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A comparative study of efficacy of midazolam and triclofos as oral premedication in children undergoing minor surgical procedures

Meenal Agarwal[1], Surendrakumar Agarwal[2*] and Sunil Khyadi[1]

[1]Department of Anesthesiology and Pain Medicine, Al Ameen Medical College and Hospital, Athani Road, Vijayapura-586108, Karnataka, India and [2]Department of General Surgery, Al Ameen Medical College and Hospital, Athani Road, Vijayapura-586108, Karnataka, India

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Abstract: *Background:* In Paediatric population, premedication is oftenly used to decrease preoperative anxiety, facilitate separation from parents and to get acceptance for face mask induction. Our study was aimed to compare the efficacy of oral midazolamandoral Triclofos as premedicants in children as sedatives, anxiolytics and to promote acceptance of facemask. *Patients & Methods:* Our study is prospective, randomized, double blind, controlled study involving fifty ASA-1 children between 1 to 10 years of age, undergoing elective surgery. Group A patients was allotted oral Midazolam 0.5mg kg^{-1} while Group B patients received Triclofos 75mg kg^{-1} orally as premedication. Assessment of the allowance of premedication, degree of sedation, level of anxiolysis and acceptance of face mask was done by separate scoring methods at intervals of 30 minute (till a maximum of 3 assessments) up to the child was shifted to the operating room. A parental questionnaire was useful to judge the parental satisfaction. Results: In Group A, 21 patients (82%) were awake, but calm and 4 patient (18%) was asleep during the first assessment done 30 minutes after the administration of the drug, while in Group B, only 2 patients (10%) were awake and calm and 23 patients (90%) of the patients were asleep (p value 0.000). In Group I, 13 patients (55%) did not resist the face mask and 12 patients (44%) showed slight resistance while in Group B, 2 patients (11%) showed no resistance to face mask and 13 patients (55%) showed slight resistance. Facemask acceptance was more in Group A (p value of 0.014). *Conclusion:* Conclusion from our study was that oral Triclofos has better premedication effect as children were sedated, calm and asleep whereas children those received oral midazolam as premedication were awake but calm and quality of face mask acceptance was better.

Keywords: Premedication, Triclofos, Midazolam, Sedatives, Anxiolytics, Facemask Acceptance.

Introduction

Operation theatre environment, IV cannulas and injections fear, are all traumatizing experiences that leads to maladaptive behavioral changes in young children. Paediatric patients about to undergo surgery can be usually more anxious, apprehensive, and fearful for surgery compared to adults. The anxiety of parental separation and the presence of strangers around worsens the apprehensiveness in children [1-4]. The purpose of premedication is to yield the patient calm, free of anxiety and pain, sedation but easily arousable and fully cooperative.

Kain et al [5-7] observed that those patients receiving premedication showed fewer changes including regressive behavior, aggression, sleeping and eating disturbances, regression of toilet training and other postoperative negative behavioral changes. However developing a good rapport with the child during the preoperative visit will lead to allaying anxiety and apprehension, but for children above6months of age needs some premedicant drugs to provide sedation, anxiety and discomfort. So far several comparative studies are been done with midazolam and other premedicants like Ketamine, Trimeprazine, Methadone and Chloral hydrate but Midazolam was more commonly used as premedicant [8-14].

Our aim was to do the comparative study of efficacy of oral Midazolam and oral Triclofos as premedicants in children undergoing

elective surgery. Assessment and comparison of the level of sedation, anxiolysis, acceptance of face mask and parental satisfaction produced by these two drugs were done by separate scoring methods.

Material and Methods

This prospective, randomized, controlled, double-blinded, study was conducted at Al Ameen medical college, Vijayapur during January 2022 to October 2022. Fifty Paediatric patients between1 to 10 years of age with ASA status I, undergoing elective surgeries under general anesthesia were selected randomly. Institutional ethical committee approval and informed consent were obtained. Exclusion criteria- children with gastrointestinal dysmotility, those on treatment with enzyme inducers or inhibitors, anxiolytics and those allergic to the study drugs were excluded.

The sample size was determined by power analysis. Routine preoperative evaluation of all children undergoing surgery on the day prior to surgery was done. They were assigned to one of the two groups. Group A (Midazolam group) and Group B (Triclofos group) using random selection by picking chits-lots containing numbers from a sealed bag On the day of surgery, the patients were shifted to the preoperative room of the operation complex and premedication was administered by an anesthetist not participating in the study.

