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# BETTER FIRST LINE MANAGEMENT OF INFANTILE SPASM? A COMPARATIVE STUDY TO ASSESS THE EFFECTIVENESS & SAFETY OF VIGABATRIN VERSUS CORTICOTROPIN

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**Abstract:**

***Objective:*** *We aimed to assess the safety and effectiveness of two drugs in IS cryptogenic and symptomatic forms.*

***Patients and Methods:*** *Research sample comprised of 26 patients with 9 females and 17 males who were diagnosed with IS in the light of ILAE criteria at Sir Ganga Ram Hospital, Lahore in the timeframe of February to November 2017. Symptoms had characteristics of 2 to 10.5 months. Every hospitalized patient underwent metabolic workup, clinical and Wood's lamp assessment. We also performed EEG and CT Scan on the brain for every patient. Patients had a further subdivision of secondary IS and symptomatic aetiology in 14 and 12 patients respectively.*

***Results:*** *As an outcome, there were 26 infantile spasm cases. Patients had a further subdivision of secondary IS and symptomatic aetiology in 14 and 12 patients respectively as per the presentation, history and investigations. We treated eleven patients with Corticotrophin as Tetracosactrin and remaining fifteen patients treated with Vigabatrin (VGB). VGB response was significant than steroids with the respective proportion of 73% to 63% without any discrimination of aetiology. It speaks for the effectiveness and safety of the VGB for being first line infantile spasm management therapy.*

***Conclusion:*** *Undoubtedly, VGB is more effective and safer than Corticotrophins in order to manage infantile spasms, without any aetiology difference as monotherapy; although, the sample included in the research was not that much large. There is an equal effectiveness of synthetic corticotrophins in the low dose presence to control IS seizures with parallel side-effects. We can avoid steroid induced toxicity by using VGB as it a major concern for both parents and physicians. This research also assures the effectiveness and safety of the VGB for being first line infantile spasm management therapy.*

**Keywords:** *Adrenocorticotropin (ACTH), Infantile Spasm (IS), Tetracosactin, Electroencephalography (EEG) and Vigabatrin (VGB).*

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## INTRODUCTION:

Infantile Spasm (IS) is very rare and unique infancy epileptic encephalopathy which is age specific and it may cause a situation of mental retardation and uncontrolled seizures in the infants. Numerous authors have studied this clinical feature but it was first defined back in 1841 [1]. ILAE defined the present state of Epileptic and Epilepsy as a spasm of IS, psychomotor arrest and EEG hypsarrhythmia pattern [2]. Infantile Spasm (IS) is also symptomatic in the presence of known aetiology and in case the cause is unidentified than it is cryptogenic [3].

Derivates of Adrenocorticotrophic hormones or Adrenocorticotrophic hormones itself are among the major treatments of IS; however, its wide acceptance is limited because of the associated side effects [3]. In the recent developments, another corticotrophin synthetic polypeptide (Tetracosactrin) has also proved its effectiveness and usefulness [4]. Various other anti-epileptic drugs such as sodium valproate, phenobarbitone and benzodiazepines have also proved certain effectiveness and safety standards in order to manage IS in infants [5]. The effectiveness of Pyridoxine is also reported better in the Japanese studies; whereas, no randomized control trial proved its original and real-time effectiveness. Similarly, few other new management such as topiramate, zonisamide, IV immunoglobulins (IVIG), thyrotropin-releasing hormone (TRH) and ketogenic diet proved no significant positive aspects for the treatment of IS patients [5]. Vigabatrin (VGB) is among suicidal GABA transaminase inhibitors which were introduced to treat Infantile Spasm having tuberous sclerosis (TS); it effectively controlled the Spasms [6, 7]. Therefore, we aimed to assess the safety and effectiveness of two drugs in IS cryptogenic and symptomatic forms.

## METHODS:

Research sample comprised of 26 patients with 9 females and 17 males who were diagnosed with IS in the light of ILAE criteria at Sir Ganga Ram Hospital, Lahore in the timeframe of February to November 2017. Symptoms had characteristics of 2 to 10.5 months. Every hospitalized patient underwent metabolic workup, clinical and Wood's lamp assessment. We also performed EEG and CT Scan on the brain for every patient. Patients had a further subdivision of secondary IS and symptomatic aetiology in 14 and 12 patients respectively. Research sample treatment commenced in two different groups as eleven patients received Tetracosactrin injection on daily basis (0.03 mg/kg) with a maximum dose limit of (125 micrograms) given for two weeks with respect to dose response. Dose remained the same for every patient and no more injections were given after the course completion. Tetracosatrinis contains similar features of corticotrophin as it is a polypeptide synthetic derivative that is a treatment of various conditions. Two doses of Vigabatrin (VGB) were also orally administered to fifteen patients with a dose rate of (100 mg/ kg/ day). The dose may have an increase from 125 to 150 mg/ kg in the period of two weeks in case of spasm inadequacy. ECG and Clinical response evaluation and assessment also complied with and documented as well. Seven VGB administered children also underwent an ophthalmologic evaluation during a follow-up visit. We measured the outcomes through relapse rate, EEG normalization and complete spasms cessation.

