Original Article

Safety and efficacy of oral Triclofos in the ophthalmic evaluation of children with pediatric glaucoma: An observational study

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Purpose: Oral Triclofos is widely used as a sedative agent in children. However, the role of Triclofos as a sedative agent in children undergoing ophthalmological procedures has not been adequately studied. The aim of this study was to determine the safety and efficacy of oral Triclofos in children suffering from pediatric glaucoma who were undergoing ocular examination. **Methods:** 80 children aged less than 5 years were assessed for eligibility for the trial after taking hospital ethical committee approval. The children were administered 80 mg/kg of oral Triclofos and Ramsay sedation score was measured every 5 min starting from 20 min after administration of the drug. If the child was not adequately sedated after 30 min, additional dose of 05 mg/kg was administered every 5 min till 60 min of drug administration. The procedure was considered a failure and general anesthesia (GA) administered if Ramsay sedation score was ≤4 after 60 min of initial drug administration. Heart rate and arterial oxygen saturation were measured throughout the period of sedation. The duration of sedation and incidence of side effects was also noted. **Results:** A total of 73 patients underwent the study. The mean age of children was 23.4 months (SD – 14.72) and mean weight was 12 kg (SD – 3.84). The mean dose of Pedicloryl (Triclofos) used was 83.8 mg/kg and the median duration of onset was 25 min. 64 children completed examination successfully, 2 children had to be administered GA during the procedure. There were no major side effects. **Conclusion:** Administration of oral Triclofos in a dose of 80 mg/kg body weight was safe and effective in children less than 5 years of age undergoing ocular examination.

Key words: Glaucoma, pediatrics, sedation, triclofos

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Examination under anesthesia (EUA) is the cornerstone in management of children with pediatric glaucoma. These young children require such evaluations multiple times for monitoring their intraocular pressure (IOP) and status of the optic nerve head. However, there are growing concerns regarding the long-term safety of anesthetic agents on these young, developing brains. Single or repeated administration of anesthetic agents has been shown to adversely affect cognition, memory, and behavior among exposed children.[1-5] Therefore, whenever possible the clinician wishes to avoid multiple exposures of general anesthesia (GA).

Several drugs have been used for years in clinical practice for the sedation of children. Considering the potential higher risk of desaturation and adverse sedation-related events, many argue that GA should be given to children. However, it should also be noted that intubation and ventilation with GA could cost a long time and increase the risk of adverse incidents. Even the short-lived incidents of this kind may lead to airway trauma and atelectasis. Apart from the major issues of safety and utility, another important concern is the cost effectiveness of the procedure. GA administration obviously requires extra resources and healthcare personnel and additional financial burden.

Chloral hydrate is one of the most commonly used sedatives in the clinical setting despite the availability of other sedatives such as midazolam and pentobarbital.[6] It is considered a safe sedativehypnotic and has been shown to be effective.[7,8] However, it has the disadvantages of pungent odor with a bitter caustic taste and causes a high incidence of nausea and vomiting.

Triclofos is the pharmacologically active metabolite of chloral hydrate. Chemically, it is the phosphate ester of trichloroethanol. Oral triclofos has been successfully used as a sedative for young children in doses of 75–100 mg/kg.[6,9] Triclofos has been successfully used for sedating children for procedures like echocardiography and electroencephalography.[10,11] Studies have found it to be safe for use in children with congenital heart disease and in neurologically compromised children.[12,13] However, there is a paucity of literature on use of Triclofos in ophthalmic anesthesia. Triclofos may be a better sedative in view of better palatability and less gastric irritation as compared to chloral hydrate.

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Considering the short-term and long-term side effects of GA on young children there is a quest for a safer yet effective sedating agent which would calm the child for a few minutes for ophthalmic evaluation. Triclofos could prove to be this sedative agent. However, there are reports documenting adverse effects of Triclofos when used for sedation.[14,15] Hence, there was a need to conduct a clinical trial to determine the safety and efficacy of oral Triclofos in these patients.

We proposed to study whether use of oral triclofos can be used as a safe and effective sedation protocol to perform satisfactory ocular examinations of young or uncooperative children with pediatric glaucoma. We also wanted to determine the time needed to achieve sedation, duration of sedation, and the dose needed for the procedure.

Methods

This prospective observational study was carried out in the operating room of a tertiary care hospital from April 2018 to March 2019. The study was approved by the Institutional Ethics Committee (INT/IEC/2018/000291 dated 21/03/2018) and registered prospectively with the Clinical Trials Registry of India (CTRI/2018/08/015532). The study adhered to the principles of the 2013 Declaration of Helsinki. Written informed parental consent was obtained for all patients who were enrolled into the study.

