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Original Article

Nasal dexmedetomidine in sedation of electroencephalogram (EEG) in comparison with chloral hydrate as a clinical trial

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Abstract: Background: An electroencephalogram (EEG) is a test that measures the brain's electrical activity. Here we decided to evaluate and compare the effectiveness of two drugs, hydrate, and nasal dexmedetomidine, in creating sedation during EEG in children. Methods: This clinical trial was performed in 2020-2022 on 65 children that were candidates for sedation for EEG with the Iranian Registry of Clinical Trials (IRCT) code IRCT20210614051574N8 (https://www.irct.ir/trial/61860). Pediatrics were randomized into two groups. Children in the first group received intranasal dexmedetomidine at a dose of 2-3 μg/kg 10 minutes before the procedure. The second group received 5% chloral hydrate syrup at a dose of 50-100 mg/kg orally 10 minutes before the procedure. For each patient, sleep onset latency and sleep duration were also measured. It should be noted that the patient's level of consciousness and sleepiness were checked by AVPU (alert, verbal, pain, unresponsive) criteria. Results: There was no significant difference between the two groups regarding the mean sleep onset latency (P = 0.59), sleep duration (P = 0.12), heart rate (P = 0.30), respiratory rate (P = 0.26), and SPO2 (P = 0.27). Analysis of covariance by adjusting for age and sex in both groups showed that the mean sleep duration (P = 0.04) and heart rate (P = 0.03) in the oral chloral hydrate group were significantly higher than in the nasal dexmedetomidine group. But the mean of other variables was not significantly different between the two groups (P>0.05). Conclusion: The mean sleep duration and heart rate were significantly lower in the intranasal dexmedetomidine group compared to the oral chloral hydrate group.

Keywords: Electroencephalogram, chloral hydrate, dexmedetomidine, pediatrics

Introduction

An electroencephalogram (EEG) is a test that measures the activity of the brain [1-3]. Seizures, recurrent sleep apneas, brain infections, or brain tumors are some of the most important reasons children need an EEG. In addition, brain scans today are usually done when children are stunted or have symptoms such as loss of consciousness, movement, or abnormal behavior [4, 5].

During the EEG process, the areas connected to the electrodes will be marked on the child's head, and the EEG process will begin after the electrodes are connected. EEG measures brain electrical activity by placing EEG sensors on the patient's scalp. The pediatrics need to be asleep or sitting during this process [6, 7]. EEG recording is a long-duration procedure and requires the patient's cooperation to set up the device and perform the work steps. This issue is a challenging process in pediatrics. Therefore, sedation and sleeping using some agents as preoperative medication are often caused in children undergoing EEG [8]. Due to the long recording time of the EEG, many children lose their cooperation and start moving or crying during the operation [9, 10].

Various drugs have been used to induce sedation in children undergoing EEG. The ideal sedative should have a rapid onset, predictable duration, short duration of action, and low incidence of side effects [11].

Chloral hydrate is a colorless solid drug and one of the prescribed medications for insomnia and sleep disorders. It belongs to the category of sedatives and hypnotics. It is also used to control pain after surgery [12]. The mechanism of action of the drug is not entirely known; however, the CNS depressant effects of Chloral Hydrate are believed to be mainly due to the active metabolite trichloroethanol. It is also prescribed as a sedative and in some cases, is used orally to control pain and to relax children [9]. Different studies have explained that chloral hydrate could be substituted with other medications, including melatonin, clonidine, and dexmedetomidine [13-15].

Dexmedetomidine, sold under the brand name analgesic Precedex and other letters, is an, sedative, and analgesic. Sedation with dexmedetomidine can increase the patient's tolerance to airway intubation [16]. It is also used in the anesthesia process to prepare the patient for surgery or medical procedures. It is a selective alpha-2 adrenergic agonist with anesthetic and sedative properties [17]. Dexmedetomidine is thought to inhibit the secretion of norepinephrine due to the activation of G proteins by alpha-2 adrenergic in the brainstem. The sedative and anxiolytic effects of the drug are mediated through the stimulation of central α2-receptors. Dexmedetomidine can be given as one microgram per kilogram of intravenous infusion over 10 minutes, followed by continuous intravenous infusion of 0.2 to 0.7 micrograms per kilogram per hour [12]. The sedative properties of this drug are produced by stimulating α2 receptors in presynaptic neurons, and the net effect is to reduce the secretion of norepinephrine from presynaptic neurons by inhibiting postsynaptic activation, which reduces central nervous system stimulation. It can also be used as a nasal form [18].

