

Response and Outcome of Moderate Dose Adrenocorticotrophic Hormone in the Treatment of West Syndrome

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Abstract

Background: West Syndrome (WS) consist of a triad of epileptic spasms, hypsarrhythmia on EEG and arrest or regression of psychomotor development. Although ACTH has been found to be effective in the treatment of WS, questions remain regarding the optimum dosage, type of ACTH, duration of therapy, and its comparative efficacy with other treatment options. **Objective:** To assess the response and outcome of treatment with moderate dose (100 IU/m²) ACTH in children of west syndrome. **Methodology:** This was a prospective observational study and done over 1-year period (July 2017 to June 2018) in Pediatric Neurology OPD, National Institute of Neuroscience and Hospital (NINS&H), Dhaka among the patients with West syndrome. All study participants were treated with moderate dose ACTH (100 unit/m²) (I/M) and treatment completed within 12 weeks. Patients were followed up at 2, 4, 6 and 12 WKs of treatment. **Results:** Total 52 cases were for enrolled. In this study it was found that complete cessation of spasm 21/50 (42%), $\geq 50\%$ reduction of spasm 12/50 (24%), $< 50\%$ reduction of spasm 8/50 (16%) and non-responder 9/50 (18%). At the end point of 12 weeks observation resolution of hypsarrhythmia occurred in 19/50 (38%) cases. About 78.0% patients developed any kind of the adverse effect. **Conclusion:** Moderate dose ACTH is effective in cessation of spasm and resolution of hypsarrhythmia in the studied children. [Journal of National Institute of Neurosciences Bangladesh, July 2021;7(2):108-112]

Keywords: West syndrome; response; outcome; epileptic spasm; hypsarrhythmia; ACTH

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Introduction

West syndrome (also known as infantile spasm because of its main seizure type) is a rare form of epilepsy that begins during early infancy characterized by 3 features, namely, epileptic spasms, developmental delay, and characteristic electroencephalogram (EEG) pattern called hypsarrhythmia. West Syndrome remains to be one of the most challenging epilepsies to treat¹. Prognosis of

this condition depends on the etiology and adequate treatment².

The peak age of onset of West Syndrome is 4 to 6 months, and the overall incidence of WS is 2-3 cases per 10,000 live births^{3,4} with a lifetime prevalence rate of 1.5 to 2 per 10,000 children⁵. There appears to be a slightly higher incidence rate in males than in females⁶. The optimal treatment of West Syndrome is unknown, as the

disease is commonly refractory to many antiepileptic drugs. Adrenocorticotrophic hormone (ACTH) has been reported to be an effective treatment of WS; however, it has extensive and severe adverse effect profile that deters its use. Serious adverse effects of ACTH include hypertension, infection, electrolyte abnormalities, Cushing syndrome, cardiac hypertrophy, and reversible cerebral atrophy⁷.

The exact pathophysiology of IS remains to be elucidated, and various mechanisms have been hypothesized. The rationale behind the usage and efficacy of ACTH and oral steroids in IS is the hypothesized dysregulation of hypothalamo-pituitary-adrenal (HPA) axis in the pathophysiology of IS, which has been tested recently⁸. In addition to ACTH, several other treatment options have been investigated for use in WS, including oral corticosteroids, vigabatrin, valproic acid, pyridoxine, zonisamide, intravenous immunoglobulin, topiramate, thyrotropin-releasing hormone, levetiracetam, and the ketogenic diet. With the exception of vigabatrin, these medications lack sufficient evidence to support their use for treatment of infantile spasms⁹. Although ACTH has been found to be effective in the treatment of WS, questions remain regarding the optimum dosage (low-dose versus high-dose), type of ACTH (synthetic vs natural), duration of therapy, and its comparative efficacy with other treatment options⁷. American academy of pediatrics describes that typically, treatment consists of either medium (100 IU/m² per day) or high-dose (150 IU/m² per day) ACTH injected intramuscularly for as few as 2 weeks or as many as 2 months¹⁰.

There is a paucity of prospective studies and even fewer randomized or controlled treatment trials in this disorder¹¹. Therefore, this present study was undertaken to see the response and outcome of once daily moderate dose ACTH in the treatment of West Syndrome.

