



ORIGINAL ARTICLE

Comparison of efficacy and safety of corticosteroids and vigabatrin plus corticosteroids in infantile spasm: An open label randomized control trial.

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ABSTRACT... Objective: To compare efficacy and safety of corticosteroids and combined therapy with corticosteroids and vigabatrin in infantile spasm. **Study Design:** Randomized Controlled Trial. **Setting:** Department of Neurology, Children's Hospital and the Institute of Child Health Multan, Pakistan. **Period:** November 2020 to November 2022. **Material & Methods:** A total of 320 children of either gender aged 1-24 month with clinical diagnosis of infantile spasm were included. Infants were randomized into either receiving prednisolone (Group-A) or vigabatrin plus prednisolone (Group-B). Demographical information along with treatment outcomes and adverse effects were noted. Final outcomes were labeled at day-180. **Results:** In a total of 320 children, 170 (53.1%) were male. Overall, the mean age was 1.3 ± 0.5 years while 166 (51.9%) children were aged between 1 to 2 years. A total of 166 (51.9%) children responded to allocated treatment. The response rate was significantly better in Group-B (n=118, 73.8%) versus Group-A (n=48, 30.0%), $p < 0.0001$. Significantly more children in Group-A missed follow-ups in comparison to those in Group-B (11.8% vs. 1.9%, $p = 0.0006$). Mortality was statistically similar in both study groups (2.5% vs. 1.9%, $p = 0.7023$). The most treatment related adverse effect was noted to be increased appetite and/or weight, gastrointestinal symptoms and sleep disturbance in 253 (79.1%), 121 (37.8%) and 117 (36.6%) respectively. Increased appetite and/or weight gain was significantly more in Group-A ($p < 0.0001$). **Conclusion:** The findings of this study are in support of using combination therapy of prednisolone and vigabatrin instead of monotherapy for patients with infantile spasm as reflected by higher number of responders to therapy.

Key words: Epilepsy, Infantile Spasm, Prednisolone, Steroid, Vigabatrin.

INTRODUCTION

Infantile spasms or West syndrome is a kind of epilepsy that impacts infants, typically in their first year of life.¹ Infantile spasm is characterized by brief, sudden movements or contractions of the muscles, typically in the neck, torso, and arms. The spasms typically occur in clusters of up to 100 and can occur several times per day.² Infantile spasm often occur in the morning and during periods of wakefulness, and can be triggered by sudden noises or movements.^{1,2}

The diagnosis and treatment of infantile spasms is often considerably delayed, it can have a significant impact on an infant's development, as they can interfere with normal brain development and lead to long-term developmental delay and

cognitive impairment.³ Treatment for infantile spasms typically involves the use of anticonvulsant medications, such as adrenocorticotrophic hormone (ACTH) or vigabatrin, which can help in reducing the frequency and severity of the spasms. In some cases, surgery may be required to remove a structural lesion that is contributing to the seizures.^{4,5} Prompt diagnosis and treatment can help to prevent long-term developmental complications and improve outcomes.^{6,7} In some cases, other therapies such as physical therapy, occupational therapy, and speech therapy may be recommended to help with developmental delay and improve overall outcomes.^{8,9}

Corticosteroids (Adrenocorticotrophic hormone and Vigabatrin are considered as effective means

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to treat infantile spasm but the choice of treatment in terms of efficacy and safety among these is still controversial.⁸⁻¹⁰ Few recent studies showed that corticosteroids with Vigabatrin were more effective than corticosteroids and Vigabatrin alone.^{1,11} The present study aimed to compare the efficacy and safety of corticosteroids and combined therapy with corticosteroids and vigabatrin in infantile spasm.