The use of chloral hydrate and dexmedetomidine in sedation during EEG in children has been previously studied. But no study comparing dexmedetomidine nasally with chloral hydrate has been performed. This is especially important because of the ease of sedation and the appropriate drug effects. Administration of oral agents, including oral dexmedetomidine, could also be challenging, especially in patients with risks of aspiration. Therefore, this study seeks to investigate whether nasal dexmedetomidine could be a suitable substitute for oral chloral hydrate.

Methods and material

Study design

This clinical trial was performed in 2020-2022 at Imam-Hossein hospital, affiliated to Isfahan University of Medical Sciences. The current study was conducted on pediatrics that were candidates for sedation for EEG. The the study protocol was approved by the Research Committee of Isfahan University of Medical Sciences and the Ethics committee has confirmed it (Ethics code: IR.MUI.MED.REC.1400.780, Iranian Registry of Clinical Trials (IRCT) code: IRCT20210614051574N8).

Inclusion and exclusion criteria

The inclusion criteria were age from 6 months to 10 years, candidates of EEG for any reason, requiring sedation for EEG, and signing the written informed consent by the parents for entering the study. Patients with the following criteria did not enter the study history of respiratory diseases, peptic ulcer or hepatic diseases, treatments with drugs that interact with chloral hydrate or dexmedetomidine, presence of a specific underlying condition that affects the interpretation of goals such as the duration of sedation and lack of consent. The exclusion criteria were any previous allergic reactions to chloral hydrate or dexmedetomidine and the patient's or parent's will to exit the study.

Intranasal dexmedetomidine prepration

The preparation method of intranasal dexmedetomidine is also described below.

Due to the vial's low concentration, it is impossible to make a spray with a concentration higher than five μg/puff, according to the hospital facilities. Therefore, concentrations of 1, 2, 3, 4 and 5 μg/puff are recommended; depending on the weight of the child, a combination of these sprays should be used, taking into account the acceptance of 5 puffs for children from very low weights (0.5 kg) to 12.5 kg. These calculations are based on dexmedetomidine at a dose of 2 μg/kg. How to calculate the amount of medicine needed to make a spray: The volume of each spray is considered to be 5 ml

(about 50 puffs), which is effective for 28 days due to the stability of the drug and the duration of the effect of the protective agents in the isotonic nasal saline spray solution. Eight vials of dexmedetomidine are needed to make the sprays. It should be noted that all drugs are sprayed evenly because the drug is completely soluble and compatible with a basis of isotonic nasal saline spray. Since the isotonic nasal saline spray is used, which has already been tested in the factory, it can be ensured that each puff of the spray has a constant volume and uniformity. The shelf life of the drugs is 28 days and the desired temperature is 25 degrees at room temperature. How to use it is as follows.

First, disinfect the spray with alcohol, then lower the baby's head, apply the spray to one of the nostrils, and hold the other nostril with the hand. The child takes a slow, deep breath through the nose and, at the same time, presses the spray to release the medicine. The child takes a slow, deep breath through the nose and at the same time, presses the spray to release the medicine. It is best to spray the spray on the outside of the nose.

Patient data and grouping

Sixty-five patients were recruited based on the mentioned criteria and were randomly assigned to the study groups by Random Allocation Software. The patients' names were entered into the Statistical Package for Social Sciences (SPSS) software and were randomized into two groups.

At the beginning of the study, patient's demographic data, including age, gender, and the reason for undergoing EEG, were collected by a checklist.

Grouping and interventions

Children in the first group received intranasal dexmedetomidine at a dose of 2-3 μg/kg 10 minutes before the procedure. The prescribed dose is to start with a dose of 2 μg/kg, and if there is not enough sedation, one μg/kg is added. The second group received 5% chloral hydrate syrup at a dose of 50-100 mg/kg orally 10 minutes before the procedure. In addition, for chloral hydrate, a dose of 50 mg/kg was given first; if sedation was insufficient, a dose of 100 mg/kg was used.

Patients were monitored by the Pediatric Anesthesia Fellowship. During the EEG process, information on the heart rate, respiratory rate, and SPO2 of patients were collected every 5 minutes and then every ten minutes.

Data collection

Sleep onset latency and sleep duration were also measured for each patient. The sleep onset latency was defined as the interval between drug administration and falling asleep. A chronometer measured this indicator. Sleep duration was defined as sleep onset until awakening, also calculated by a chronometer.