## RESULTS:

As an outcome, there were 26 infantile spasm cases. Patients had a further subdivision of secondary IS and symptomatic aetiology in 14 and 12 patients respectively as per the presentation, history and investigations. We treated eleven patients with Corticotrophin as Tetracosactrin and remaining fifteen patients treated with Vigabatrin (VGB). VGB response was significant than steroids with the respective proportion of 73% to 63% without any discrimination of aetiology. It speaks for the effectiveness and safety of the VGB for being first line infantile spasm management therapy.

The first group received steroids as it included eleven IS cases (detailed distribution of the first group is available in Table – III). Seven patients successfully recovered from spasms among these seven patients three patients were symptomatic and four patients were cryptogenic. One of the patients died because of perinatal hypoxia during the first two weeks of treatment. Those who did not respond to the steroids were shifted to VGB on the prior permission of parents. Four patients recovered in three weeks and one patient recovered in two weeks.

VGB treated group included fifteen patients (detailed distribution of VGB group is available in Table – III). Out of these fifteen; seven were symptomatic and eight were cryptogenic. Further distribution was such as three patients of tuberous sclerosis, one each for cortical dysplasia & perinatal hypoxia and two patients of porencephaly. An oral intake delivered in two equal doses at the start at the rate of (100 mg/ kg/ day) which was gradually enhanced up to (125 mg/ kg/ day) after four to seven days of treatment; we did not exceed from (150 mg/ kg/ day) in any case. An early response did happen in a cryptogenic group within (13 – 22) days; whereas, the symptomatic group responded late within (25 – 35) days of treatment. Cryptogenic and Symptomatic group

showed better indicators as seven and four cases responded well to VGB respectively. Better outcomes of VGB reported in the tuberous sclerosis patients. Researcher failed to report long-term outcomes like a number of patients failed to continue with the follow-up.

While comparing both the groups; the researcher reported significant better VGB response than steroids with the respective proportion of 73% and 63% as shown in Table – II. Tetracosactrin group responded earlier than VGB group respectively as (8 – 16) days and 22 days. We also analyzed the recovery of EEG in both groups with a respective recovery rate of 56% against 38% with better clinical outcomes in the VGB group. There were three cases who showed side effects because of the management of steroids (27%); he also reported cushingoid in two cases and hypertension in one case. VGB group did not pose any side effect and retinal assessment was also fine as reported in the follow-up visits. Hospitalization was more in Tetracosactrin than VGB group with a respective stay of 26 versus 64 days.

**Table – I:** Patients' Distribution

| Patients | Symptomatic | Cryptogenic | Total |
|---|---|---|---|
| Number | 17 | 9 | 26 |

