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A Single-center Randomized Clinical Trial Comparing the Treatment Efficacy of High Dose Oral Prednisolone with Intramuscular Adrenocorticotropic Hormone in Patients with Infantile Spasm

Shima Imannezhad[1], Javad Akhondian[1], Farah Ashrafzadeh[1], *Mehran Beiraghi Toosi[1], Narges Hahemi[1], Maryam Emadzadeh[2], Mohammad Reza Akhondian[31]

[1]Department of Pediatric Neurology, Faculity of Medicine, Mashhad University of Medical Siences, Mashhad, Iran. [2]Department of Social Medicine, Faculity of Medicine, Mashhad University of Medical Siences, Mashhad, Iran. [3]Mashhad University of Medical Siences, Mashhad, Iran.

Abstract

Background

Infantile spasm is a rare condition in infants from 4 to 7 months old. Treatment varies in different cases. Corticosteroids and adrenocorticotropic hormone (ACTH) are the most widely used treatment options; however, there are debates on their efficacy. The aim of our study is to compare corticosteroid treatment with ACTH in patients with infantile spasm.

Materials and Methods: In a randomized clinical trial, 51 patients with infantile spasm were enrolled in the study and distributed into two groups, including the corticosteroid (twenty-six patients), and ACTH (twenty-five patients) groups. The patients in the corticosteroid group received a dose of 8 mg/kg/day (max: 60 mg) of prednisolone in three divided doses for three weeks, and the dose was later tapered in responders. Non-responders after two weeks received 2-3 U/kg/day of ACTH (max: 100 U) for five days. The outcome was assessed using EEG and clinical remission of the disease. The comparison of the two groups was made using SPSS software version 20.0.

Results: Twenty-six patients were treated with prednisolone and 25 patients with ACTH. There was no significant difference in gender, age, age of seizure onset, and growth abnormalities. At the end of the study, 13 patients in the prednisolone group and 17 patients in the ACTH group had normal EEG rhythm with no significant difference (p=0.33). As to clinical response, 18 patients in the prednisolone group (69.2%), and 19 in the ACTH group (76%) responded to treatment with no significant difference regarding the treatment outcome (p=0.58).

Conclusion

There was no considerable difference regarding treatment of infantile spasm with high dose prednisolone or ACTH in in this study.

Key Words: Adrenocorticotropic hormone, Epileptic spasm, Infantile spasm, Prednisolone.

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Corresponding Author:

Mehran Beiraghi Toosi, MD, Department of Pediatric Neurology, Faculity of Medicine, Mashhad University of Medical Siences, Mashhad, Iran.

Email: beiraghitm1@gmail.com

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1- INTRODUCTION

Infantile spasm is a condition composed of specific types of seizures, psychomotor retardation, and a usual typical electroencephalogram (EEG) finding called hypsarrhythmia (1). It is alternatively known as West's Syndrome, after Dr. William James West who was the first to define the condition (2). Several accompanying/comorbid abnormalities are associated with infantile spasm, some of which are discovered at the time of birth such as Down's syndrome, and some are found in later evaluations, including tuberous sclerosis and neuronal migration disorders (3). It is believed that around 60-70% of the cases are found in the presence of another underlying disease (4). Infantile spasm is a rare type of epilepsy occurring in about 1 to 4 cases out of 10,000 children, and the peak age is from 4 to 7 months (5). Several etiologies, including genetics and structural, metabolic, and perinatal disorders have been suggested as causes of infantile spasm (6).

