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Efficacy of oral Triclofos compared with oral Midazolam as premedication in paediatric age group

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Keypoints

Oral premedicants are most suited in paediatric anaesthesia. Both oral triclofos and oral midazolam can be safely used for this purpose. However, Oral midazolam is suitable in children of all age group and its effects are achieved sooner compared to oral triclofos.

Abstract

Introduction

Operation theatre environment, surgery and anaesthesia cause stress and anxiety which can induce psychological disturbances in children. Sedative anxiolytic premedication is used to prevent such outcomes. Oral route is least traumatic and easily accepted. Triclofos and Midazolam have both been used for oral premedication in children. We designed this study to compare the efficacy of oral triclofos with oral midazolam as paediatric premedicants.

Materials and methods

0 ASA PS 1 and 2 children aged > 1 yr and weighing < 25 kg were allocated into one of the two groups randomly. Group T received Triclofos 70 mg/kg (Pedichloryl). Group M received 0.5 mg/kg of midazolam in 2 ml of honey. The sedation and anxiety scores were monitored on 5 point and 4 point scales respectively. Additionally, reaction at the time of separation from the parents. IV cannulation and induction were noted.

Results

86.7% of younger (<5 yr) and 80% of older (>5 yr) of patients in Triclofos group and 100% in midazolam group were satisfactorily sedated after 45 and 30 minutes respectively. Anxiety scores were satisfactory in 93.3% in younger children and 80 % of patients in Triclofos group and in all the children in midazolam group. There was a significant difference between the groups in producing satisfactory sedation and anxiolysis. Parental separation was equally good in both the groups in younger children. however it was significantly better with midazolam in older children. There was no significant difference between satisfactory induction score between the two groups. Reaction to IV cannulation was more satisfactory with midazolam.

Conclusion

From the present study it may be concluded that both oral midazolam 0.5 mg/kg and triclofos 70 mg/kg produces satisfactory conditions of sedation and calm behavior in children of 1-12 years of age, how ever they are achieved sooner with oral midazolam. Both the drugs also help in IV cannulation and separation from parents. Both these drugs may be recommended for safe oral paediatric premcdication.

Keywords

Anaesthesia, paediatric, oral, premedication, triclofos, midazolam.

Introduction

Children undergoing surgery face preoperative anxiety and fear which are attributed to the operation theatre environment, anaesthesia, surgery and the fear of physicians. These anxiety and fear produce negative effects on the child causing preoperative psychological disturbances, nightmares, enuresis and behavioral regression.[1,2]

Separating such anxious children from their parents is necessary before induction and is challenging. A suitable premedication may ease this separation and lessen the drive of parents to remain with the child.[3]

For children, premedication should be ideally pleasant, acceptable rapid and reliable in onset and atraumatic, with little adverse effects. Many drugs have been tried for premedication in children. There is no single premedicant with all the ideal characteristics. Triclofos and Midazolam fulfil many of these ideal characteristics. Both have been used as premedicants in paediatric age group.

Midazolam is a newer, short acting, water-soluble benzodiazepine having sedative/hypnotic, anxiolytic and amnestic properties, which make it suitable for prcmedication in children. It has been shown to achieve effects rapidly even by oral route.[4]

Triclofos, a chloral derivative, is one such drug used as sedative premedicant which is safe and effective in paediatric age group. It not only provides safe sedation, but also increases the gastric pH, gives better antisialogogue effect in combination with atropine compared to other drugs. It is found to produce better anxiolysis score without respiratory depression.[5]

There have been several studies which show that oral midazolarn is an effective premedicant in paediatric age group. Triclofos is also popular as paediatric prcmcdicant. But there is no consensus whether triclofos or midazolam is better oral premedicant. This study was designed to evaluate the efficacy of two agents with respect to the degree of sedation and anxiolysis, the ease of separating the child from parents to facilitate the shifting of the patient to the operating room, the behaviour at induction and the reaction of the child to intravenous cannulation.

The relative advantages and disadvantages of these agents also were studied.

Materials and methods

With the approval of the ethical committee, the patients were selected from ASA I or 2 physical status cased aged more than 1 yr and weighing less than 25 Kgs, attending various elective surgeries in M. S. Ramaiah Teaching Hospital. Children on sedatives, antiepileptics and anticoagulants were excluded from the study. We also excluded children with neurological disorders, allergy to any of the study drugs.

On the day of surgery parents were allowed to stay with the child in the preoperative room and they were asked to administer the study drugs orally. All the children were observed for the sedation and anxiety. The levels were recorded at 5 minute interval till patient was received inside the operation theatre. Any child who did not achieve desirable sedation and anxiolysis was separated from parents after waiting for a maximum period or 45 mins. The major data collected were the sedation and anxiety scores based on a 5point or 4 point scale respectively (table 1).