It should be noted that the patient's level of consciousness and sleepiness were checked by AVPU criteria (alert, verbal, pain, unresponsive) as follows.

A for alertness or alertness: The patient is open-eyed and answers questions. The answers do not matter if they are inaccurate or incorrect.

V for Voice: The patient uses only unintelligible sounds in answering questions.

P for pin: The patient responds to pain. This response is either accompanied by repulsion of the pain agent or only by stretching and expansion in the limbs.

U for unresponsive: The patient is without any response to sound and pain.

Statistical analysis

The data were entered into SPSS software (version 24, SPSS Inc., Chicago, IL). Quantitative data were reported as mean ± standard deviation and qualitative data as frequency distribution (percentage). Independent t-test, and Chi-square were used to analyze the data. *P*-value <0.05 was considered as a significance threshold.

Results

Study population

Data from 65 pediatrics were analyzed. The study population consisted of 2 groups. The first group had 32 children receiving nasal dexmedetomidine with an age range of 11 months to 5 years, and the second group had 33 chil-

Table 1. Comparison of demographic data in the study population

Variable		Oral chloral hydrate (N = 32)	Nasal dexmedetomidine (N = 33)	*P*-value
Gender (N (%))	Boy	23 (69.7%)	12 (37.5%)	<0.001
	Girl	10 (30.3%)	20 (62.5%)	
Age (year) (mean ± SD)		3.3±2.1	2.5±1.4	0.28

Table 2. Comparison of the mean of slightly different variables between boys and girls

Variable	Boy		Girl		*P*-value
	Mean	S.D	Mean	S.D	
sleep onset latency	36.6	3.9	35	4.5	0.79
sleep duration	23.4	2.3	24.8	2.5	0.68
Heart rate	100.5	3	103.1	2.3	0.51
Respiratory rate	22.5	0.8	24.5	0.9	0.08
SP02	94.1	0.4	95	0.3	0.09

Table 3. Pearson correlation coefficients between age and sleep onset latency, sleep duration, heart rate, respiratory rate, and SP02

Variable	Age	
	r	P
sleep onset latency	0.064	0.61
sleep duration	-0.165	0.18
Heart rate	-0.323	0.009
Respiratory rate	-0.442	>0.001
SP02	0.163	0.19

dren receiving oral chloral hydrate with an age range of 7 months to 10 years. Analysis of demographic data is shown in **Table 1**. Primary data analysis showed that the ratio of boys to girls was 1.17. Evaluation of age distribution showed that four patients (6.2%) had six months-1 year of age, six patients (9.2%) had 1-2 years, 37 patients (56.9%) had 2-3 years, ten patients (15.4%) had 3-4 years, two patients (3.1%) had 4-5 years, three patients (4.6%) had 5-6 years, one patient (1.5%) had 6-7 years, and two patients (3.1%) had 7-10 years.

Data showed that there were no significant differences between boys and girls regarding the mean sleep onset latency (P = 0.79), sleep duration (P = 0.68), heart rate (P = 0.51), respiratory rate (P = 0.08) and SP02 (P = 0.09) (**Table 2**).

Correlations

Pearson correlation coefficient showed that age was inversely related to heart rate (P = 0.009) and respiratory rate (P<0.001) but age had no significant relationship with sleep onset latency (P = 0.61) and sleep duration (P = 0.18) and SP02 (P = 0.19) (**Table 3**).

Comparison of two groups

Independent t-test showed that there was no significant difference between the two groups regarding the mean sleep onset latency (P = 0.59), sleep duration (P = 0.12), heart rate (P = 0.30), respiratory rate (P = 0.26) and SP02 (P = 0.27). Analysis of covariance was used to control the effect of age and sex variables. Analysis of covariance by adjusting for age and sex in both groups showed that the mean sleep duration (P = 0.04) and heart rate (P = 0.03) in the oral chloral hydrate group were significantly higher than in the nasal dexmedetomidine group. But the mean of other variables was not significantly different between the two groups (P>0.05) (**Table 4**).

Discussion

In this study, we assessed 65 pediatrics undergoing EEG procedures. By administering intranasal dexmedetomidine and oral chloral hydrate, we observed that the mean sleep duration and heart rate in the oral chloral hydrate group were significantly higher than in the intranasal dexmedetomidine group. Still, the two groups had no significant differences regarding mean sleep onset latency, respiratory rate, and SP02. Other findings of this study were that age was inversely related to heart and respiratory rates.