Although some 160 years have passed since the first description of infantile spasm, its diagnosis, management, and treatment have remained challenging. The main goal of the treatment is to ensure the cessation of seizures, and better developmental outcomes are expected with controlled seizures (7). The treatment choices are varied and include antiepileptic drugs, pyridoxine, adrenocorticotropic hormone, and the ketogenic diet. Conventional antiepileptic treatments are usually ineffective and cannot control spasms (8). Among these drugs, vigabatrin can be effective for infantile spasms secondary to tuberous sclerosis (1). Hormone therapy, including adrenocorticotropic hormone (ACTH), is generally recommended as an effective treatment for infantile spasm (9) and has been in use as a first-choice treatment. However, adrenocorticotropic hormone (ACTH) is expensive and not readily available; therefore, many clinicians try corticosteroids as an alternative treatment for this condition (10). No significant difference between the two treatment options has been found in previous studies, including United Kingdom Infantile Spasms Study (UKISS) (11). However, they have called for further investigations to reach more precise conclusions. Our study is aimed to compare the efficacy of treatment with high doses of oral prednisolone with intramuscular adrenocorticotropic hormone in patients with infantile spasms.

2- MATERIALS AND METHODS

2-1. Study Design

This randomized clinical trial was conducted in the Pediatric Neurology ward of Ghaem Hospital in Mashhad, Iran, from March 2018 to September 2018. Fifty-one patients with a confirmed diagnosis of the infantile spasm using purposive sampling were randomly divided into two groups. The random sequence number generated by computer was used as the randomization method, and patients' number was calculated according to Wanigasinghe et al.'s study (12).

2-2. Inclusion Criteria

The included patients had abnormal EEG with infantile spasm and were 2 to 12 months old. Also, the initiation of the seizures were at most one month before and the seizures were uncontrolled.

2-3. Exclusion Criteria

Patients with previous usage of corticosteroids or ACTH, known metabolic disorder, brain structural disorder, active infection, and history of hypertension, gastrointestinal bleeding, and renal and cardiovascular diseases were excluded from this study. Also, patients who developed treatment complications or were prescribed other antiepileptic drugs

and those who did not want to continue the study were also excluded.

2-4. Treatment protocol and outcome measurement

The first study group (including 26 patients) received 8 mg of prednisolone (sold as nisopred in Iran) per kg of body weight per day in three separate doses. In case of no positive clinical response (i.e., absence of a seizure for 24 hours), the dosage was first tapered to 6 mg/kg/day TDS, then to 4 mg/kg/day BID, and finally to 2 mg/kg per day for 5 days. In all cases, the maximum dosage was 60 mg per day. If the patients did not show signs of improvement within two weeks of treatment, they were planned to receive intramuscular biologic ACTH (Synacran) immediately after the failure of corticosteroid therapy. The patients received five daily doses of 2-3 IU/kg of ACTH (max: 100IU) and the treatment was then changed to the oral corticosteroid. In the second group (25 patients), patients first received five daily doses of 2-3 IU/kg of ACTH.

The treatment was continued with 2 mg/kg of prednisolone per day (max: 60 mg per day) for three weeks, and then changed to the same dose every other day. The patients' parents were advised not to give prednisolone to their infants on an empty stomach, avoid vaccination during the study time, and follow sanitary rules. All the infants were given Proton-pump inhibitors (PPIs), and continued to receive their previous antiepileptic drugs. In case of response to our treatment, a decision was made to either taper, discontinue, or continue previous treatments. If the patients showed no response to ACTH treatment, other anti-seizure drugs were tried. The measurement of the treatment outcome was mainly based on the parents' reports. The patients also underwent EEG, first at the beginning of the treatment and next after two weeks from the beginning. We also evaluated the developmental state of patients according to Denver Developmental Screening Test.

2-5. Ethical Consideration

Written informed consent was obtained from patients' parents, and they could discontinue the study at any time. All the recorded data were encoded and kept confidential. The study was under Helsinki's ethical principles. Furthermore, all the stages of the study were approved by the Ethics Committee of Mashhad University of Medical Sciences (IR.MUMS.MEDICAL.REC.1398.745).

2-6. Data Analyses

All the gathered data were entered into SPSS software version 20. Calculated descriptive measurements included mean, standard deviation (SD), frequency, and percent. Quantitative data were analyzed using t-test, and qualitative data were analyzed using the chi-square test. A p-value under 0.05 was considered significant.