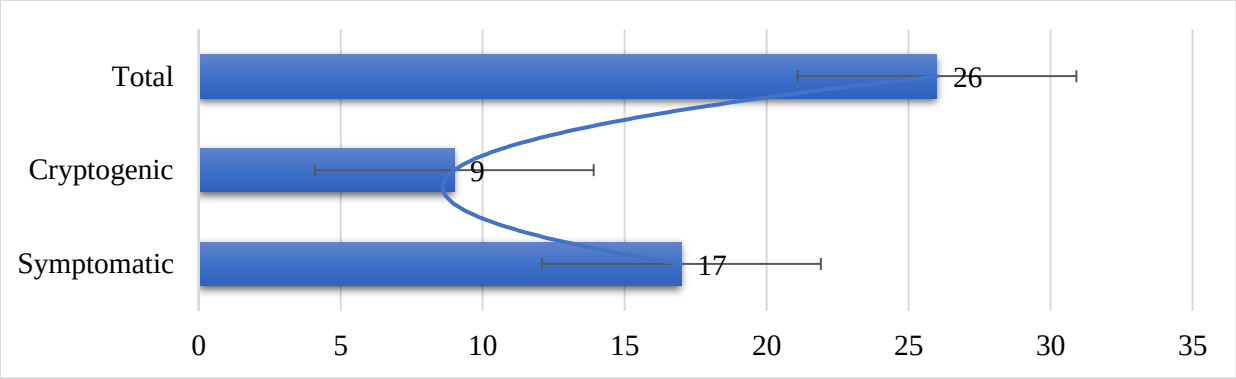



**Table – II:** Response Rate

| Response | Percentage |
|---|---|
| VGB | 73.00 |
| Steroids | 63.00 |

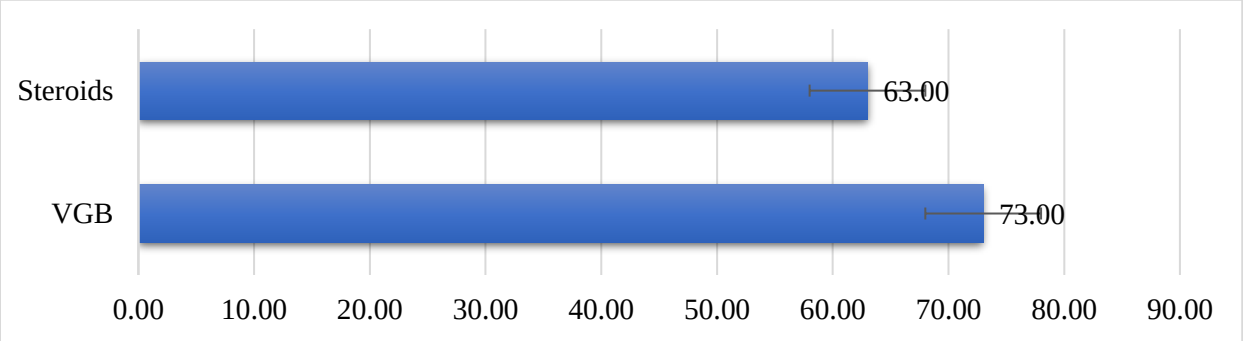
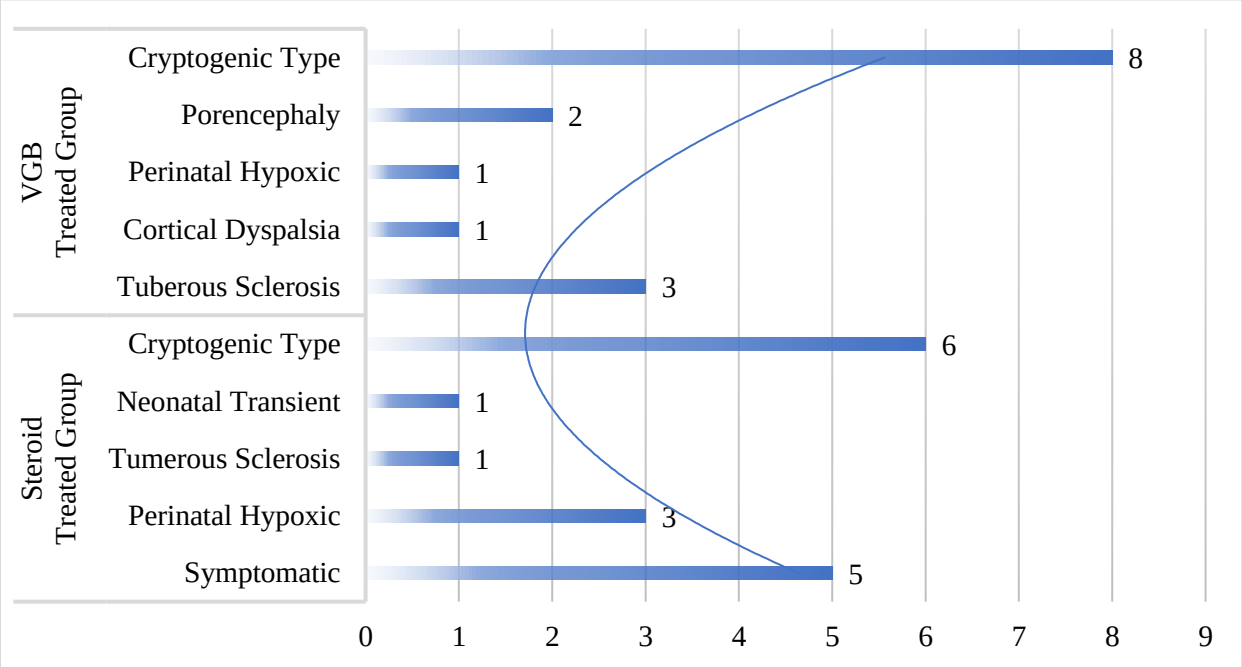
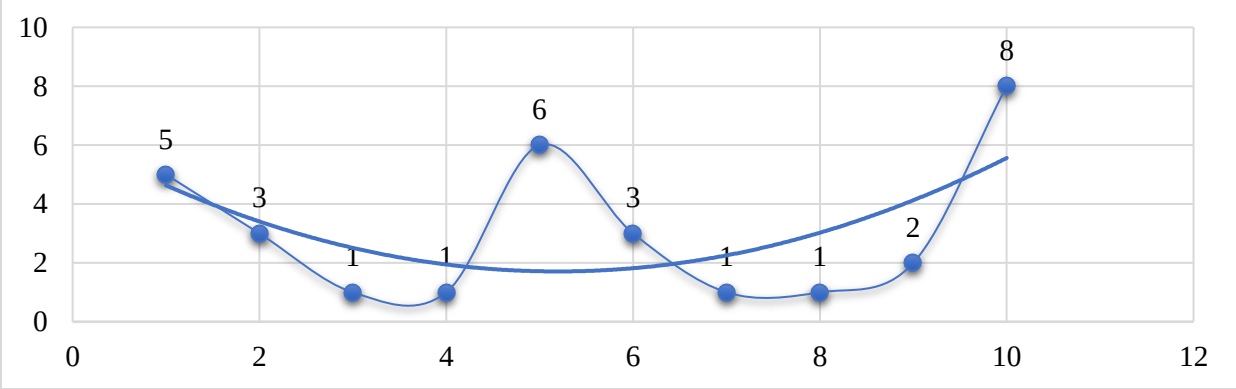