Vitals were also recorded and monitored during this period without disturbing the child. Any score < 3 was considered satisfactory for sedation. Anxiolysis was considered satisfactory if the score was 1 or 2. The child was separated from parents and taken to the operation theatre. Reaction of the child to separation was noted (table 2). IV cannulation was attempted in the operation theatre and child's reaction assessed. Reaction to venepuncturc was assessed by scoring system (table 3). The final sedation, final anxiety, separation and induction scores were analysed using the student 't' test. A close watch was kept to note the

occurrence of any adverse effects like vomiting, respiratory depression.

Sedation	Score	Anxiety	Score
Barely arousable (fully asleep	1	Calm and sleepy	1
Eyes closed (light sleep)	2	Apprehensive but withdrawn from surroundings	2
Eyes open but appears drowsy	3	Crying	3
Awake	4	Agitated and difficult to Control	4
Agitated	5		

Table 1. Sedation and Anxiety Score

Behaviour during separation from parents	Score	Behaviour at Induction	Score
Easy separation	1	Unafraid, cooperative, accepts mask readily	1 (excellent)
Whimpers but easily reassured, not clinging to parents	2	Slight fear of mask, easily reassured	2 (good)
Cries, cannot be easily reassured ,not clinging to parents	3	Moderate fear of mask, easily reassured	3 (fair)
crying and clinging to parents	4	Terrified, crying, combative	4 (poor)

Table 2. Separation and Induction score

Reaction to venepuncture	Score
Crying or struggling	3
Wincing or vocalising	2
Moving the hand	1
none	0

Table 3. Score for reaction to venepunture

Time to reach sedation score <=2 (minutes)					
	N	Mean	Std deviation	Min	Max
Triclofos	25	32,2	7,23	20,00	45
Midazolam	30	17,5	7,51	5,00	35

Table 4. Time to achieve satisfactory sedation between the groups (P value 0.000)

Results

The two groups were identical with respect to age, sex and weight distribution. These data were analysed using standard error of difference in means and Chi square test wherever applicable. Student t test was used to determine statistical difference between the groups in the parameters measured. The "p" value of <0.05 was accepted as indicating statistical significance in all the tests. The data analysis was carried out using SPSS, V 1 0 .5.

The sedative effect was evident from 20 minutes after administration of the drug in Triclofos group and in Midazolam group it was evident from 10 minutes after administration of the drug, There was significance difference between the two groups in onset of satisfactory sedation (table 4). There was 100% satisfactory sedation in midazolam groups by 35 min, in both <5 and >5 yr age groups, where as only 86.7% of children in 5 yr and 80% of children of>5 yr in triclofos group had satisfactory sedation al 45 ruins. This was again statistically significant (p value <0.0 1).

Similar significant trends were noted in terms of satisfactory anxiolysis between the two groups. With midazolam, all the children of both the age groups achieved satisfactory anxiolysis (score 1 or 2) with in 20 min. In triclofos group 93.3% of children in <5 yr achieved satisfactory anxiolysis in 45 min, whereas 80% of>5 yr achieved satisfactory anxiolysis by 45 min.

Parental separation was 100% satisfactory with both triclofos and midazolam in children

<5 yr (Fig 1). However these children could be separated from their parents as early as 15 min in midazolam groups. In triclofos group, this vas achieved only after a minimum period of 25 min and maximum period of 45 min and in older children a significant difference noted with respect to parental separation between the two groups. Only 66.7% of them had satisfactory behaviour during parental separation while the remaining 33.3% had unsatisfactory behaviour.

The ‘p’value obtained was 0.022.

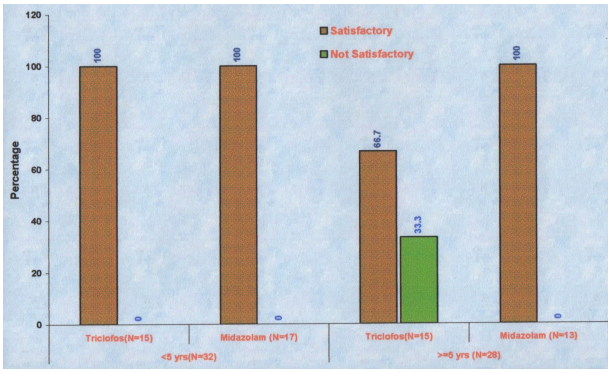

Figure 1. satisfactory parental separation between groups P value 0.022

Favourable reaction to intravenous cannulation was achieved in 30% of patients sedated with triclofos, with fair outcome in 46. 7%. The reaction was favourable in a good number of patients (59%) sedated with midazolarn, where as 41 % of them were fair. Forty seven percent of children in triclofos {<5 yr) group had satisfactory demeanour during induction with 40% of them behaving fairly during induction (fig 2). Seven children in triclofos group had poor response to 1.V cannulation with significant difference of0.015 (fig 3).