The study was conducted using a double blind method where Group A patients received oral midazolam, 0.5mg kg-1, the solution containing a mixture of 1mg ml-1 of Midazolam (intravenous preparation) with a sweet, clear fluid (soft drink) to overcome the bitter taste of the preparation to a total volume that did not exceed 15ml. Group B patients received commercially available Triclofos syrup (Pedicloryl) 100mg/ml in the dose of 75mgkg-1orally.

While administering premedication, any kind of resistance offered by patients during intake of premedicant in the form of vomiting, spitting, crying or the need to hold the child down was assessed and recorded according the grade given below:

Grading of acceptance of premedication:

- Not resisted
- Resisted (cried/needed to be held down)
- Vomited/Spitted out

After administration of the premedication, in the preanaesthesia room the child was kept undisturbed with the parent and continuous monitoring of vital parameters were done.

In Group A patients, the first assessment was done 30 minutes after administration of the drug (Midazolam) and in Group B patients, 90 minutes after administration of the drug (Tricholfos). As it was a double blinded study, an anesthetist who was blinded carried on assessment and was unaware of the administered drug and time of administration. The vital parameters recorded were heart rate, non invasive blood pressure, oxygen saturation, level of sedation (chart 1) and level of anxiolysis (chart 2).

Chart-1: Assessment of the Sedation level was as per the following score	
1.	Alert/Active
2.	Awake/Calm
3.	Drowsy but responds to verbal commands or touch
4.	Asleep
1 = Poor, 2 = Fair, 3 = Good, 4 = Excellent	

Chart-2: Assessment of the level of anxiolysis was as per the following score	
1.	Tearful / Combative
2.	Anxious but easily assured
3.	Calm
4.	Asleep
1 = Poor, 2 = Fair, 3 = Good, 4 = Excellent	

30 minutes after the first assessment or just before shifting the patient into the operating room, whichever was earlier, second assessment of all above parameters was done by the same anesthetist who did the first assessment. Third assessment was done just before shifting the patient into the operating room, in case if the patient was shifted to the operating room later than the initial two

assessments. Inside the operating room, grading of the acceptance of face mask by the child was done by using a separate scoring system (chart 3), through the same anesthetist who did the first, second and third assessments.

Chart -3: Assessment of the acceptance of face mask was as per the following score	
1.	Strong Resistance
2.	Slight Resistance
3.	No resistance but awake
4.	No resistance and asleep
1 = Poor, 2 = Fair, 3 = Good, 4 = Excellent	

After administering the premedicant drug, Patients were closely observed for any adverse effects like apnea, airway obstruction, dysphoria, irritability, violent behavior, vomiting, hypoxia, hypotension and bradycardia. A separate questionnaire with documentation in the affirmative or negative by the parents, was used for the parental satisfaction assessment. Independent samples 't' test was used to analyze all the vital parametric data and Pearson chi square test for analysis of non-parametric data.

Results

A total number of 50 pediatric patients were included in the study. Demographic variables showed no significant difference between the two groups (table 1). While administration of premedication, 21 patients (82%) in Group A (midazolam) did not resist the while 4 patients (18%) resisted. In Group B (Trichlofos) patients 19(76%) showed no resistance to the administration of premedication, while 6 patients (24%) did not resist. Statistical difference was insignificant (p value 0.705) (Table 1).

Table-1: Acceptance of premedicants				
Group	**No Resistance**	**Resistance**	**Vomit**	**P value**
Group A (Midazolam)	21 (82)	4 (18)	0 (0)	
Group B (Triclofos)	19 (76)	6 (24)	0 (0)	0.705
Total	40 (80)	10 (80)	0(0)	

Table-2: Assessments of Vitals in groups						
Group	1st assessment			2nd assessment		
	BP	HR	RR	BP	HR	RR
Group A (Midazolam	98.70/60.70	108.85 (14.29)	20.15 (4.26)	95.65/61.45	106 (14.63)	22.4 (2.38)
Group B (Triclofos)	94.8/56.9	105.25 (15.55)	23.75 (3.07)	94.46/57.38	98.75 (12.82)	21.95 (3.08)
P value	0.017	0.657	0.085	0.008	0.137	0.177

During the first assessment, the mean heart rate in Group A (midazolam) was 108.85 (±14.29) per minute and in Group B (trichlofos), it was 105.25 (±15.55) per minute. During the second assessment the mean heart rate in Group A (midazolam) was 106 (±14.63) per minute and in Group B (Trichlofos) was 98.75 (±12.82) per minute. The difference in the mean heart rates, between the two groups was not statistically significant (p value 0.657 and p value 0.137 for first and second assessments respectively) (Table 2).