The study included uncooperative and young children below the age of 5 years requiring EUA following surgery for pediatric glaucoma. Children with cardio-respiratory distress, liver disease, or an acute medical condition were excluded from this study. Parents were told to keep the child nil per oral as per standard guidelines and a detailed pre-anesthetic clinical examination was performed in all patients. They were taken to a quiet, semi-dark environment of preoperative area of the operating room accompanied by their parents and oral Triclofos (Pedicloryl™, Dr. Reddy`s Laboratories Ltd., Hyderabad, India) 80 mg/kg body weight was administered as the sole sedating agent. Heart rate, oxygen saturation (spO_2), and respiratory rate was recorded in all the patients throughout the period of sedation. 20 min after administration of sedative administration, Ramsay sedation score was assessed every 5 min. If the score was ≤4 after 30 min; same drug was administered in additional dose of 5 mg/kg per oral and the Ramsay sedation score was reassessed at every 5 min till 60 min from starting. When adequate sedative score (≥5) was achieved, the time of onset was recorded and desired non-painful ophthalmic procedure was started. If after 60 min Ramsay score was ≤4; procedure was considered as failure and GA was administered to the child.

The ophthalamic parameters that were noted included intraocular pressure (IOP) by applanation tonometry (Goldmann's/Perkin's), anterior segment evaluation and disc & fundus evaluation using indirect ophthalmoscope and 20D lens. An experienced operating ophthalmologist evaluated the ease of procedure completion and was rated as: Procedure done with ease (excellent), Procedure done with mild difficulty (satisfactory), or Procedure could not be done and resort to GA (unsatisfactory). Once the examination was completed, the time of recovery was noted.

Post the procedure, the monitoring of the heart rate, oxygen saturation, and respiratory rate was continued. Occurrence of any adverse effects like oxygen desaturation (arterial oxygen saturation <90%), respiratory depression (respiratory rate <10/min), etc., was documented.

Patients were discharged after they were deemed fit for discharge by an anesthesiologist. The total time from the onset of sedation to time of discharge was also noted.

Study statistics

The statistical analysis was carried out using Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, version 16.0 for Windows). Demographics and health characteristics of the study population that were continuous variables were summarized using means and standard deviations (SD), and all categorical variables were expressed as percentages. A power analysis was not done due to absence of published data on the subject.

Results

A total of 80 children were assessed for eligibility to participate in the study. 7 patients had to be excluded because their parents did not give consent for inclusion in the trial.

The mean age of the 73 children participating in the study was 23.4 months (SD – 14.72) and mean weight was 12 kg (SD – 3.84). 67 children were classified as ASA I while 6 children were labeled as ASA II. 10 children had a history of premature birth while 8 patients were born with low birth weight. 37 children were males while 36 were females. The average dose of oral Pedicloryl used for examination was 83.8 mg/kg and the mean time of onset of sedation was 25 min. The mean duration of the ophthalmological examination was 6 min [Table 1].

Out of the 73 patients who participated in the trial, 7 had to be administered GA because of inadequate sedation even after 60 min. Among the rest 66 children, 60 completed the examination without any movement while 4 children demonstrated some movement during the procedure, however they did complete the examination. 2 children cried during the procedure and had to be converted to GA.

A total of 15 children had not attained adequate sedation (RSS ≥ 5) after 30 min of administration of first dose of triclofos and had to be administered additional dose of 05 mg/kg. Out of these 15, seven children were adequately sedated 5 min after the additional dose of Pedicloryl, whereas 1 child needed 2 additional doses before being adequately sedated. All of these 15 children completed the procedure, although 2 of them showed minor movements during the procedure. Table 2 demonstrates the number of children adequately sedated as a function of time.

Table 1: Demographic characteristics of the patients

Characteristics	*n*=73
Mean age	23.4±14.72 months (mean±SD)
Mean weight	12±3.84 kgs (mean±SD)
Male patients	37
Female patients	36
Mean duration of ophthalmological exam	6 min
Average dose of oral Pedicloryl	83.8±4.8 mg/kg (mean±SD)
Median time of onset of sedation	25 min

In 58 out of 66 children who underwent the procedure, the operating conditions were rated as "excellent" by the ophthalmologist; 6 were rated as "satisfactory," while 2 were rated as "unsatisfactory" [Table 3].

The heart rate pattern of the children pre- and post-sedation are described in Fig. 1. The mean heart rate was measured every 10 min after administration of Triclorofos.

2 children developed arterial saturation of <90% post procedure which was managed by administering oxygen via facemask. None of these children needed airway manipulation or hospital admission.

All children maintained O2 saturation >96% on room air before discharge. The median time between first dose of Pedicloryl administration and discharge from clinic was 90 (IQR: 70–140) min.

