes prior to induction. Assessment of behaviour longer time after administration cause wearing off the sedative action because the half-life of oral midazolam is short. This could be the reason for similar behaviour in children with oral midazolam and placebo.

In a double blind randomized placebo controlled trial the frequency of satisfactory behaviour was significantly higher in triclofos group who received 70 mg /kg orally 90 minutes before operation compared to placebo, parental presence and EMLA cream.¹⁹ In our study we found that the proportion of children with satisfactory behaviour was higher in triclofos group who received 100mg/Kg orally 45 minutes before induction of anaesthesia compared to midazolam and ketamine groups.. But this difference was statistically not significant.

On comparing oral midazolam 0.5mg/Kg and oral ketamine 5mg/Kg investigators have found vomiting in five children, hallucination in one child in the ketamine group and minimum side effects in midazolam group.²⁰ In our study we found vomiting in two children and abnormal movements in another two children. We found no side effects attributable to oral midazolam and oral triclofos in the present study.

CONCLUSION

Children premedicated with oral midazolam oral triclofos sodium and oral ketamine were co-operative during induction of anaesthesia. The quality of induction of anaesthesia was comparable in all the three groups. All premedicants provided effective and satisfactory behaviour inside the operation theatre. All premedicants were found to be safe in paediatric anaesthesia.

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