Efficacy of Combined Therapy of ACTH plus Vigabatrin Compared to ACTH Alone for Treatment of Infantile Spasm-A RCT

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Abstract

Background: *Infantile spasms (epileptic spasm) is difficult to treat and has a high morbidity. So it's crucial to initiate an early effective therapy. ACTH, Prednisolone and Vigabatrin have shown better efficacy on cessation of spasms.*

Objective: *To compare the efficacy and tolerability of combined ACTH and Vigabatrin with ACTH alone in treatment of infantile spasms.*

Materials & Methods: *This randomized controlled trial was conducted from June, 2017 to June, 2018 at outdoor and indoor, department of Paediatric Neurology of National Institute of Neurosciences and Hospital, Dhaka. Fifty (50) patients aged 2 months to 24 months who had a clinical diagnosis of infantile spasms and hypsarrhythmia (classical or modified hypsarrhythmia) in EEG were enrolled. With parent's written informed consent, they were randomized (1:1 by lottery method) into two groups, 25 in each. One group got ACTH only and another group got both ACTH and vigabatrin. At the end of the treatment two groups were compared regarding efficacy and safety of the drugs.*

Result*: The primary outcome was assessed in 50 children at 91st day. The primary outcome was cessation of spasms from 14th day to 42nd day after initiation of therapy. Cessation of spasms (between 14 to 42 days) occurred in 18 children (72%) in combination therapy and 11 children (44%) in hormonal therapy (p=0.045). Treatment response was faster on combination therapy (p=0.001). Treatment was well tolerated in both groups with few adverse effects.*

Conclusion: *Combination therapy of ACTH plus Vigabatrin was found better than ACTH therapy alone in cessation of infantile spasms.*

Keywords: *Infantile spasm, Combination Therapy, Vigabatrin.*

Introduction:

Infantile spasms (epileptic spasm) are difficult to treat and associated with a poor outcome.[1] Delayed treatment can lead to worse outcome.[2-5] Infantile spasm affects approximately 2-3.5/10,000 live births and occur between 3 and 12 months of age with a peak incidence around 6-7 months.[6] In most cases, they resolve by the age of three, although rarely can persist up to 10 to 15 years of age.[7,8] In infantile spasm, the EEG findings are classical hypsarrhythmia but modified or atypical hypsarrhythmia may also present. The goal of treatment is to prevent or ameliorate the encephalopathy by stopping the spasms. Infantile spasms are resistant to most of the conventional antiepileptic drugs.[9] The current first line treatments options for infantile spasm are corticosteroid either adrenocorticotropic hormone (natural ACTH or synthetic Tetracosactoid) or prednisolone and vigabatrin.[6] Conventional antiepileptic agents like valproate, topiramate, zonisamide, ketogenic diet and pyridoxine have been used with incomplete success when first line agents fail. Vigabatrin is an irreversible inhibitor of the enzyme gamma- aminobutyric acid transaminase. Inhibition

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of this enzyme results in increased levels of GABA in the brain. ACTH promotes the release of steroid (natural glucocorticoids) from adrenal gland. Steroids decrease the production and release of CRH in certain brain regions. Multicenter study ICISS (International collaborative Infantile spasm study) showed that a combination of hormonal and vigabatrin therapy was significantly more effective at stopping spasms compared to hormonal therapy alone without significant adverse effect.[10,11] No study was conducted in Bangladesh till date to see the efficacy of combination therapy. This study will give an opportunity to evaluate the efficacy and adverse effect of combination therapy of hormone plus vigabatrin and single therapy of hormone in treatment of infantile spasm in our population.

Materials & Methods:

This randomized controlled trial was done from June, 2017 to June, 2018 in outdoor and indoor of department of Paediatric Neurology, National Institute of Neurosciences and Hospital (NINSH),Dhaka. Total fifty (50) patients aged 2 months to 24 months who had a clinical diagnosis of infantile spasms and a hypsarrhythmia (classical or modified hypsarrhythmia) in EEG were enrolled in this study. Detailed history was taken and thorough examination was done in every child. Children of tuberous sclerosis, infantile spasm mixed with other seizure type, neurometabolic diseases (confirmed or suspected), previously treated with steroid or vigabatrin or ACTH were excluded. Cranial neuroimaging (MRI or CT), TORCH screening were done if indicated. After taking ethical permission from local ethical review committee, participants were randomly assigned (1:1) by lottery method, 25 children in each group. Before being finally included into the study, parents were explained about the purpose of the study including advantages and disadvantages of drugs and parents were advised to maintain a seizure diary for next 90 days.

