Randomised Controlled Trial

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Melatonin versus chloral hydrate on sleep induction for recording electroencephalography in children: a randomized clinical trial

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Background: Electroencephalography (EEG) plays an essential role in the diagnosis of seizures. EEG recording in children is done with partial sleep deprivation and sedative drugs. To compare the effectiveness of melatonin and chloral hydrate on sleep induction and EEG recording in children.

Materials and methods: In a parallel blinded randomized clinical trial study, 78 patients (6 months–5 years) were included to record EEG. Patients were randomly divided into two groups to receive melatonin (0.4 mg/kg) or chloral hydrate (0.5 ml/kg). After receiving the sedative drug, the start and duration of sedation, recovery time, side effects, and epileptiform waves in the EEG were recorded. The data was analyzed using SPSS version 16, and the significance level was determined to be less than 0.05.

Results: A total of 78 children, including 34 girls (43.6%) and 44 boys (56.4%) (average age of 27.15 ± 17.15 months), were examined. Success in the induction of sedation was reported by melatonin in 36 patients (92%) and chloral hydrate in 37 patients (95%), which was similar between the two drugs ($P = 0.5$). The start time ($P = 0.134$) and the duration of sedation ($P = 0.408$) were alike between the two drugs. However, compared to the chloral hydrate, the recovery time in the melatonin group was significantly shorter ($P < 0.001$). Side effects were not seen in melatonin, while six children (15%) using chloral hydrate had mild side effects ($P = 0.013$). Epileptiform waves in EEGs were reported to be similar and positive for melatonin in 18 children (50%) and chloral hydrate in 16 children (43%) ($P = 0.410$).

Conclusion: The findings show that using melatonin in the dose prescribed in this study had similar effects to success in inducing sedation with the minimum quantity of chloral hydrate. Regardless of the start time and duration of sedation, the shorter recovery time and the absence of side effects are the advantages of using melatonin.

Keywords: child, chloral hydrate, electroencephalography, hypnotics and sedatives, melatonin, seizures

Introduction

Seizure is a common neurological condition in childhood and a major public health concern[1]. Approximately 4–10% of children experience at least one seizure (with or without fever) during the first 16 years of their lives[2]. Children with epilepsy face significant challenges, such as learning disorders and disabilities, which show the importance of early diagnosis of this disorder[3–5].

HIGHLIGHTS

- This trial demonstrated that melatonin had similar effects to chloral hydrate in inducing sleep.
- Melatonin had the advantage of causing a shorter recovery time and fewer side effects.
- The onset time and duration of sedation are similar when using melatonin and chloral hydrate.

When assessing patients with seizures, the primary focus is on obtaining a comprehensive medical history, determining the focal or generalized onset of seizures, and monitoring their vital signs. In addition to a neurological examination, electroencephalography (EEG) has emerged as a valuable diagnostic tool in this field[2,6]. EEG measures the electrical activity of the brain and can help in identifying the location and type of seizure.

EEG results are used for predicting the risk of seizure recurrence to show the physiological manifestations of abnormal excitability of the cerebral cortex. The primary purpose of EEG is to evaluate patients suffering from seizures, to accurately diagnose the type of seizures, and epileptic syndromes, and guide the correct treatment, or to detect sudden unknown attacks by showing interictal epileptiform discharges. Interictal epileptiform discharges is the most important diagnostic finding supporting epilepsy, which may be focal or generalized[7].

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EEG can be recorded in various modes, including sleep mode, which can aid in the diagnosis of several seizure disorders by increasing the likelihood of detecting epileptiform waves. However, EEG recording during sleep can present challenges, particularly in children, how are one of the most challenging groups to monitor. Different methods, such as sleep deprivation and sedative drugs, are utilized to facilitate EEG recording during sleep. When these methods are combined, better results and greater success in EEG recording can be achieved[8,9].

Sleep in children is not easily possible using partial sleep deprivation and is usually done using sedative drugs[8]. There are necessary pharmacological considerations in selecting sedative drugs for EEG in children. Currently, there is no ideal sedative drug[10]. In the past, many sedative drugs have been used as a sedation protocol, and chloral hydrate and melatonin are among the most widely used drugs in this field. Using chloral hydrate has a long history as a sedative for children. Studies show that its use causes unpredictable changes in EEG recordings by suppressing or intensifying epileptiform activity or rapid rhythms that can mask background waves and cover the epileptiform discharge[10,11]. Melatonin is also widely used to perform neurological actions, specifically to induce sleep for EEG recording, and its effectiveness and safety have been confirmed in some studies[12].