MATERIA & METHODS

A randomized controlled trial was undertaken at the neurology department of the Children's Hospital and the Institute of Child Health Multan, Pakistan from November 2020 to November 2022. The trial was registered in Iranian registry of clinical trials with the registration number IRCT20200414047072N2. The study was ethically reviewed and permitted by the "Institutional Ethical Committee". Written and informed consents were taken from the parents /guardians. Children of either gender aged 1-24 months with clinical diagnosis of infantile spasm as per "International League Against Epilepsy" plus hypsarrhythmia on EEG were included. Exclusion criteria were children having infantile spasm due to tuberous sclerosis, previous treatment with steroids or vigabatrin, contraindication to steroids/vigabatrin (fever, active infection and hypertension).

Information including demographics, age at onset of spasm, frequency, duration and type of spasm, underlying etiology (diagnosis) of spasm, family history, previous treatment, EEG and MRI findings were noted at the time of enrollment. Fundoscopy and blood pressure were noted in all children. A detailed general physical and neurological examination was carried out at baseline and at each follow up visit.

Sealed opaque envelope systems were used for randomization. Infants receiving prednisolone were assigned to Group-A and those receiving vigabatrin plus prednisolone as Group-B. Group-A children received prednisolone 40 mg/day in 4 divided doses along with an antacid, increased to 60 mg/day at day 8, if spasm present. Group-B children received vigabatrin plus prednisolone (same protocol as of Group-A). Vigabatrin was

started with 50 mg/kg/day on day-1, increased to 100 mg/kg/day in two divided doses on day 2 for next three days, followed by further increment to 150 mg/kg/day on day 5, if spasm present. Symptomatic and supportive treatment was provided simultaneously to both groups. All children were physically followed on day 1, 7, 21, 42, and 60 for the evaluation of efficacy and adverse drug reactions. Parents/caregivers were trained to maintain and complete a seizure diary including the details of spasms (number, duration of spasm). Parents/caregivers were advised and trained to record any event that might be adverse reactions of vigabatrin or prednisolone. EEG was performed at day-0, 14, and 60. Sleep EEG was recorded for a minimum duration of 30 minutes according to the international 10-20 system of electrode placement. Two pediatric neurologists reviewed the EEGs. At day 14, children were evaluated for primary end point- electroclinical remission. If it was achieved then the researchers labeled them as "responders" and if electroclinical remission was not achieved then these infants were labeled as "non-responders".

In children of both (responders and non-responders) groups, tapering of prednisolone was initiated at day-14 and it was discontinued at day-28. At day-14, vigabatrin was added to non-responders of Group-A according to the protocol while ketogenic diet was started to children of Group-B non-responders. If Group-A children were spasm free at day-28 with vigabatrin then therapy was continued otherwise it was tapered and discontinued at day-42. Ketogenic diet was started to non-responders of Group-A at day-28. Vigabatrin was continued till day-90 in responders after which it was tapered and discontinued at day-120. The children in whom the primary endpoint was achieved, the researchers followed those patients regularly to look for the secondary end point. At each follow up we looked at the seizure diary, ask parents about adverse drug reactions, did a detailed examination and advised the laboratory tests according to protocol. Follow up continued till day-180. Methodology flow chart is shown in figure-1.

Blood counts, C-reactive proteins, urine

examination, blood glucose, serum sodium, potassium, calcium, phosphorus, magnesium, lipid profile, EEG and MRI brain were recorded as and when deemed necessary. Blood pressure was checked daily for two weeks, twice weekly for one month and then fortnightly for six months. Adverse effects like fever, infections, vomiting, diarrhea, increase appetite, weight gain, feeding difficulty, high cholesterol and triglycerides, cushingoid facies, hypertension, hyperglycemia, fluid overload, electrolyte disturbances, irritability, drowsiness, sleep disturbances and movement disorders were noted. Primary endpoint was the electroclinical remission (cessation of spasms plus resolution of hypsarrhythmia). Secondary endpoints were the adverse effects of treatment and developmental progress.

