

Impact of Etiology on Efficacy of Oral Triclofos in Recording Pediatric Electroencephalography: A Tertiary Care Center Study

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ABSTRACT

Background and Objectives: Oral triclofos is a frequently used sedative in pediatric age to record sleep Electroencephalography (EEG). This study is aimed to assess efficacy, safety profile, need for second dose, and rescheduling of oral triclofos in relation to etiology. **Materials and Methods:** This is a retrospective study done enrolling all children aged 6 months to 5 years referred for EEG over 1 year. After a trial for natural sleep, the first dose of oral triclofos was given. If a child does not sleep after an hour, the second dose was given and rescheduled if does not sleep even with the second dose. Age, sex, diagnosis, sleep latency, sleep duration, adverse effects, EEG findings, patients needing second dose, and rescheduling were noted. Descriptive statistics and Chi-square test were used to analyze data. **Results:** A total of 384 children required oral triclofos. The common etiologies for sleep study were atypical febrile seizures, hypoxic-ischemic encephalopathy (HIE) sequelae, and behavioral disorders such as autism and attention-deficit hyperactive disorder (ADHD). Including the second dose, we were able to successfully record sleep EEG in 372 (96.8%) patients. Rescheduling was required in 3.2% of patients. Mean sleep-onset latency was 36 min and mean sleep duration was 84 min. Single dose was sufficient in 329 (85.6%) and the second dose in 55 (14.4%). Thirty (38.5%) children of HIE sequelae ($P < 0.001$) required the second dose followed by behavioral disorders (29.1%, $P = 0.03$). Irritability, vomiting, and dizziness were common side effects which resolved spontaneously. **Conclusions:** Oral triclofos was effective as sedative for recording EEG. Children with HIE sequelae and behavioral disorders such as autism/ADHD more commonly required second dosing and rescheduling.

KEYWORDS: Behavioral disorders, efficacy, hypoxic-ischemic encephalopathy, oral triclofos, pediatric electroencephalography

INTRODUCTION

Seizures are common in childhood, with varied etiology ranging from febrile seizures to specific causes such as hypoxic-ischemic encephalopathy (HIE) sequelae, infections, metabolic disorders, epileptic encephalopathy/Lennox–Gastaut syndrome, stroke, behavioral disorders and others. Behavioral disorders such as autism and attention-deficit hyperactive disorder (ADHD) often have subclinical seizures with electroencephalography (EEG) abnormalities which when treated improve clinically.

Recording of sleep EEG by attaining a natural sleep is a practical issue in children, especially in children

with developmental disabilities. It has been shown that behavioral training is successful in improving the compliance without sedation,^[1] but some cases refractory to behavioral training require sedation. Natural sleep and sleep deprivation most often increase the yield of epileptiform discharges in EEG's.^[2,3] Sedation with oral triclofos is often used to obtain sleep EEG recording in our institute.

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Oral triclofos is an older sedative-hypnotic drug. It is a stabilized form of chloral hydrate and is more palatable than chloral hydrate.^[4] Triclofos has been used as a sedative for short procedures such as dental extraction.^[5] The oral solution is well-absorbed, with onset of action in 30–40 min and produces hypnosis for 6–8 h in doses of 25–75 mg/kg.^[6]

The present study was done to look into efficacy, safety profile of oral triclofos in recording sleep EEG, to correlate it in relation to etiology, and to look into conditions which need second dose or rescheduling.

MATERIALS AND METHODS

Study design

This is a retrospective study done from June 2017 to May 2018. All the children between ages 6 months to 5 years who were referred for EEG from the Inpatient or Outpatient Departments of Niloufer Children's Hospital, a tertiary care center in South India, were included in this study.

Study protocol

All the children who were uncooperative during recording were given the same product of oral triclofos syrup (100 mg/ml).

All the necessary clinical parameters, age, sex, and diagnoses were noted. Children who are on medication other than antiepileptic drugs (AED'S) were excluded from the study.

Parents were instructed to make child sleep late in the night and awake 2 h before their usual time of awakening on the day of appointment for EEG and advised to keep nil per oral for at least 4 h before giving oral triclofos.

A trial for natural sleep was tried in a dark, quiet room for 60 min. EEG was done for 30 min after attaining sleep. If the child did not sleep, he/she was given the first dose of oral triclofos at a dose of 50 mg/kg. If the child did not sleep after an hour, a second dose of 50 mg/kg was given and wait for another hour for sleep. If child did not sleep even after second dose, appointment was rescheduled to later date. EEG findings were noted. All children were monitored for 8 h to look for adverse effects.

Endpoints

The primary endpoint of the study measured was the efficacy of oral triclofos in successfully recording EEG in uncooperative patients.

The other parameters measured include second dosing or rescheduling, sleep latency, sleep duration, and adverse effects.

Statistical analysis

Descriptive statistics were used to analyze data. All continuous variables were represented as mean \pm standard deviation.

Chi-square test was done to study the significance in children who required frequent second dosing of oral triclofos. $P < 0.05$ was considered as statistically significant.

RESULTS

A total of 446 children were enrolled for sleep EEG during the study period. Sixty-two children achieved natural sleep and were excluded from the study.

A total of 384 children required oral triclofos. Mean age of children was 33.97 ± 15.8 months, with a male-to-female ratio of 1.25:1. The most common indication for sleep study was febrile seizures with atypical presentation (39.6%) followed by HIE sequelae (20.3%) and others [Table 1].

Efficacy of oral triclofos

We were able to successfully record sleep EEG in 372 (96.8%) patients including the second dose of oral triclofos. Single dose was sufficient in 329 children (85.6%) and the second dose was required in 55 children (14.4%).