The present study aimed to compare the effectiveness of melatonin and chloral hydrate in inducing sleep for EEG recording in children aged 6 months to 5 years who were referred to Taleghani Children's Hospital in Gorgan, Iran, in 2022. The primary objective of this research was to identify a sedative drug with a shorter duration of sedation, adequate recording time for EEG, faster recovery, and fewer side effects, which pose minimal risks to the health of children.

Methods

General information

This study was conducted as a single-blind clinical trial in two parallel groups. The target group for blinding was children and parents. The researcher gave the necessary explanations to the parents of the patients about the treatment, the evaluation of the prognosis of the disease, the evaluated outcomes, and the possible side effects of the drugs used. After obtaining the patient's consent, treatment was started for the patient. Parents and patients were unaware of the dose of the medication and which of the two drugs was used.

The study population included children aged between 6 months to 5 years old. They were referred to Taleghani Hospital by a pediatric neurologist in 2022. Taleghani Hospital is a third-level referral center affiliated with Golestan University of Medical Sciences in Gorgan, Golestan province, Iran.

Based on the study of Ashrafi *et al.*[13], the sample size was determined as 39 people in each group and 78 people in total as shown in the randomization flow chart (Fig. 1). Children were classified into two groups according to the classification criteria of American anesthesiologists (class 1: healthy people, and class 2: people with mild systemic disorders such as mild asthma, controlled diabetes, and controlled seizures).

All patients and their parents entered the study with full knowledge and informed consent. The protocol of the study was approved by the ethics committee of Golestan University of Medical Sciences, Gorgan, Iran (IR.GOUMS.REC.1400.324). The reference hyperlink of the ethical approval is https://ethics.research.ac.ir/ProposalCertificateEn.php?id=231717&Print=true&;NoPrintHeader=true&NoPrintFooter=true&NoPrintPageBorder=true&LetterPrint=true. Our trial is fully in accordance with the Declaration of Helsinki and compliant with the Consolidated Standards of Reporting Trials (CONSORT) guideline. This study is registered with the Iranian Registry of Clinical Trials (IRCT) as a WHO Registry Network of International Clinical Trials Registry Platform (ICTRP) by the identifying number IRCT2022122705 6944N1. The reference hyperlink of the registry is https://www.irct.ir/trial/67662.

Inclusion criteria

The inclusion criteria include patients suffering from seizures or other seizure-like states requiring EEG examination while sleeping, the age between 6 months and 5 years, classes 1 and 2 of the ASA classification, and complete partial sleep deprivation.

Exclusion criteria

Entry criteria include a severe allergic reaction to chloral hydrate and melatonin, a history of recent head injury, use of sedative drugs in the past 2 days, and other severe systemic diseases such as neurological, cardiac, respiratory, metabolic, and digestive diseases, and noncompliance with partial sleep deprivation.

Data collection procedure

The identity questionnaire includes personal information, the general history of the patient, and medications that are completed by the parents. After obtaining consent to participate in this study, the conditions of partial sleep deprivation were explained to the parents by waking up the child at 6:00 AM until EEG at noon of the same day (without being informed of the type of medication received). Finally, an appointment was determined for the patient's visit time for EEG recording.

In this study, melatonin and chloral hydrate were used. Melatonin was used as 3 mg tablets from Razak Pharmaceutical Company with a dose of 0.4 mg/kg, which was given to the patients as colorless and dissolved in water after random selection of the drug. Chloral hydrate was given to children as an oral sirup with a concentration of 50% (250 mg/5 ml) and a dose of 0.5 ml/kg as a colorless oral solution.

For sample randomization, the researcher wrote the name of each drug with abbreviations (letter A for melatonin and letter B for chloral hydrate) on the envelopes. These envelopes were placed in a special box quite randomly. After the patient's visit at the previously determined time, if the conditions of partial sleep deprivation are met, and there are no contraindications for the use of melatonin and chloral hydrate drugs, and after the patient's preparation, an envelope is removed from the top of the box in an orderly and nonselective manner. After seeing the abbreviation written on it, the corresponding dose that was prepared under the title A = 0.4 mg/kg and B = 0.5 ml/kg was ready for each patient based on weight by the researcher.