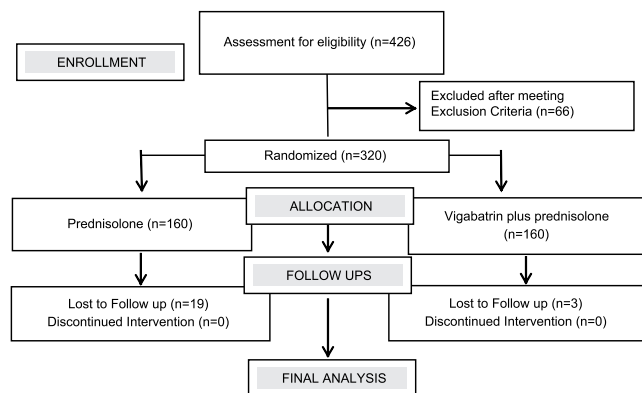


Figure-1. Methodology flow chart

Data was analyzed by “Statistical Package for Social Sciences (SPSS)”, version 26.0. Mean and standard deviation (SD) were calculated for quantitative data while proportions were ascertained for qualitative variables. Comparison was made applying chi-square test between groups taking $p < 0.05$ as significant.

RESULTS

In a total of 320 children, 170 (53.1%) were male and 150 (46.9%) female representing a male to female ratio of 1.1:1. Overall, the mean age was 1.3 ± 0.5 years while 166 (51.9%) children were aged between 1 to 2 years. Table-I is showing comparison of age and gender between both study groups.

A total of 166 (51.9%) children responded to allocated treatment. The response rate was significantly better in Group-B ($n=118, 73.8\%$) versus Group-A ($n=48, 30.0\%$), $p < 0.0001$. Significantly more children in Group-A missed follow-ups in comparison to those in Group-B (11.8% vs. 1.9%, $p=0.0006$). Mortality was statistically similar in both study groups (2.5% vs. 1.9%, $p=0.7023$) as shown in Table-II.

The most treatment related adverse effect was noted to be increased appetite and/or weight, gastrointestinal symptoms and sleep disturbance in 253 (79.1%), 121 (37.8%) and 117 (36.6%) respectively. Increased appetite and/or weight gain was significantly more in Group-A ($p < 0.0001$). The details of adverse effect distribution in both study groups are shown in Table-III.

DISCUSSION

This study showed that the combined therapy of prednisolone and vigabatrin was more effective than prednisolone alone in children having infantile spasms. Hahn et al concluded that treating infantile spasm with a combination of vigabatrin and prednisolone rather than vigabatrin alone is the most effective approach.¹¹

Variables		Group A (Prednisolone Only) n = 160	Group B (Vigabatrin Plus Prednisolone) n = 160	P-Value
Gender	Male	88 (55.0%)	82 (51.3%)	0.5015
	Female	72 (45.0%)	78 (48.7%)	
Age	Up to 6 months	26 (16.3%)	20 (12.5%)	0.1308
	6 months to 1 year	60 (37.2%)	48 (17.5%)	
	1 year to 2 years	74 (46.5%)	92 (70.0%)	

Table-I. Comparison of gender and age between infants of both study groups (N=320)

Parameters	Group A (Prednisolone Only) n = 160	Group B (Vigabatrin plus Prednisolone) n = 160	P-value
Expired	4 (2.5%)	3 (1.9%)	0.7023
Missed Follow-ups	19 (11.8%)	3 (1.9%)	0.0006
Responders	48 (30.0%)	118 (73.8%)	<0.0001
Non-responders	15 (9.4%)	36 (22.5%)	0.0013
Non-responders shifted to Group B	74(46.25%)	-	-

Table-II. Primary outcomes between Group-A and Group-B children (N=360)