Mean sleep-onset latency was 35.96 ± 3.81 min and mean sleep duration was 83.8 ± 8.49 min.

Requirement of the second dose

Thirty (38.5%) among 78 children with HIE sequelae ($P < 0.001$) and 7 (29.1%) among 24 children with behavioral disorders ($P = 0.03$) required the second dose, whereas the requirement of the second dose was not statistically significant in children with other diagnoses. Requirement of the second dose was shown in Table 2.

Table 1: Etiological distribution of children enrolled for oral triclofos

Etiology	Number of patients (n=384), n (%)
Febrile seizures	152 (39.6)
Hypoxic encephalopathy	78 (20.3)
Infections	44 (11.5)
Behavioral disorders (autism/ADHD)	24 (6.2)
LGS/EE	18 (4.7)
Stroke	17 (4.4)
Breath-holding spells	13 (3.4)
Trauma/falls	12 (3.1)
Metabolic	11 (2.9)
Others	15 (3.9)

ADHD: Attention-deficit hyperactive disorder, LGS: Lennox–Gastaut syndrome, EE: Epileptic encephalopathy

Need for rescheduling

Twelve (21.8%) children among 55, who required the second dose, underwent rescheduling. Rescheduling was done in 8 (66.6%) patients of hypoxic encephalopathy and 4 (33.4%) patients of behavioral disorders such as autism and ADHD.

A total of 89 (23.2%) patients were on AED'S at the time of doing EEG. Out of 89 who were on AED'S, 23 patients showed beta-activity in EEG. Only 7 patients who are not using AED'S showed beta-activity. EEG findings were shown in Table 3.

Irritability, vomiting, and dizziness were common side effects. Irritability was seen in 12 (3.12%) children, vomiting in 16 (4.16%) patients, and dizziness in 19 (4.94%) patients.

DISCUSSION

Although oral triclofos is frequently used in India, clinical experience is rarely reported. It is also used for preoperative sedation.^[7] Many studies have used chloral hydrate, hydroxyzine, midazolam, and melatonin as a sedative for recording EEG in children.

Our study has mean sleep-onset latency was 36 min and mean sleep duration was 84 min, with adverse effects such as irritability, vomiting, and dizziness which was similar to other studies.^[4,8,9]

Table 2: Distribution of patients requiring second dose

Etiology	Total number of patients	Number of patients who required second dose, n (%)
Hypoxic encephalopathy	78	30 (38.4)
Behavioral disorders	24	7 (29.1)
Febrile seizures	152	12 (7.9)
Infections	44	4 (9.0)
LGS/EE	18	1 (5.5)
Metabolic	11	1 (9.1)
Trauma/falls	12	0
Others/stroke/breath holding spells	45	0

LGS: Lennox–Gastaut syndrome, EE: Epileptic encephalopathy

Table 3: Electroencephalography findings of the children

EEG findings	Number of patients, n (%)
Normal	256 (66.7)
Generalized epileptiform discharges	64 (16.7)
Focal epileptiform discharges	38 (9.9)
EE	12 (3.1)
LGS (hypsarhythmia)	6 (1.6)
Nonspecific slowing	6 (1.6)
Unilateral slowing	2 (0.5)

LGS: Lennox–Gastaut syndrome, EE: Epileptic encephalopathy, EEG: Electroencephalography

In a randomized trial,^[4] oral triclofos was studied in comparison to chloral hydrate where mean sleep-onset latencies were 37.3 ± 12.1 min and 36.6 ± 14.4 min for triclofos and chloral hydrate, respectively.

A study done by Jain *et al.*^[8] using oral triclofos, from North India, showed a mean sleep duration of 90 min and mean sleep-onset latency of 30 min. In the same study Jain *et al.*, side effects are reported in 13.75% of children. Our study has reported side effects in 9.63% with dizziness (4.94%) being more common in both studies. This can be due to relatively more number of febrile seizure children in our study.

We are able to successfully record sleep EEG in 96.8% of patients including the second dose of oral triclofos, whereas a study by Jain *et al.*^[8] has reported success in 93.1% children.

There are other studies which used chloral hydrate, midazolam, and melatonin for recording sleep EEG.^[4,9,10]

A nonrandomized controlled trial^[9] from Turkey using chloral hydrate in 141 children showed sleep latency of 16.2 min and sleep duration of 88.2 min using chloral hydrate. They were able to successfully record EEG in 98% with side effects in 8%.

In a randomized trial^[10] from Iran in 2013 in 348 children comparing chloral hydrate with midazolam had concluded that midazolam is superior to chloral hydrate neither in sleep latency nor sleep duration and both can be administered for recording sleep EEG with no advantage of one over the other.

To the best of our knowledge, our study is the first one to look into the efficacy of oral triclofos in relation to etiology and analyzing the children who frequently needed second dose and rescheduling. Rescheduling was done in 12 patients (3.2%) even after second dose. Most common of them are children with hypoxic encephalopathy sequelae and behavioral disorders such as autism and ADHD with hyperactivity which is statistically significant. It can be most often due to hyperactivity and irritability in those disorders which usually have reduced, inadequate sleep and frequent sleep disturbances along with behavioral issues.

CONCLUSIONS

Oral triclofos can be an effective sedative that can be used for recording sleep EEG in pediatric patients with less side effects. Children with hypoxic encephalopathy and behavioral disorders such as autism/ADHD are more likely to need second dosing and rescheduling. More detailed randomized and comparison trials are required

to validate the safety and efficacy of triclofos in relation to etiology.

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Conflicts of interest

There are no conflicts of interest.

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