Discussion

Triclofos is the pharmacologically active metabolite of chloral hydrate. Its advantages over chloral hydrate include lesser gastric irritation easy availability, high palatability, and presence of a commercial liquid formulation.[16] Oral Triclofos has been very commonly used for sedation in pediatric patients for a number of procedures.[17,18] However, while chloral hydrate has been extensively studied as a sedative agent, the studies evaluating the sedative properties of triclofos, specially for ophthalmic procedures have been relatively scarce.[19,20] Our study demonstrated that oral Triclofos in a dose of 80 mg/kg body weight, administered 25 min prior to the procedure, was safe and effective for sedation of children aged less than 5 years who were undergoing ophthalmic examination for pediatric glaucoma.

Table 2: Number of patients with Ramsay sedation score of ≥5 as a function of time

Time from Triclorofos administration (min)	Number of patients with RSS ≥5
20	19 (26%)
25	39 (53%)
30	58 (79%)
35	65 (89%)
40	66 (90%)
45	66 (90%)
50	66 (90%)

Table 3: Operating conditions as evaluated by ophthalmologist

Operating conditions	Number of children
Excellent	58 (87%)
Satisfactory	6 (9%)
Unsatisfactory	2 (4%)

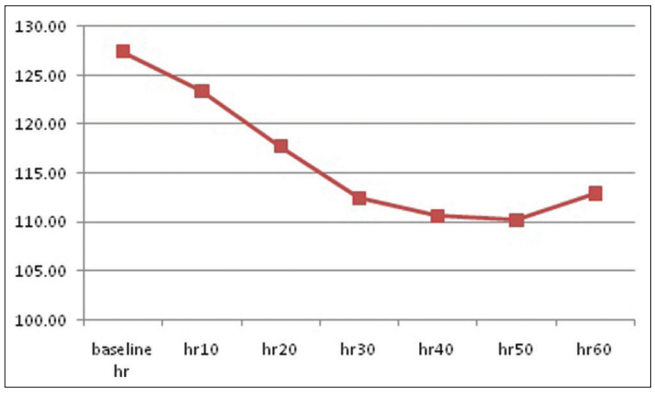

Figure 1: Mean heart rate of the patients as a function of time. (X axis – time in minutes; Y axis – heart rate in beats per minute)

Jackson *et al*. had studied the effect of sedation with Triclofos in 10 children aged less than 2 years. They suggested that Triclofos was safe for sedation in this age group upto doses of 100 mg/kg. None of their patients suffered from arterial desaturation during sedation.[12] Also, oral Triclofos in dose of 75 mg/kg has been shown to be effective premedication agent in children undergoing elective surgery.[20]

Jain *et al*. had performed an observational study in children aged 6 months to 5 years who were undergoing sleep electroencephalography (EEG) study.[16] They had administered 50 mg/kg of Triclofos. They were able to complete to successfully record EEG in 93.1% patients. None of their patients required oxygen or airway management. Also, there were no serious adverse effects noted in any of 160 patients. Kaplan *et al*. had studied the safety of oral Triclofos in 869 children with neurocognitive disorders undergoing non-interventional neurodiagnostic examinations.[21] They had administered an initial dose of 50 mg/kg followed by additional dose of 25 mg/kg after 30 min if the first dose was unable to sedate the child. The mean dose of Triclofos that they administered was 50.2 ± 4.9 mg/kg. They also concluded that oral Triclofos was effective as well as safe. Both these studies used doses lower than what we used. However, both these authors used Triclofos sedation for procedures which involved minimal stimulus and were painless, also Kaplan *et al*. used the drug in children with neurocognitive disabilities who may be having lower threshold for sedation.

The median onset of sedation was 25 min in our study. This is slightly earlier than most of the earlier studies, which mostly show a median sleep onset of around 30–40 min.[20-22] We believe this shorter latency in our patients may be a result of the dose of Triclofos used and the differences in research protocol followed. Levit *et al*. had administered only 50 mg/kg of Triclofos initially followed by a second dose of 30 mg/kg only after 20–30 min of initial dose. Also, they monitored the sedation score only at 10 min intervals while we documented sedation scores every 5 min. Similarly, Jain *et al*. administered only 50 mg/kg of oral Triclofos in their patients. We hypothesize that administration of 80 mg/kg of oral Triclofos may have a shorter latency of onset as compared to lower doses that have been used previously by other authors in their studies.

Our study has many limitations. Firstly, our patients belonged to a narrow age group of less than 5 years and the results cannot be generalized to children above this age group. Also, we included only ASA I and II patients in our study.

Conclusion

We found that oral Triclofos was effective in providing sedation to most pediatric patients aged less than 5 years undergoing ophthalmic procedures. There was no serious adverse effect in our cohort of 73 patients, demonstrating safety of Triclofos as a day-care sedative agent.

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Conflicts of interest

There are no conflicts of interest.

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