During the first assessment the Group A patients mean systolic blood pressure was 98.70 (±15.23) mm Hg and the mean diastolic blood pressure was 60.70 (±6.82) mm Hg ,while in Group B, the mean systolic blood pressure was 94.80 (±8.93) mm and diastolic blood pressures were 56.9 (±7.15) mm Hg. During the second assessment, in Group A (midazolam) the mean systolic was 95.65 (±9.17) mm Hg and the diastolic blood pressure was 61.45(±8.04) mm Hg, whereas in Group B (trichlofos) the systolic and

diastolic blood pressure was 94.46 (±7.42) mm Hg and 57.38 (±7.08) mm Hg respectively (Table 2).

Statistically the difference between two groups was insignificant in regards to blood pressures. During the first assessment, the mean respiratory rate in Group A patients was 20.15 (±4.26) per minute and in Group B patients it was 23.75 (±3.01). There was no statistically significant difference between the two groups (p value 0.085).During the second assessment, mean respiratory rate was 22.40(±2.38) per minute in Group A patients, whereas in Group B patients was 21.95 (±3.08). There was no statistically significant difference between the two groups (p value0.177) (Table 2). During the first and second assessments, the oxygen saturation was maintained at 98%-99% in both the groups.

During the first assessment, in Group A (midazolam) 3 patients (12%) were alert/ active, 18 patients (72%) were awake/ calm2 patient (8%) were drowsy but readily responded to verbal commands or touch and 2 patient (8%) were asleep. In Group B, during the first assessment, 1 patient (4%) was alert/active, 2 patients (8%) were awake/ calm, 3 patients (12%) patients were drowsy but readily responded to verbal commands or touch and 13 patients (65%) were asleep. On comparing the two groups for the level of sedation, the difference was statistically significant (p value of 0.000) with the patients in Group 2 being better sedated (Table 3). During second assessment, the level of sedation between two groups was statistically insignificant (p value -0.204).

Table-3: Level of sedation in the two groups during the first assessment

Group		Sedation level				Total	P value
		Alert/ Awake	Active /Calm	Drowsy/ responds touch/ verbal commanads	Asleep		
Group A (Midazolam)	No. of patients % within the group	3 (12)	18 (72)	2 (8)	2 (8)	25(100)	0.00
Group B (Triclofos)	No. of patients% within the group	1 (4)	2 (8)	3 (12)	19 (76)	25 (100)	0.00
Total	No. of patients% within the group	4(16)	20(80)	5(20)	21(84)	50 (100)	0.00

Comparison between two groups for the level of anxiolysis was done and observed that during first assessment in Group A (midazolam) 5(20%) patients were anxious but readily assured, 18(72%) calm and 2(8%) were asleep. Whereas in Group B (Trichlofos) 4(16%) were anxious but easily reassured, 2 (8%) were calm and 19 (76%) were asleep. There was statistically significant difference between the two groups (p value 0.000), with Group B (Trichlofos) patients having more anxiolysis effect (Table 4). There was no statistically significant difference in the level of anxiolysis during the second assessment, between the two groups (p value 0.227) and only one patient required the third assessment and was in Group B, was fearful/ combative and the p value could not be elicited.

Table-4: Level of anxiolysis in the two groups during the first assessment

Group		Anxious but easily reassured	Calm	Asleep	Total	P value
Group A (Midazolam)	No. of patients (% within the group)	5 (20)	18 (72)	2(8)	25 (100)	
Group B (Triclofos)	No. of patients (% within the group)	4 (16)	2(8)	19 (76)	25 (100)	0
Total	No. of patients (% within the group)	9 (36)	20 (80)	21(84)	50 (100)	

Table-5: Acceptance of face mask *in the two groups*						
Group		**Strong resistance**	**Slight resistance**	**No resistance but awake**	**Total**	**P value**
Group A (Midazolam)	No. of patients (% within the group)	3 (12)	8 (32)	14 (56)	25 (100)	
Group B (Triclofos)	No. of patients (% within the group)	8(32)	13 (52)	4 (16)	25 (100)	0.014
Total	No. of patients (% within the group)	11(44)	21(84)	18 (72)	50 (100)	

Comparison between the two groups for the acceptance of face mask was observed. In Group A (midazolam), 3(12%) patients showed a strong resistance, 8 (32%) showed a slight resistance and 14(56%) patients showed no resistance inspite of awake. In Group B (Tricholfos), 8(32%) showed a strong resistance, 13(52%) patients showed a slight resistance and 4 (16%) showed no resistance though awake. There was statistically significant difference between the two groups (with a p value of 0.014), as with the Group A patients showed better acceptance of face mask (Table 5). In parental satisfaction comparison there was no statistically significant difference between the two groups (p value 0.744).