**Table – III:** Group Wise Distribution

| Group Wise Distribution | | Number |
|---|---|---|
| Steroid Treated Group | Symptomatic | 5 |
| | Perinatal Hypoxic | 3 |
| | Tumorous Sclerosis | 1 |
| | Neonatal Transient | 1 |
| | Cryptogenic Type | 6 |
| VGB Treated Group | Tuberous Sclerosis | 3 |
| | Cortical Dysplasia | 1 |
| | Perinatal Hypoxic | 1 |
| | Porencephaly | 2 |
| | Cryptogenic Type | 8 |



## DISCUSSION:

The introduction of Corticotrophin and its associated derivatives dates back to 1958 to treat IS on the neuro-allergic encephalitis suspicion as one of the fundamental pathogenesis [7]. They are also among the standard IS treatment option since then; however, there are also few side-effects such as hypertension, infections, hypertrophic cardiomyopathy, adrenocortical dysfunction and electrolyte disturbances in the course of treatment. There is no specification of the optimum dose schedule for this condition [8]. Higher doses also pose no extra advantage rather pose side effects such as cerebral shrinkage and hypertension in case of the patients receive a large amount of the drug dosage [4].

USA and Europe still use natural ACTH widely as synthetic ACTH has numerous associated side effects [4]. Our patients received Tetracosactrin, which is a corticotrophin's synthetic derivative with low drug dosage (0.03 – 0.04) mg/ KG that produced better and safe outcomes. Our patients presented such side effects like transient hypertension and cushingoid features; these side effects much lower (27%) than the other literary references [9]. The researcher also speculated about the ineffectiveness of the low dosage of natural ACTH which makes the high dose employment necessary and unavoidable with associated side effects. Ninety-one percent of the cases reported Spasm cessation in IS with Tuberous sclerosis [10]. This spasm cessation is also the same as reported in other literature references [6, 11]. The effectiveness of VGB is also evident from other randomized placebo trials as well [12]. While comparing both the groups; the researcher reported significant better VGB response than steroids with the respective proportion of 73% and 63%. Every other series reported better success rates such as Aicardi and Vigveno reported respectively 68% and 48% [11, 12]. Therefore, our research showed the better response of the VGB treated group in porencephaly and spasms with TS; whereas, spasm controlled through corticotrophin were also better in infantile spasm having perinatal hypoxic, as reported in other research studies. VGB produced minimal side effects of the drugs as it decreased the dose escalation; whereas, we cannot avoid adverse outcomes in the group of corticotrophins.

It is also interesting to note that spasms control in EEG and clinical response by using corticotrophin dose is early than VGB with a respective number of days (9 – 13) and (12 – 22) days; which is not same as reported in other research studies [11]. Higher VGB dose may be a possible cause of this delayed response in our research study. VGB produced a better response with no spasm reoccurrence and hypsarrhythmia pattern disappearing. An early reoccurrence was also evident in two of the patients of corticotrophin group requiring treatment modification.

Our research confirms the effectiveness of corticotrophin's low dose than higher dosage and even in the presence of delayed response of VGB the side effects and reoccurrence of spasm are reduced.

## CONCLUSION:

Undoubtedly, VGB is more effective and safer than Corticotrophins in order to manage infantile spasms, without any aetiology difference as monotherapy; although, the sample included in the research was not that much large. There is an equal effectiveness of synthetic corticotrophins in the low dose presence to control IS seizures with parallel side-effects. We can avoid steroid induced toxicity by using VGB as it a major concern for both parents and physicians. This research also assures the effectiveness and safety of the VGB for being first line infantile spasm management therapy.

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