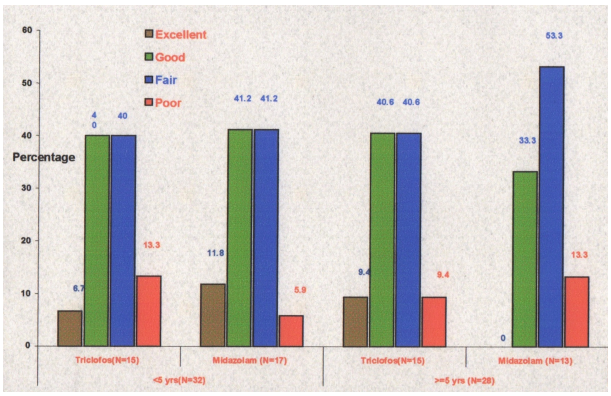

Figure 2. Distribution of Induction score

In midazolam group behaviour at induction was found to be satisfactory in 53.3%. and 41 % or them behaved fairly. In older children, only 33% satisfactory behavior was noted and 53% of them behaving fairly at induction. With midazolam, the satisfactory behaviour was better (60.7%) and 31 % of them behaved fairly. But this difference was not statistically significant.

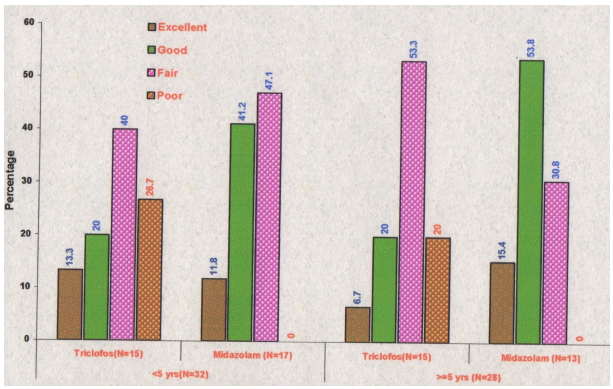

Figure 3. Distribution of Satisfactory IV cannulation

Both the drugs were safe during this study as assessed by heart rate, blood pressure and oxygen saturation. There was no significant variation in the vital parameters after the administration of the drugs with respect to heart rate and mean arterial pressure. But the maximum fall in $Sp0_2$ of 96% in two children, which was noted with midazolam was statistically significant with p value of 0.01. But the drop in saturation to a value of 96% was not taken as clinically significant.

Discussion

It is well recognised now that the experiences of forced separation from parents and induction of anaesthesia can cause long lasting effects on the behaviour of the children. Many methods have been tried to alleviate the anxiety associated with surgery and anaesthesia. Pharmacological methods appear to be more predictable in their efficacy for this purpose. Barbiturates and bcnzodiazepines have been used with predictable effects. Anxiolytic property is desired for any such medication. Midazolam has good anxiolytic activity. Triclofos has also been used as sedative prcmedicafion in children with good anxiolysis.

We observed that onset of sedative action was earlier with midazolam when compared to triclofos. The mean onset or satisfactory sedation with triclofos was 32.2 ± 7.23 min and with midazolam it was 17.5 ±

7.51 min. the difference of which was highly significant (0.000). Neerja singh and R.K. Pando obtained highly significant results in onset of sedative of action with midazolam with mean time of onset being 19.12 ± 0.68 min when compared to Triclofos with 35.22 ±0.77 min.[6] This difference was highly significant with p<0.001. The sedative scores were significantly better again with midazolam group. In our study, satisfactory sedation score (of <3) was better with midazolam. In Triclofos group 86.7% of children in < 5 yr and 80% in >5yr group attained satisfactory sedation at 45 min.