Methodology

This hospital based prospective observational study was done in the Outpatient and inpatient department of Pediatric Neurology at National Institute of Neuroscience and Hospital, Sher-E-Bangla Nagar, Dhaka, Bangladesh from July 2017 to June 2018. Patient of West syndrome, age of more than 2 month to 2 years, diagnosed by history presence of clinical spasm that occur mainly in clusters either flexor, extensor or both or asymmetric by direct observation or video recording of the spasm along with h/o developmental delay or regression, and EEG demonstrating hypersarrhythmia or modified hypersarrhythmia without

prior treatment of ACTH, prednisolone or vigabatrin therapy were included in this study. Diagnosed case of tuberous sclerosis, having infantile spasm in addition to other seizure type and having neurometabolic diseases diagnosed clinically were excluded from the study. Children were evaluated thereafter through detail history and clinical examination. History related to seizure type, frequency, age at onset, antenatal, natal and postnatal details, family history, developmental history and the ongoing treatment were noted. Through general examination, systemic examination including neurological examination were done. A base line complete blood count, electrolyte, SGPT, and creatinine were obtained. Baseline CT-scan of brain and EEG were done. Informed written consent both in Bangla and English were obtained from parents or attendants after full explanation of the details of the research process. Findings of observation were recorded in a prescribed data collection form. All study participants were treated with moderate dose (100 IU/ m²) ACTH (I/M). In this study natural ACTH was used, named Acton prolongatum injection which contains carboxymethylcellulose (1 mL=60 Unit) made by Ferring company. Dose of ACTH was used in 100 IU per m² per day, once daily single dose for 4 weeks then 80 unit per m² per day, every alternate day single dose for 4 weeks then 60 unit per m² per day, twice weekly single dose for next 4 weeks. The observational period for each patient was 12 weeks after starting of ACTH treatment. Every patient was followed at 2, 4, 6 and 12 wks. Some investigations (CBC, RBS, Serum electrolyte) were done at 2nd and 4th weeks. During 12 weeks of observation parents were asked to maintain a daily seizure dairy, recording frequency of seizure. Time to reduction or complete cessation of spasms after initiation of treatment, were recorded. A repeat EEG was done at 14 to 21 days or later but within 42 to 49 days after starting treatment and electrographic changes were recorded. Patient recorded daily BP chart from local pediatricians if available but otherwise BP was maintained at least weekly. All patient's blood pressure was checked during routine follow up of the study. At each follow up adverse effects were documented in data collection sheet. Information were recorded over phone from those case who were lost to follow up. The child who developed infection during ACTH treatment were treated properly. Data were collected, compiled and tabulated according to key variables. The analysis of different variables were done according to standard statistical analysis. Qualitative data were expressed as frequency and percentage and quantitative data were

expressed as mean and standard deviation. Data were processed and analyzed using software Statistical Package for Social Science (SPSS) version 20.0. 95.0% confidence interval were calculated. Mann-Whitney U test, Chi-square test and Wilcoxon signed ranks test and unpaired t test were done to see the level of significance. A value of p less than 0.05 was considered statistically significant for all test.

Results

In this study according to the selection criteria total 52 were enrolled. Data were documented in data collection form. One patient did not complete treatment and one patient expired before completion of treatment. So, finally total 50 patients were analyzed. In this study demographic variable such as age, sex, weight, clinical variables like age of onset of spasm, type of spasm, frequency of spasm, family history of consanguinity, presence of perinatal asphyxia, developmental history before spasm, presence of microcephaly, brain abnormalities and main outcome variables like reduction of spasms, complete cessation of spasms, resolution of hypsarrhythmia and adverse events were evaluated. Mean age of the patients was 12.61 ± 7.11 months. Males (58.0%) were predominant than females (42.0%) (Table 1).

Table 1: Demographic profile of the patients (n=50)

Variables	Frequency	Percent
Age Group		
• ≤12 months	29	58.0
• 13 to 24 months	21	42.0
Mean±SD	12.61 ± 7.11	
Gender		
• Male	29	58.0

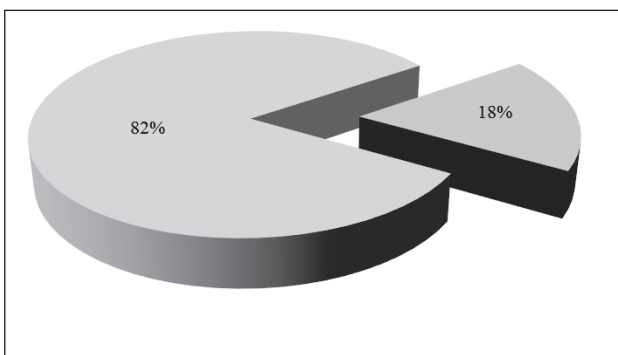


Figure I: Classification of study patients of West syndrome (n=50)

Majority (82%) were symptomatic and 18% were either cryptogenic or idiopathic (Figure I).