After determining the appropriate dose based on weight, melatonin tablets were powdered and dissolved in water for ease of use. After receiving the medicine and accurately recording the time of drug administration in the specific forms for each patient, the children were transferred to a dark room with their parents until

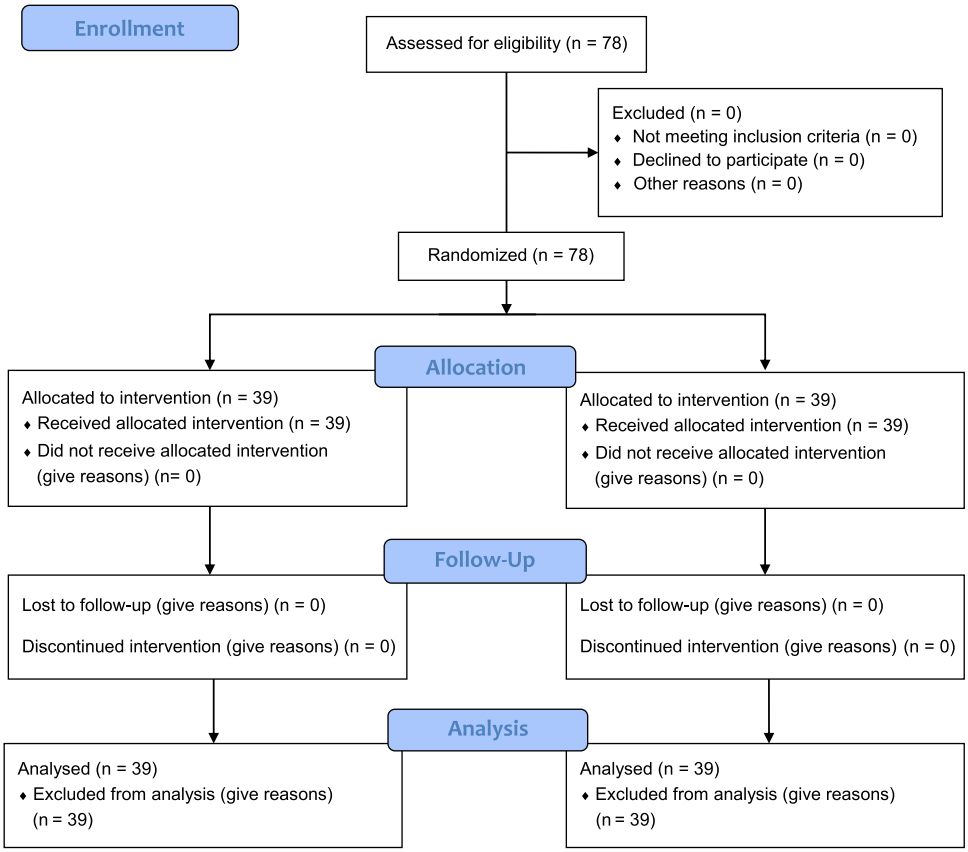

Figure 1. CONSORT flowchart of the study.

bedtime, and the parents were encouraged to establish suitable conditions for sleep according to their child's sleeping habits.

After drug consumption, the Ramsay Sedation Score system[14] was used to check the level of sedation of all patients. According to this system, in the stages of sleep (score 4–6), a soft tap on the glabella bone or loud auditory stimulation can be accompanied by a fast, slow, or no response based on the depth of sedation.

In this study, the target level of sedation of the patients to start EEG recording was to reach a score of 4 and more, which was considered a success in sleep induction. In the case of failure to achieve a score of 4 and more, after 1 h of using both drugs, the second dose was avoided, and the patient outcome was recorded as a failure in creating sedation and included in the analysis.

After reaching the complete sedation level (Ramsay Sedation score, greater than or equal to 4), the exact time was recorded in the relevant form, and the patient was transferred to the EEG recording room. Electrodes were placed on the head according to the international 10–20 system for EEG recording. The time from the start of taking the drug until reaching complete sedation was recorded in the patient's case as a sedation onset time. The EEG recording process lasted about 20 min on average from placing the electrodes, and the recording time was between 2:00 PM and 4:00 PM.

After completing the EEG recording, the children were transferred to another room. Then, their sedation depth was checked. In the case of a decrease in the amount of sedation and leaving the state of complete sedation (a score of less than 4 in the Ramsay Sedation scoring system), the exact time of going into sedation was recorded. The duration of sedation means the interval between full sedation (Ramsay Sedation score, greater than or equal to 4) until leaving sedation (Ramsay Sedation score, less than 4) was calculated in the relevant form.