M Thakur et al who have compared oral triclofos (100 mg/kg) with midazolam (0.5 mg/kg) in pediatric patients (1 month - 5 yr) undergoing ECHO. They obtained onset or sedative action with in 3 min with rnidazolam and within 6 min with triclofos respectively.[7]

In a study conducted by Debnath and Pande, where they have compared midazolam (0.5 mg/kg) with ketamine 6 mg/kg orally,

only 36 % of the children had satisfactory sedation with midazolam.[8] None of their patients in rnidazolam group were fully asleep unlike in our study. we used 5mg/ml solution which limited the volume whereas Debnath et al who used 1mg/ml solution which resulted in a dilute preparation. Midazolam is a rapidly acting benzodiazepine causing sedation by enhancing GABA activity. Triclofos takes little longer time to provide sedation. Both the drugs are absorbed rapidly by oral route. But both undergo extensive first pass metabolism in the liver, thus requiring higher dosage for oral use. One of the reasons for higher sedation with these doses in studies conducted in Indian population could be the smaller build of Indian children. The dosage used for children in developed countries could be high for our children.

Previous studies using triclofos have administered it, 45-90 mins before induction which could be the reason in achieving more favourable results with triclofos.

Anxiolysis is one of the important objectives of preanaesthctic medication. Assessment of emotional state of children is difficult. Our study found a satisfactory anxiolysis in all the children with midazolam, where as, it was 93.3% in <5 yr group and 80% in >5 yr group. B. Page et al administered triclofos 90 min before induction.[9] The frequency of unsatisfactory demeanor with triclofos in this study was, half that in the placebo group with significant difference with p<0.005. The difference in overall anxiolysis score found in our study compared to previous ones could be due to the fact that B. Page el al included children or 1-5 yr of age, whereas our study included children of 1-10 yr of age with mean age being 4.47.

Behaviour of childrcn when separating from their parents was equally good with both triclofos and midazolam in younger children in our study, however older children could be separated better with midazolam. This observation with triclofos was similar to that found in study conducted by Necrja Singh et al and other similar studies.

The satisfactory behaviour or children at induction in terms of mask acceptency, found in previous studies involving triclofos and midazolam, has been similar to our findings.

Mara McErlean et al[10] found midazolam syrup (0.5mg/kg) was effective in reducing the discomfort associated with IV cannulation. The observer's pain scores in midazolarn group were lower than in the placebo group. Our study also demonstrates the superiority of midazolam in reducing the unsatisfactory behavior of children during IV catheter insertion when compared to oral triclofos.

It has been shown that giving small volumes of fluids (less than 10 ml) does not increase the risk or aspiration of gastric contents.[11, 12] In the current study honey was used as the carrying agent because a small volume was sufficient to mask the bitterness of midazolam, We limited the total volume administered to 0.2 ml/kg or 10 ml whichever was lower, by using com-

mercially available midazolam parenteral preparations in concentrations of 5 mg/ml. There is no incidence of aspiration in any study including ours.

When compared with other routes of premedication, oral route is well accepted. The onset of satisfactory sedation is quite rapid with nasal and rectal route (5 to 15 min). But oral route provides comparable effects by l 5 to 20 minutes. In our study 87% were satisfactorily sedated by the end or 20 minutes with midazolam though maximum success was seen after 30 minutes. The nasal route although attractive, is not preferred as most children do not like drugs being squirted into the nose. Rectal administration is disliked by children especially older ones.

It is clear from the present study that both triclofos and midazolam have wide safety profile after their oral administration. In midazolam group, three of the children had vomiting, following its administration. But this was not statistically significant. Charles J Cote el al and other studies which have used oral midazolam as prcmedication, also have experienced few incidences of nausea and vomiting.[13] These events may have been related to the drug or to the patient's response to ingesting something he or she did not want. It is difficult to separate a true pharmacodynamic effect from the psychologic response of a child. In a study conducted by Chavasse et al[14] who sedated infants with triclofos (100-120 mg/kg) to compare the airway resistance measured by interruptive technique and by passive mechanics. In this study, all the infants had been reported by parents to have either persistent wheeze for 6 weeks, or at least three episodes of wheeze over 3 months before the study and all had a family or personal history of atopy. This study has not reported any adverse respiratory events after administration of triclofos which emphasises that triclofos can be safely used even in such children.

M Thakur and S Salgaonkar et al have used both triclofos and midazolam for oral sedation in infants ranging from 1 month to 5 yr for echocardiography without any adverse events.[7] Virendra Sharma et al have safely used triclofos, 500mg orally in infants < 7 months for sedation to perform probing and syringing. [15]

Conclusion

Preoperative sedation is an integral part of paediatric anaesthesia. Oral triclolos is very convenient to administer and is suitable in children less than 5 yrs. Oral midazolam is suitable in paediatric patients of all the age groups and has an added attraction of rapid onset of action in comparison with oral triclofos.

Disclosures

1. *No funding has been received for conduct of this study.*
2. *The authors declare that there is no conflict of interest in the study.*

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