Adverse Effects	Group A (Prednisolone Only) n = 160	Group B (Vigabatrin Plus Prednisolone) n = 160	P-Value
Hypertension	17 (10.6%)	21 (13.1%)	0.4894
Respiratory tract infections	29 (18.1%)	32 (20.0%)	0.6694
Gastrointestinal symptoms	62 (38.8%)	59 (36.9%)	0.7295
Increased appetite and/or weight gain	141 (88.1%)	112 (70.0%)	<0.0001
High cholesterol	12 (7.5%)	13 (8.1%)	0.8350
Electrolyte imbalance	8 (5.0%)	6 (3.8%)	0.5846
Sleep disturbance	49 (30.6%)	68 (42.5%)	0.0274

Table-III. Comparison of adverse effects in both study groups (N=320)

The combination therapy was able to elicit twice as much response as monotherapy with vigabatrin alone after controlling for certain confounders. Another study revealed that the clinical outcomes, electroclinical outcomes, and time to cessation of infantile spasm were comparatively better in the combination therapy group than in the corticosteroids therapy alone group. There was a striking increase in the occurrence of adverse events such movement abnormalities and drowsiness/encephalopathy, which can be symptoms of VGB-associated MRI toxicity, in the combined therapy group.¹² Gupta conducted research in which 766 children were screened, and 377 were randomly allocated to either corticosteroids therapy with vigabatrin (n=186) or corticosteroids therapy alone (n=191).¹³ Infantile spasm prevention was significantly enhanced when hormone therapy was paired with vigabatrin. The four-week interval of spasm cessation necessary for a primary clinical response to treatment suggested that the observed impact may be long-lasting.¹³

Similarly, the drug vigabatrin (100-180 mg/kg/day) was administered to 14 newborns with idiopathic West syndrome (Class IV) and 14 children were treated with ACTH in a retrospective

multicenter research (100 IU on alternate days).¹⁴ Eighty percent of patients on vigabatrin stopped having spasms after 2 weeks, whereas 88% of patients taking ACTH did the same. Normal cognitive findings were seen in 100% of patients treated with ACTH early (within 1 month), 67% of patients treated with ACTH later, and 54% of patients treated with vigabatrin (p = 0.03).¹⁴ In contrast, for the study by Mohamed et al, 61% of individuals responded to prednisolone 40 mg/day and 42% to vigabatrin.¹⁵ The cryptogenic group responded much better to corticosteroids than the symptomatic group. Spasms ceased much faster following corticosteroid medication (8-days) than following vigabatrin therapy (16 days).¹⁵

Another study revealed that 57 patients were given vigabatrin as their first line treatment after being diagnosed with infantile spasms. Twenty patients (35.1%) did not improve after receiving vigabatrin as initial treatment.¹⁶ This study found that ACTH was associated with a higher rate of spasm-freedom in the short-term but there was no difference in the rate of spasm-freedom in the long-term. However, vigabatrin proved especially useful for treating spasms in a subset of children with tuberous sclerosis complex (TSC), a rare genetic disorder that causes benign tumours

throughout the body, including the brain.¹⁷ When comparing ACTH (all dosages) to vigabatrin and OCS, Knupp et al discovered that the former was linked to a higher early response rate.¹⁸

In this study, some of the possible reasons that rendered the therapy ineffective could be underlying metabolic disorders, inappropriate dose of either steroids and vigabatrin before trial, poor patient follow-ups, sudden discontinuation of steroids or Vigabatrin and delayed or very early presentation of the patient. However, further research is required to ascertain the factors associated with failure of therapy.

CONCLUSION

The result of this study is in support with the recent advancements that support use of combination therapy of prednisolone and vigabatrin instead of monotherapy. However, further large scale studies are required to ascertain the toxic profiles of the therapies offered to patients with infantile spasms.

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




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AUTHORSHIP AND CONTRIBUTION DECLARATION

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3	Faisal Zaffar	Methodology, Discussion.	
4	Naveed Anjum	Data analysis, Literature review.	
5	Fawad Saleem	Data collection, Literature review.	
6	Zia ul Rehman	Data collection, Literature review.	