In this study, another scoring system named Steward Recovery Score[15] was used to calculate the recovery time. According to this scoring system, patients receive a score between 0 and 2 in each part as a level of consciousness, respiratory and airway status, and spontaneous mobility. Reaching a score of 6 in this scoring system means complete recovery, and no score indicates the need for emergency actions.

From leaving full sedation (Ramsay Sedation score less than 4) until reaching full recovery and a score of 6 in the Steward Recovery Score system, it was recorded as the recovery time in the patient's medical case. During this period, the patients' clinical symptoms, including blood pressure, pulse, and breathing rate, were checked for 1 h after completing the EEG recording. All patients were examined for possible side effects of melatonin and chloral hydrate, such as restlessness, drowsiness, headache, dizziness, hypotension, nausea, and vomiting. The recorded EEGs of all children were examined by a pediatric neurologist to check the presence of epileptiform waves. If these waves were present, they were recorded in the patient form.

Data analysis procedure

The data was analyzed using SPSS 16 software. Graphs, frequency distribution tables, and mean and SD were used to describe the data. Shapiro–Wilk test was used to check the

normality of data distribution, and Leven's Test was used to check the homogeneity of variances. For independent data, Student's *t*-test was used, if the assumptions of parametric tests, such as normality of data distribution and homogeneity of variances, were established. Welch's *t*-test was used if homogeneity of variances was not found. Mann–Whitney *U* test was used to examine independent data in which the assumption of normality of data distribution was rejected. χ^2tests or Fisher's Exact test were also used to check nominal or classified qualitative data. The significance level for all tests was considered equal to 0.05.

Results

The present study was conducted to determine and compare the effects of two drugs, melatonin, and chloral hydrate, for inducing sleep in EEG recording on patients aged 6 months to 5 years in 2022. A total of 78 children who needed EEG while sleeping were included in the study 39 children were in both the melatonin and chloral hydrate groups. The demographic and clinical information of these patients is presented in Table 1.

The comparison results of induction of sedation, side effects, amount of epileptiform discharge, sedation onset time, duration of sedation, and recovery time in two groups of melatonin and chloral hydrate are presented in Table 2.

Of the 78 patients studied, 73 children (94%) had success in the induction of sedation, and five children (6%) had a failure in the induction of sedation. As shown in Table 2, the rate of failure or success in the induction of sedation is similar between the two medicinal groups of melatonin and chloral hydrate. It is not statistically significant ($P = 0.5$).

As shown in Table 2, side effects occurred in six children (15%) using chloral hydrate drug, which was significantly less for melatonin drug, and 0%, which had a significant difference ($P = 0.013$).

Epileptiform discharge in EEG performed by two drugs was similar and positive for melatonin in 18 children (50%) and chloral hydrate drug in 16 children (43%). According to the statistical test, this difference is insignificant ($P = 0.410$).

The time to induce sedation among the patients who succeeded in sedation induction between two similar drugs was reported as 23.92 min for melatonin and 26.30 min for chloral hydrate. The average sedation onset time was not significantly different in the two drugs ($P = 0.134$).

The duration of sedation was almost similar for both drugs, so it was 29.69 min on average for melatonin and 29.86 min for chloral hydrate. The average time of sedation in the two groups has a slight difference, so based on the statistical test, this difference is not significant ($P = 0.408$).

The average duration of recovery in the melatonin drug was 13.64 min, and in the chloral hydrate drug, it was reported as 30 min with a significant difference ($P > 0.001$).

Table 1

Frequency distribution of demographic and clinical variables

	Melatonin	Chloral hydrate	*P*	Statistic test
Number of patients, *n* (%)	39 (50)	39 (50)	–	–
Sex, *n* (%)				
Female	20 (51.3)	14 (35.9)	0.171	χ^2
Male	19 (48.7)	25 (64.1)		
Age, Mean (SD)	27.36 (15.707)	26.95 (18.687)	0.695	Man–Whitney
ASA classification, *n* (%)				
Class 1	14 (36)	23 (59)	0.041	χ^2
Class 2	25 (64)	16 (41)		

Table 2

Comparison of sedation induction outcome, adverse effects, epileptiform discharge, sedation onset time, and duration of sedation and recovery between melatonin and chloral hydrate groups