Table 2: Response of treatment of study patients (n=50)

Response	Frequency	Percent
Complete cessation of spasm	21	42.0
>50% reduction	12	24.0
≤50 reduced	8	16.0
Non responder	9	18.0
Total	50	100.0

Complete cessation of spasm was achieved in 42.0%, >50% reduced in 24.0% cases, ≤50% reduced in 16.0% cases & non responder was 18.0% patients (Table 2).

Table 3: Response of Treatment between symptomatic and cryptogenic West syndrome

Response	Symptomatic	Cryptogenic/ Idiopathic	Total	P value
Complete cessation of spasm	16 (39.0)	5 (55.6)	21 (42.0)	
Non responder	9 (22.0)	0 (0.0)	9 (18.0)	
≤50 reduced	7 (17.1)	1 (11.1)	8 (16.0)	0.389
>50 reduced	9 (22.0)	3 (33.3)	12 (24.0)	
Total	41 (100.0)	9 (100.0)	50 (100.0)	

Chi-square test was done to measure the level of significance

Complete cessation of spasm occurs 16/41(39%) in symptomatic cases and 5/9 (55%) in cryptogenic cases there is no statistical significance (p=0.389). spasm >50 reduced 9/41(22%) in symptomatic cases and 3/9 (33%) in cryptogenic cases (Table 3).

Table 4: Resolution of Hypsarrhythmia in EEG (n=50)

Resolution	Frequency	Percent
Absent	19	38.0
present	31	62.0

Complete resolution of hypsarrhythmia occurred in EEG 38.0% cases after treatment (Table 4).

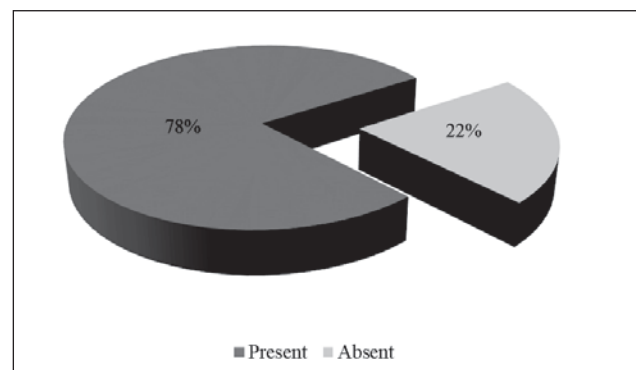


Figure II: Adverse effect during treatment

Adverse effect was found in 78.0% cases during treatment (Figure II).

of CPSP (OR 3.4; 95% CI 1.5-8.4; $p=0.003$) in comparison to those with lesions in the left. Similarly, participants with ischemic stroke had higher risk of CPSP (OR 3.5; 95% CI 1.4-9.0; $p=0.007$) in comparison to those with hemorrhagic stroke (Table 4).

Table 5: Pattern of Adverse effect after treatment (n=50)

Adverse Effect	Frequency	Percent
Infection	20	40.0
Hypertension	12	24.0
Irritability	35	70.0
Sleep disturbance	31	62.0
Electrolyte imbalance	3	6.0
Hospital admission due to adverse effect	1	2.0

Maximum patients had irritability (70.0%) followed by sleep disturbance (62.0%), infection (40.0%), hypertension (24.0%) and electrolyte imbalance (6.0%) (Table 5).

Discussion

West Syndrome remains to be one of the most challenging epilepsies to treat. Adrenocorticotrophic hormone (ACTH) has been reported to be an effective treatment of WS; however, it has extensive and severe adverse effect. In this study demographic data such as age and sex, weight were evaluated. It was found mean age of patients was 12.87 ± 7.15 months when they started ACTH treatment. One study¹² showed mean age of presentation was 9.4 months that was lower age than this study patients and another study¹³ has showed that 13.1 months that finding was nearly consistent with this study.