The primary outcome was cessation of spasm which was defined as no witnessed spasms on and between day 14th to day 42nd after starting treatment as recorded by parents or caregivers. Maximum patients were treated in out-door and follow-up was given almost every day for first 2 weeks for adverse effect. Every child was followed up on days 7th, 15th, 43th and 91st. History was recorded from parents about frequency of seizure, date of cessation of spasm, any relapse of spasms and body weight & blood pressure were measured. Any adverse reaction like fever, infection, irritability, sleep disturbance, drowsiness, hyperpigmentation of skin, weight gain etc were noted. We treated the children promptly who had developed fever, gastrointestinal upset or hypertension.

Complete blood count, RBS, serum electrolyte were done in day 7th and 14th for monitoring any adverse reaction. For that purpose 4 ml blood was drawn and CBC test was done by Cell Dyn/Sysmex xn1000/Elite 580 mechine and RBS and S. electrolyte were done by Architect CI 4000/Erba XL 200 mechines. Those children who developed severe life threatening infection and severe symptomatic hypertension after getting ACTH, they were withdrawn from this protocol. It was allowed to change treatment if the child was considered to be in late-responder and non-responder or relapse of spasm. Data were collected in a pre-designed questionnaire and statistical analysis was performed by SPSS.

ACTH therapy: Total twenty five (25) children were treated with ACTH (high dose ACTH protocol).

Dose of Natural ACTH was given as below

150IU/m^2/day BD×2 wks (14 days)
↓
30IU/m^2 morning× 3 days
↓
15IU/m^2×3 days
↓
10IU/m^2 ×3 days
↓
10 IU/m^2 every alternate day× 6 days.

Combination therapy (ACTH+Vigabatrin therapy): 25 children were treated with combination therapy. ACTH and vigabatrin was given simultaneously. ACTH was given as same dose mentioned above. Vigabatrin was given orally, twice a day. The initial two doses was 25 mg/kg per dose twice a day. Dose was increased to 50 mg/kg per dose given twice a day after 24 hours. At 96 hours after the starting of treatment, if any spasms had occurred in the previous 24 hours, or if spasms reappeared after this but before day 14 increased the dose to 75 mg/kg per dose given twice a day (150 mg/kg per day). Vigabatrin treatment was continued at the same dose on a body weight basis, for 3 months from Day 0. The vigabatrin was withdrawn over the next four weeks. The dose was reduced weekly by one-fifth of the maximum total daily dose being given prior to the commencement of the reduction.

Result:

There was no significant difference between the two treatment groups in terms of age and sex. The primary outcome was assessed on 91st day after initiation of treatment.

Table I

Demographic profile of the patients in groups (n=50)

	ACTH	ACTH+ Vigabatrin	p value
Age(months) [mean±SD]	11.28 ± 5.19	9.72 ± 5.41	[a]0.220
Gender			
Male	15 (60 %)	15 (60 %)	[b]1.000
Female	10 (40 %)	10 (40 %)	

[a]MannWhitney U test was done to measure the level of significance
[b]Chisquare test was done to measure the level of significance

Table II

Cessation of spasm in groups (n=50)

Cessation of spasm (14- 42) days	ACTH	ACTH + Vigabatrin	OR (95%CI)	p value
Responder	11 (44%)	18 (72%)	0.306 (0.094-0.992)	0.045
Non responder	14 (56%)	7 (36%)		

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

Table III

Time of Cessation of Spasm (response to treatment) to the patients in groups (n=50)

Cessation of spasm	ACTH	ACTH + Vigabatrin	p value
2 – 6 days	16 (64%)	21 (84%)	0.001
7 – 14 days	8 (32%)	4 (16%)	
>14 days	1 (4%)	0	
Mean±SD days	5.88 ± 2.83	3.72 ± 1.64	

Unpaired t test was done to measure the level of significance.

Combination therapy was found better than hormonal therapy alone in cessation spasm. Treatment response was faster on combination therapy than hormonal therapy [p=0.001]. There was no significant difference between two treatment groups regarding adverse effects (P = 1.00). The most common serious adverse reaction was infection occurring in two children in hormonal therapy and three children in combination therapy. Hypertension developed in four patients in both groups. Between them two patients were admitted into hospital for hypertension. There was no death attributable to trial treatment.