	Melatonin	Chloral hydrate	*P*	Statistic test
Sedation induction outcome, *n* (%)				
Failed	3 (8)	2 (5)	0.5	χ^2
Success	36 (92)	37 (95)		
Adverse effects, *n* (%)				
Positive	0 (0)	6 (15)	0.013	χ^2
Negative	39 (100)	33 (85)		
Epileptiform discharge, *n* (%)				
Positive	18 (50)	16 (43)	0.410	χ^2
Negative	18 (50)	21 (57)		
Sedation onset time, Mean ± SD (range)	23.92 ± 6.389 (12–36)	26.30 ± 11.232 (9–55)	0.134	*t*-test
Sedation duration, Mean ± SD (range)	29.69 ± 7.410 (18–48)	29.86 ± 7.878 (20–52)	0.408	Man–Whitney
Duration of recovery, Mean ± SD (range)	13.64 ± 6.863 (0–25)	30 ± 7.792 (16–46)	< 0.001	*t*-test

Discussion

Seizures, the most common childhood neurological condition, bring significant complications, such as learning disorders and various disabilities; this shows the importance of timely diagnosis and accurate evaluation. Recording EEG during sleep is one of the crucial methods in evaluating children suffering from seizures. For this purpose, it is necessary to induce sleep in children. The effectiveness of using sedative drugs for EEG recording in children has been investigated in various studies (for example, comparing melatonin with triclofos[16], comparing melatonin with partial sleep deprivation[17], comparing melatonin with chloral hydrate[13,18], investigating the role of melatonin in EEG recording[8,19–23], and the effectiveness of melatonin, hydroxyzine, and chloral hydrate[24].

Melatonin and chloral hydrate are the most commonly used hypnotic drugs for inducing sleep in children. In this study, we investigated the effectiveness of these two drugs in sedation induction, sedation onset time, sedation duration, recovery duration, and epileptiform waves.

The study of Dirani *et al.* (2015) showed a significant difference between the success in inducing sedation between melatonin and chloral hydrate. This amount was reported as 44.6% for melatonin and 95.1% for chloral hydrate. But in the present study, the findings showed that the success rate in inducing sedation was similar between the two drugs (92% for melatonin and 95% for chloral hydrate), and even though this rate was slightly higher for chloral hydrate, there is no significant difference between the use of chloral hydrate and melatonin and the

success in inducing sedation, which is inconsistent with the findings of the study by Dirani *et al*.[24]. According to the sedation protocol in Diani *et al*.'s study, melatonin was prescribed only to children who did not fall asleep spontaneously after 20 min, and if children fell asleep spontaneously, the success rate of melatonin medication increased significantly. Another point is the difference in the sedation protocol. In Dirani *et al*.'s study, in case of failure to induce sedation, the old protocol (chloral hydrate) was compared with the new protocol (the sequential use of melatonin, hydroxyzine, and chloral hydrate). In the case of failure in inducing sedation, a second dose of chloral hydrate was used in the old protocol, while in this study, the sedation protocol was fixed for all patients, and after randomization, only one type of drug was used for each patient, and giving a second dose was also avoided. Other reasons are the difference in the age group and the dose of melatonin and chloral hydrate used.

Ashrafi and colleagues (2008), in a study, showed that the onset of sedation was similar between melatonin and chloral hydrate. Still, there was a significant difference in the length of sedation and recovery time between the two drugs so that the length of sedation And the recovery time for the melatonin drug was shorter[13]. In the present study, the onset of sedation and the length of sedation were similar between two drugs, melatonin, and chloral hydrate. In comparison, a significant difference was reported in the recovery time between the two drugs used. In terms of the duration of sedation, the current study was inconsistent with Ashrafi's study. Among the reasons for the disparity, we can point out that assessing the amount of sedation is not the same between the two studies. In this study, the Ramsay Sedation score system was used to evaluate the achievement of full sedation. Based on this system, the sedation onset time and the duration of sedation were calculated after reaching a score of 4 and above. However, in Ashrafi's study, the method of assessing the sedation depth and onset time is not mentioned. Another reason for the shorter duration of sedation in the Ashrafi study is the lower dose of melatonin compared to the present study and the different clinical conditions and ages of the study population. The side effects reported in the Ashrafi study were similar between the two drugs. In contrast, in the present study, the number of side effects was significantly different between the two drugs. So, in this study, the melatonin drug has no side effects, and the chloral hydrate drug has been associated with mild and controllable side effects. Eisermann *et al*.[23] and Fallah *et al*.[21] have also reported similar results to the current study. So, in these studies, melatonin was without having any side effects. The comparison between the observed results shows that the melatonin, with the dose used in the current study, is more valuable than Ashrafi's study.