These data support using nasal dexmedetomidine for pediatrics undergoing EEG because our study showed that pediatrics receiving intranasal dexmedetomidine had similar mean sleep onset latency, respiratory rate, and respiratory rate SP02 to cases that received oral chloral hydrate. Furthermore, they had lower mean sleep duration and heart rate, which could be

Table 4. Comparison of the mean of slightly different quantitative variables between the two groups

Variable	Nasal dexmedetomidine		Oral chloral hydrate		*P*-value[1]	*P*-value[2]
	Mean	S.D	Mean	S.D		
sleep onset latency	34.2	4.1	37.4	4.2	0.59	0.69
sleep duration	21.4	2.3	26.7	2.4	0.12	0.04
Heart rate	99.7	2.3	103.8	3.1	0.3	0.03
Respiratory rate	24.1	1	22.8	0.6	0.26	0.99
SPO2	94.8	0.3	94.2	0.4	0.27	0.42

P1: using Independent samples t-test, P2: using ANCOVA.

considered a positive advantage of intranasal dexmedetomidine. Therefore, using nasal dexmedetomidine could be helpful in clinical practice, and we observed beneficial effects.

There have been previous studies comparing the sedative properties of these drugs. Most previous studies have been conducted on pediatrics undergoing imaging procedures, including computed tomography (CT) scans. In 2017, an analysis was performed by Yuen and colleagues in China on 196 children before a CT scan. Comparing the effects of oral chloral hydrate and intranasal dexmedetomidine showed no significant differences between the two groups regarding sedation levels and onset duration. It was also reported that children receiving oral chloral hydrate had complications, including vomiting after procedures, but patients that received intranasal dexmedetomidine had no complications [19]. Zhang and others reported similar results by evaluating data from children undergoing magnetic resonance imaging scans [20]. These data are in line with the findings of our study, showing the effectiveness of oral chloral hydrate and intranasal dexmedetomidine in children.

Reynolds and colleagues evaluated data from children that underwent auditory brainstem response (ABR) testing. This study showed that oral chloral hydrate and intranasal dexmedetomidine are effective in sedating children, and intranasal dexmedetomidine administration is easier. They also reported that administration of intranasal dexmedetomidine was associated with a shorter time to desired sedation level and a more stable heart rate [21]. Li and others stated that intranasal dexmedetomidine could significantly be used after failed sedation with oral chloral hydrate and this drug could provide sufficient sedation with more stable hemodynamics [22]. These data were in line with our findings.

The critical point is that we administered oral chloral hydrate and intranasal dexmedetomidine in cases undergoing EEG, and this procedure requires sufficient sedation level. Further studies have also confirmed the use of intranasal dexmedetomidine in similar situations.

Cao and others performed another study in 2017. They compared the effects of intranasal dexmedetomidine and oral chloral hydrate on sedation in 141 children undergoing ophthalmic examination. It was reported that administration of intranasal dexmedetomidine was associated with a significantly higher success rate than oral chloral hydrate. They also reported that oral chloral hydrate induced higher percentages of vomiting and altered bowel habit after discharge than dexmedetomidine [23]. Cozzi and colleagues declared that dexmedetomidine was as effective and safer than chloral hydrate in children undergoing different procedures [15]. These data are not in line with the findings of our study. We showed no significant differences between the two groups regarding different variables, but mean sleep duration was shorter in the oral chloral hydrate group. These differences could be due to variations in the study population and characteristics. But intranasal dexmedetomidine is believed to be an effective drug with high clinical value in sedating pediatrics.

The most important properties of intranasal dexmedetomidine could be an easier administration route, especially in children with risks of aspiration and fewer complications than oral chloral hydrate. Another important finding of our study was that we observed significant inverse relationships between age, heart rate, and respiratory rate in patients. Therefore, it is suggested that these drugs should be used with more caution in pediatrics of lower ages. The limitations of this study were the restricted study population and administering only one

dosage of the drugs. We suggest that further research should be performed on larger study populations with different dosages.

Conclusion

Administration of nasal dexmedetomidine is a suitable and proper sedation option in children before EEG. Compared to chloral hydrate, the privileges of this therapy are the easier route of administration, lack of aspiration risks, and lower systemic effects.

Disclosure of conflict of interest

None.

Abbreviations

EEG, Electroencephalogram; IRCT, Iranian Registry of Clinical Trials; AVPU, Alert, Verbal, Pain, Unresponsive; SPSS, Statistical Package for Social Sciences.

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