Table IV

Adverse effect of the patients in groups (n=50)

Adverse effect	ACTH	ACTH + Vigabatrin	p value
Yes	20(80%)	21(84%)	1.000
No	5 (20%)	4(16%)	

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

Table V
Adverse effects of the patients in groups (n=50)

	ACTH n (%)	ACTH + Vigabatrin n (%)
Weight gain	20 (80.0)	20(80.0)
Hypertension	4 (16.0)	4 (16.0)
Irritability	20 (80.0)	18 (72.0)
Sleep disturbance	15(60.0)	16(64.0)
Electrolyte imbalance	3 (12.0)	3 (12.0)
Dystonia	2 (8.0)	3 (12.0)
Gastrointestinal upset	2 (8.0)	3 (12.0)
Pneumonia	2 (8.0)	2 (8.0)
Varicella	0 (0.0)	1 (4.0)
Drowsiness	0 (0.0)	5 (20.0)

Table VI
Hospital admission due to adverse effect of the patients in groups (n=50)

Hospital admission due to	ACTH	ACTH + Vigabatrin	p value
Infection	2 (8%)	3(8%)	1.00
Hypertension	2 (8%)	—	
Hypokalemia	—	1 (4%)	
Total	4 (16%)	4 (16%)	

Chi square test was done to measure the level of significance

There is no significant difference regarding hospital admission among two treatment groups.

Discussion:

In this study, mean age at randomization (mean age ± SD) was 11.28±5.19 month in hormonal therapy and 9.72±5.1 months in combination therapy. This study showed a male predominance with the gender ratio (male:female) being 3:2 which was consistent with other study (58.5% vs. 41%).[12] This study showed that more infants achieved the primary outcome (cessation of spasm from days 14th to 42nd day after initiation of therapy) in combination therapy than hormonal therapy alone. It also took a shorter time to cessation of spasms in combination therapy. A Cochrane review of infantile spasms had determined that hormonal treatment was the best single treatment for the cessation of spasms.[13] ICISS study showed that combination therapy was better than hormonal therapy alone with few adverse effects.[10] Dressler A et al. also found that combination of therapy might be the most effective way of treating severe epilepsy syndromes in childhood.[14] In this study the primary outcome of cessation of spasm from 14th to 42nd day was 72% in combination therapy and 44% in hormonal therapy which was similar to ICISS study (OR 0.306, [95% CI 0.094-0.992], p=0.045). ICISS study showed that the primary outcome was assessed in 377 infants and cessation of spasm occurred in 133(72%) of 186 infants on combination therapy and in 108(57%) of 191 infants on hormonal therapy (difference 15.0%, 95% CI 5.1-24.9, P=0.002). Treatment response was faster in combination therapy which corresponds to ICISS study. Our study showed that median response time (time to cessation of spasm) was 3.72 ± 1.64 days in combination therapy and 5.88 ± 2.83 days in hormonal therapy (p value = 0.001). ICISS study showed that median response time was 2 days (2-4) in combination therapy and 4 days (3-6) in hormonal therapy.

Adverse reactions were a clinically significant problem with both treatment groups. Irritability and sleep disturbance were common adverse effect. Irritability and sleep disturbance occurred in 20 (80.0%) and 15(60%) children in hormonal therapy and 18(72.0%) and 16(64%) children in combination therapy. These side effects were present in 7-14 days after starting treatment then gradually resolved. Drowsiness was present in 5 (20.0%) children in combination therapy which was similar to ICISS study. ICISS study showed that drowsiness was present in 24% in combination therapy. Electrolyte imbalance (hypokalemia) developed in 3 patients (12%) in both groups. In hormonal therapy one patient developed hypokalemia within 7 days and 2 patients developed in 14 days. In case of combination therapy three patients developed hypokalemia between 7-14 days. ICISS studies showed that electrolyte imbalance occurred in 17% in hormonal therapy and 10% in combination therapy. Dressler A et al. Found hypokalaemia in 54% patients.[14] Movement disorders (dystonia) developed during the trial and were an unexpected adverse event. Dystonia developed in 2(8%) children in hormonal therapy and 3(12%) children in combination therapy. Fong CY, Osborne JP. Edwards SW et al. showed that movement disorder was important concern with vigabatrin therapy in infantile spasm and they

concluded that it was not possible to attribute these movement disorders to vigabatrin, and they were probably related to underlying neurological disease.[15] In hormonal therapy, four patients were admitted in hospital due to adverse effects. Two patients were admitted due to pneumonia. One child was admitted within 14 days and another child was admitted after 4 weeks. ACTH was discontinued in one patient due to adverse effects and other antiepileptic drug was introduced. Two children were admitted due to hypertension within 1st week after getting ACTH. BP was controlled with antihypertensive and ACTH was continued subsequently. In combination therapy three children were admitted due to infection. The strength of the trial was that treatment was randomized. Other strength was the complete follow –up of 50 children for the primary outcome.

Conclusion:

Combination therapy of ACTH plus vigabatrin was better than ACTH therapy alone in cessation of infantile spasms. Treatment was well tolerated in both groups and few adverse effects were observed during study period.

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