3- RESULTS

From a total of 51 patients, 26 cases (51%) were randomly selected for the prednisolone group and 25 cases (49%) for the ACTH group. 37.3 percent of the total number of patients were female and 62.7 percent were male. There was no significant difference regarding gender (p=0.180), age (p=0.97), age of seizure onset (p=0.56), and growth abnormalities (p=0.89) between the two groups (**Table.1**). **Table.2** shows the comparison of initial EEG assessment between the prednisolone and ACTH groups. In the prednisolone group, eleven patients had hypsarrhythmia, nine had burst suppression, and six had other conditions. In the ACTH group, 14 cases showed Hypsarrhythmia patterns, five had burst suppression, and six showed patterns. However, the differences were not significant (p=0.47).

Table-1. Baseline characteristics in two groups, n=51.

Variables		Prednisolone	ACTH	P-value
Age months (mean ± SD)		8.1±2.8	8.2±3.8	0.97
Age at the first seizure episode months (mean ± SD)		6.8±2.4	6.2±2.7	0.56
Gender, Number (%)	Male	14 (53.8)	18 (72)	0.180
	Female	12 (46.2)	7 (28)	
Developmental pattern, Number (%)	Normal	14 (53.8)	13 (52)	0.89
	Abnormal	12 (46.2)	12 (48)	

SD: Standard deviation.

Table-2: Comparison of the results of initial EEG assessment between the Prednisolone and the ACTH groups, n=51.

Variables	Hypsarrhythmia	Burst suppression	Others	P-value
Prednisolone, Number (%)	11 (42.3)	9 (34.6)	6 (23.1)	0.47
ACTH, Number (%)	14 (56)	5 (50)	6 (24)	
Total, Number (%)	12 (23.5)	14 (27.5)	25 (49)	

ACTH: Adrenocorticotropic hormone.

Table.3 demonstrates the comparison of secondary EEG assessment at the end of the two-week treatment between Prednisolone and ACTH groups. The results showed that thirteen patients in prednisolone group and seventeen patients in ACTH group had a normal EEG rhythm. However, the difference in the type of EEG pattern was not significant between the groups (p=0.33). Comparison of the initial and secondary EEG patterns in corticosteroid group also showed that five patients with hypsarrhythmia, five with burst suppression, and three with other types of EEG patterns had normal EEGs at the end of the two-week study. However, the differences were not significant (p=0.36). **Table.4** shows the results in detail. **Table.5** compares the initial and subsequent EEG reports in the ACTH group. The results showed that nine patients with hypsarrhythmia, four patients with burst suppression, and four with other patterns had a normal EEG at the end of the study (p=0.89). At the end of the study, eighteen patients in the prednisolone group and nineteen in the ACTH group responded to treatment with no significant difference regarding the treatment outcome (p=0.58). **Table.6** compares the outcomes.

Table-3: Comparison of the results of secondary EEG assessment between the Prednisolone and the ACTH groups after two weeks.

Variables	Normal	Hypsarrhythmia	Burst suppression	Others	P- value
Prednisolone, Number (%)	13 (50)	1 (3.8)	4 (15.4)	8 (30.8)	0.33
ACTH, Number (%)	17 (68)	0 (0)	1 (4)	7 (28)	
Total, Number (%)	30 (58.8)	1 (2)	5 (9.8)	15 (29.4)	

ACTH: Adrenocorticotropic hormone.

Table-4: Comparing initial and secondary EEG reports in the Prednisolone group.

Variables	Normal	Hypsarrhythmia	Burst suppression	Others	P- value
Hypsarrhythmia Number (%)	5 (45.5)	1 (9.1)	1 (9.1)	4 (36.4)	0.36
Burst suppression Number (%)	5 (55.6)	0 (0)	3 (33.3)	1 (11.1)	
Others Number (%)	3 (50)	0 (0)	0 (0)	3 (50)	

Table-5: Comparing initial and subsequent EEG reports in the ACTH group.

Variables	Normal	Hypsarrhythmia	Burst suppression	Others	P- value
Hypsarrhythmia Number (%)	9 (64.3)	0 (0)	1 (7.1)	4 (28.6)	0.89
Burst suppression Number (%)	4 (80)	0 (0)	0 (0)	1 (20)	
Others Number (%)	4 (66.7)	0 (0)	0 (0)	2 (33.3)	

ACTH: Adrenocorticotropic hormone.