Discussion

Psychological preparation of children along with reduction of anxiety, calm - sedated child in pre-anesthesia room results in better pre-operative outcome and post-operative emergence. Kain et al [5] demonstrated the role of premedication in children to produce amnesia, anxiolysis and attenuate stress response during pre-induction period.

In our institution various combination of premedicants with the either oral /rectal routes have been used for providing high quality and safe sedation outside the operating room .Among them midazolam, chlorhydrate most oftenly used. The prospects of good anxiolysis, sedation and analgesia with single oral dose along with excellent bioavailability of Trichlofos, prompted us to study its efficacy as premedication and to compare it with gold standard premedication drug that is oral midazolam in pediatric population. Triclofos sodium is phosphate ester of trichloro ethanol which is pharmacologically active metabolite of chloral hydrate. This is less gastric irritant and more acceptable and available as a sweet preparation [15]. As we did not have access to the midazolam syrup formulations which are modified to remove the bitter taste of midazolam and to make it more palatable in children we mixed the intravenous preparation with a sweet, clear liquid/syrup.

The first assessment in Group A patients was done at 30 minutes after administration of oral midazolam as the peak effect of oral midazolam is 25-30 minutes [16-17]. Whereas the first assessment in Group B patients after receiving oral Trichlofos was timed in such a way to match the peak effect of Trichlofos which is 90 minutes. We followed the dosage of 0.5 mg kg-1 of midazolam in our study as various studies have reported safety of midazolam in doses ranging from 0.5 mg/kg to 1.0 mg/kg and midazolam in greater doses has no additional benefit instead resulted in a higher incidence of adverse effects [16]. The dose for Trichlofos is ranged 50-100 mg kg-1 and with reference to study by Lindgren et al [18].we chose to use 75mg kg-1 in our study.

The delayed time to onset of peak effect with Trichlofos could be limiting factor, while comparing midazolam and Trichlofos especially when considering a busy OR schedule for reallocating the surgical list. However, if sufficient time is provided for the peak effect to set in, as was done in our study, the sedation and anxiolysis it produces is significantly better than midazolam.

A limitation of our study was that we did not assess the degree of amnesia produced. Midazolam produces amnesia within 10 min of administration orally [19], which probably plays a major role in keeping the postoperative behavioral stress response in the

adaptive range for many children. Whether Trichlofos has any such role to play is not known.

In our study, during first assessment, those children in Group B received oral Trichlofos as premedicant were calm and asleep compared to Group A children who received oral midazolam. While, during second assessment, followed 30 minutes after first assessment in some children, the sedation produced by oral trichlofos had reduced, making these patients awake but calm during second assessment, inspite they were asleep during first assessment. Certain studied described trichlofos to produce prolong drowsiness up to 24 hours. But according to our study, even though in children who received oral Trichlofos as premedicant, there was a significant sedation and drowsiness during first assessment, this did not last for more than 30 minutes. Lacunae in our study was that post-operative sedation levels in these patients were not.

Our study studied proposes that the quality of acceptance of facemask was better with midazolam that correlates with the effect of midazolam in other studies. In a study by Chaudhary et al [20] and Geetha et al [21] midazolam had greater percentage of sedation score and anxiolysis than Trichlofos. But, our study goes with Parameswari et al [22] where Trichlofos was found to be better to midazolam.

The Majority of complications arising from sedation are related to control of respiration, airway obstruction either due to positional or secretions, hypoventilation or apnea leading to hypoxemia. Due to smaller functional residual capacity and increased oxygen consumption as compared to adults they develop hypoxemia rapidly after cessation of ventilation. Hence close clinical monitoring of the breathing pattern of the patients was done in our study. We did not see any adverse effects due to the effect of premedication in any of the patients included in the study groups.

Conclusion

In conclusion, our study succeeded in demonstrating oral Trichlofos in the dose of 75mg kg-1 as better alternative to oral midazolam 0.5 mg kg-1, in respect to anxiolysis with minimal hemodynamic changes. However, oral midazolam is superior over oral Trichlofos in quality of face mask acceptance. The short comings of Trichlofos are the variable onset of peak effect, unpredictable long recovery time. Triclofos is time tested drug for use in Paediatric sedation (0.75mg/kg) but at the cost of slower onset, longer duration and long recovery time.

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Conflicts of interest: There are no conflicts of interest.

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*All correspondences to: Dr. Surendrakumar Agarwal, Associate Professor, Department of General Surgery, Al Ameen Medical College and Hospital, Athani Road, Vijayapura-586108, Karnataka, India. E-mail: dr.surenagarwal@gmail.com