In 2016, Yuen *et al*. showed that the number of epileptiform waves in the EEG recorded after melatonin was significantly higher than that of chloral hydrate[18]. In the current study, despite the nonsignificance of the difference in the number of epileptiform waves between the two drugs, this amount was reported to be higher for the melatonin drug than the chloral hydrate drug, which is in line with the results of Yuen *et al*.'s study and based on the results, the use of the melatonin drug has not been associated with the effect on background waves and reduction of epileptiform waves.

In the present study, there was no significant difference between classes 1 and 2 in ASA classification between the two drug groups, as well as the rate of success or failure in the induction of sedation based on age and sex.

Conclusion

The findings of this study show that the use of melatonin in the dose prescribed in this study, in addition to being safe, has similar success in inducing sedation with chloral hydrate, which is a powerful sedative drug with some dangerous side effects. Sufficient duration of sedation, shorter recovery time, and absence of side effects are among the features of using melatonin, which can make melatonin an ideal drug for recording EEG during sleep in children. Also, the use of chloral hydrate drug with the minimum dose used in this study has had favorable effects on the success of sedation induction, which reduces the need to use higher doses of this drug. Although using this drug with the minimum dose needed to induce sedation was still associated with side effects, melatonin has a significant superiority over chloral hydrate drugs in this field. Among other important cases in the EEG recording was the occurrence of epileptiform waves, which are reduced by many sedative drugs; while the use of melatonin did not reduce the incidence of epileptiform waves. Therefore, the use of this drug did not have any negative effect on the diagnosis of epileptic disorders. In general, based on the results obtained from this study, melatonin can be used as the first drug in the sedation induction protocol, and chloral hydrate can be used as a secondary drug in case of failure in sedation induction to record EEG during sleep in children.

Limitations and recommendations

In this study, there were many difficulties in dealing with patients, especially children, which caused some limitations. Among these problems was the inability of the children's parents to establish the child's sleeping conditions in the hospital. This factor can affect the duration of the onset of sedation after taking the drug and cause a delay in sedation and even failure in sedation. Another problem of this study is the parents' lack of knowledge about the importance of observing relative sleep deprivation entirely and keeping the child awake until EEG recording. By teaching parents, the day before EEG recording and monitoring children after taking sedative drugs, we tried to improve these conditions and eliminate the influencing factors of this study.

The limitations of this study are generally related to the monitoring of patients after recovery to investigate side effects further. Due to the facilities of the hospital and the large number of visiting patients, it has not been possible to monitor the patients after recovery. In this study, 1 h was determined as the required period for examining clinical symptoms and side effects. Other limitations include not examining children with neurodevelopmental disorders, genetic disorders, and other specific diseases.

It is recommended to investigate the effects of higher doses of melatonin on children with neurological diseases in a clinical trial with a more considerable study population. Also, it is recommended to check background waves and other nonepileptic disorders such as hypoactivity, focal or generalized slowness, and suppression after periods of hyperactivity in patients' EEG.

Ethical approval

The protocol of the study was approved by the ethics committee of Golestan University of Medical Sciences, Gorgan, Iran (IR.GOUMS.REC.1400.324). The reference hyperlink of the ethical approval is: https://ethics.research.ac.ir/ProposalCertificateEn.php?id=231717&Print=true&NoPrintHeader=true&NoPrintFooter=true&NoPrintPageBorder=true&LetterPrint=true.

Consent

All patients and their parents entered the study with full knowledge and informed consent.

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Author contribution

B.F., S.A.H., N.B., A.L., and M.H.K.: developed the protocol and were involved in the design, selection of study, data extraction, quality assessment, statistical analysis, result interpretation, and development of the initial and final drafts of the manuscript. All authors read and approved the final draft of the manuscript.

Conflicts of interest disclosure

The authors declare that there is no conflicts of interest regarding the publication of this paper.

Research registration unique identifying number (UIN)

1. Name of the registry: Iranian Registry of Clinical Trials (IRCT) as a WHO Registry Network of International Clinical Trials Registry Platform (ICTRP).
2. Unique identifying number or registration ID: IRCT20221227056944N1.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): https://www.irct.ir/trial/67662

Guarantor

The Guarantor(s) of this study is Seyed-Ahmad Hosseini who accept full responsibility for the work and/or conduct of the study, had access to the data, and controlled the decision to publish.

Data availability statement

The data presented in this study will be available on request from the corresponding author by this journal representative at any time during submission or after publication.

Provenance and peer review

This manuscript was not invited by the journal and underwent external peer review. Therefore, we confirm that the paper is 'Not commissioned, externally peer-reviewed'.

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