Table-6: Comparison of the treatment response results between the Prednisolone and the ACTH groups after two weeks of treatment.

Variables	Treatment response		P- value
	Yes	No	
Prednisolone, Number (%)	18 (69.2)	8 (30.8)	0.58
ACTH, Number (%)	19 (76)	6 (24)	

ACTH: Adrenocorticotropic hormone.

4- DISCUSSION

Our study aimed to compare the outcome of treatment with ACTH and prednisolone in patients with infantile spasm. At the end of the study, 50% of the patients in the prednisolone group and 68% in the ACTH group had normal EEGs. However, there was no significant difference regarding these changes. Also, the clinical response rate to treatment was 69.2% in the prednisolone group and 76% in the ACTH group. This difference was not significant. Several studies have been conducted using different drug forms, different doses, and even different treatment protocols. In agreement with the findings of our study, Gowda et al. (13) reported no significant differences between prednisolone and ACTH treatment regarding EEG and clinical response of the patients. They used 4 mg/kg/day of prednisolone and 100 units per body surface area of intramuscular ACTH, which was similar to our study. However, their treatment protocol was different. They also used a smaller sample size than our study, but both studies showed similar results. Baram et al. (14) also reported that ACTH treatment was superior to the treatment with corticosteroids. However, they used a corticosteroid dosage of 2 mg/kg/day and an ACTH dosage of 150 IU/day. Their prednisolone dose was lower compared to our study and other similar studies in the literature. Hrachovy et al. (15) reported that ACTH at lower doses has a similar outcome compared to prednisolone. United Kingdom Infantile Spasms Study reported that high dose

treatment with corticosteroid (40–60 mg/d) compared with the usual ACTH treatment dosage showed no significant difference in short-time treatment (16). Eliyan et al. (17) conducted a similar study to ours with a similar treatment protocol. The patients were first treated with a dose of 8 mg/kg/day of prednisolone (maximally 60 mg/day) in three separate doses for two weeks. After two weeks, the prednisolone dose was tapered in the responding group. The non-responders were then treated with a dose of 150 U/m^2/day of intramuscular ACTH for another 14 days. The dose of corticosteroid was not tapered in this group. The results showed that 59% of the patients responded to corticosteroid treatment. They concluded that short-term results of corticosteroid treatment are satisfactory, and those who did not respond to corticosteroids achieved good results with ACTH treatment. However, they also mentioned that the exact comparison of ACTH and corticosteroids as treatments for infantile spasm remain unclear. Our study showed a response rate of around 70% for a short-term treatment with prednisolone. However, there was no significant difference between ACTH and Prednisolone regarding treatment outcome.

Differences in study results can be attributed to three main factors. One is the type of ACTH which can be synthetic or natural. Natural ACTH has 39 amino acids while synthetic ACTH has 24. The dose of the prescribed drugs is another effective factor. Different studies use different doses from high (150 IU/m 2 /day) to low (20 to 30 IU/day), and to even very low doses (10 IU/day) of ACTH (18-21). Prednisolone doses also range from as high as 40-60 mg/day to as low as 2 mg/kg/day. Our study, although limited in the number of patients, still had a better sample size than many previous studies. It should also be noted that the type of the ACTH and corticosteroids used in our study was different from other studies, as they both were made by Iranian brands. This study is also ethnicity-specific, and should be generalized to other ethnicities. However, our study was strengthened by randomization, which was not included in several previous studies (17). Another strong point of our study was the clinical assessment combined with EEG that further added to the accuracy of our findings.

5- CONCLUSION

No advantage was found in treatment with ACTH over high dose prednisolone in patients with infantile spasm. A short-term treatment with corticosteroids resulted in around 50% EEG response, while the response in the ACTH group was about 60 to 70%. The clinical response rate was also around 70% in the prednisolone group and 75% in the ACTH group. Future investigations are needed to complete the results of our study.

6- CONFLICT OF INTEREST: None.

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