It was found that among study patients male were 29/50(55.8%) and female were 21/50(44.2%). Other two studies also found male preponderance 72.0% and 81.0% respectively that were also similar to our study¹²⁻¹³. The reason of male preponderance may be due to more attention of family members to treat male babies.

Main outcome variables like reduction of spasms, complete cessation of spasms, resolution of hypsarrhythmia and adverse events were evaluated in our study. In this study reduction of spasm were divided the by four categories such as complete cessation of spasm, $\geq 50\%$ reduction of spasm, $\leq 50\%$ reduction of spasm and no reduction of spasm and categorize the response by four types such as responder (complete cessation of spasm), partial response($>50\%$ reduction), poor

response($<50\%$ reduction) and non-responder (no reduction of spasm).

At the end of the 12 weeks of follow up it was found that complete cessation of spasm (responder) 21/50(42%), $\geq 50\%$ reduction of spasm (partial response) 12/50(24%) $<50\%$ reduction of spasm (poor response) 8/50(16%) and no reduction non responder 9/50 (18%) cases. One study reviewed to determine the efficacy of various ACTH dosages of treatment response where majority of the patients got intermediate dose (60-100 IU /m²) and showed (17/26) 65% cases had complete cessation of spasm. This study had higher response rate than our study¹⁴.

Complete cessation of spasm occurred 39% in symptomatic group and 55% in cryptogenic group ($p > .05$) in this study. Response was better in cryptogenic group which has a clinical significance but it was not statistically significant. If study sample size would be high then results may be statistically significant. This was also found consistent with a Japanese article¹⁵. It is difficult to compare the results of this study to this Japanese article because they use low dose synthetic subunits of ACTH which may not be biologically equivalent to corticotrophin (natural ACTH). Unfortunately our study was compared to synthetic ACTH because most of the countries use synthetic ACTH of the treatment of infantile spasm¹⁶⁻¹⁷.

Very few data were available using natural ACTH where they used high and low dose and low to moderate dose ACTH¹⁸⁻²⁰. In addition to there is no consensus on the use of synthetic versus natural ACTH. The dosing conversion between the two products is unclear and there are no comparative studies available. For clinical purpose, 1 mg of synthetic ACTH is equivalent to 100 IU of natural ACTH¹⁵.

In this study it was observed that hypsarrhythmia resolution occurred in 19/50(38.0%) cases after treatment. Ibrahim et al¹⁴ reviewed twenty six patients and majority of the patients got intermediate dose (60 to 100 IU/m²) and showed resolution of hypsarrhythmia occurs in (17/26) 65.0% cases. This study had higher hypsarrhythmia resolution rate than this present study. In this study it was found at the end point of 12 weeks observation 78.0% patients shows any kind of adverse effect and 22.0% had no adverse effect. Adverse effects are hypertension (24.0%), infections (40.0%) like (fever, respiratory tract infection, loose motion, soft tissue infection, oral thrush), irritability (62.0%) and sleep disturbance (70.0%), electrolyte imbalance (6.0%) were present.

During treatment adverse effects were managed

properly. Irritability and sleep disturbance were managed by proper counseling but no benzodiazepines were used because it may change the treatment response. There was no life threatening infections. Infections that developed treated with oral antibiotics. Hypertension was managed by giving tab Nifedipine. Hypertension subsided gradually during tapering of treatment. No symptomatic hypertension developed. In a randomized control trial¹³ comparing the effectiveness of high and low dose natural ACTH therapy the adverse effect profiles were very similar between two groups included irritability, oral thrush, infection and hypokalemia but higher incidence of hypertension (31.0% vs 4.0% respectively).

In this study 28.0% cases develop relapse within 12 weeks of follow up after complete cessation of spasm. Ibrahim et al¹⁴ found 12% cases of relapse that was not consistent with this study. In a randomized control trial²¹ comparing the effectiveness of high and low dose natural ACTH therapy no significant difference relapse rates (15.0% vs 21.0% respectively) after end of 1 year follow up; however, this present study showed high relapse rate than this study.

Conclusion

Results of the study documented that moderate dose ACTH is found to be effective in cessation of spasm and resolution of hypsarrhythmia in the studied children of west syndrome. The adverse effects are observed in majority of patients and some cases develop relapse of spasm during study period.

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