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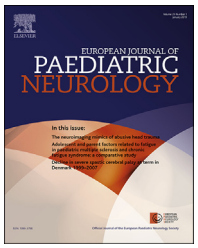

Original article

Safety, tolerability, and effectiveness of oral zonisamide therapy in comparison with intramuscular adrenocorticotropic hormone therapy in infants with West syndrome

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ABSTRACT

West syndrome is a distinct, infantile onset, epileptic encephalopathy, associated with poor neurodevelopmental outcome. The present study was designed as a randomized, open-label, pilot study to evaluate the safety, feasibility, and effectiveness of oral zonisamide therapy in comparison with adrenocorticotropic hormone therapy in infants with West syndrome. Thirty infants with West syndrome were randomized to receive treatment with either synthetic, intramuscular adrenocorticotropic hormone (30–60 IU) or oral zonisamide (4–25 mg/kg/day). The study participants had a long treatment lag and preponderance of male sex (90%). The primary effectiveness outcome measure was the cessation of epileptic spasms at 2 weeks of initiation of therapy and persistent till 6 weeks as per West Delphi consensus statement recommendations. Comparison of efficacies of zonisamide versus adrenocorticotropic hormone was as following: the cessation of epileptic spasms (27% vs. 40%, $p = 0.70$), resolution of hypsarrhythmia at 14 days (20% vs. 33%, $p = 0.68$) and resolution of hypsarrhythmia at 6 weeks (36% vs. 71%, $p = 0.14$). Overall, the study observed a poor efficacy of both adrenocorticotropic hormone and zonisamide therapy, which is probably due to long treatment lag and a high proportion of structural aetiology. However, oral zonisamide appeared to be safe and tolerable in the study.

Abbreviations: ACTH, adrenocorticotropic hormone; DASII, developmental assessment scale for Indian infants; EEG, electroencephalogram.

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1. Introduction

West syndrome, a form of epilepsy, is defined by the combination of clustered epileptic spasms and hypsarrhythmia in the electroencephalogram (EEG).[1] The term "hypsarrhythmia," a peculiar EEG pattern, is characterized by high-voltage slow waves with variable amplitude, spikes and waves from various foci and variability with time, and a lack of synchrony resulting in a chaotic appearance.[1] This syndrome is typically refractory to common antiepileptic drugs, and high-quality evidence on efficacy is mainly limited to adrenocorticotropic hormone (ACTH), oral steroids and vigabatrin. However, the major limitations with the use of ACTH are a parenteral route of administration, high cost and frequent adverse effects.[2,3]

Zonisamide (3-sulfamoylmethyl-1, 2-benzisoxazole), an effective antiepileptic drug, is commonly used in focal epilepsy.[4] The exact mechanism of action of zonisamide is complex and unclear, but it probably acts by inhibiting slow sodium channels and T-type calcium channels.[5] Earlier studies on children with West syndrome evaluated zonisamide as initial monotherapy at doses 4–13 mg/kg/day and observed low (0–25%) responder rate with respect to cessation of spasms.[6–9] Subsequently, studies with high-dose (8–35 mg/kg/day) zonisamide as initial monotherapy suggested a variable and slightly higher efficacy (0–33%).[5,10,11] Administration by an oral route, ease of administration and cheaper cost are its advantages. However, main limitations of studies were lack of comparator, non-randomized controlled design, and diversity of protocols.

The present study, therefore, was conducted to determine the safety, tolerability, and effectiveness of oral zonisamide therapy in comparison with adrenocorticotropic hormone in infants with West Syndrome.

2. Method

2.1. Participants

All newly diagnosed cases of West syndrome attending the outpatient services of the Division of Pediatric Neurology, Department of Pediatrics at the Post graduate Institute of Medical Education and Research, Chandigarh were screened for eligibility. The eligibility criteria were: (1) infants 6–12 months of age at presentation; (2) a diagnosis of West syndrome confirmed by clinical assessment and EEG; and (3) signed informed consent from a parent. Patients were excluded if: (1) they were suspected or proven cases of (i) tuberous sclerosis complex, (ii) neurometabolic disease or (iii) degenerative brain disease; (2) they had received previous treatments with ACTH, oral steroids or zonisamide; (3) had a contraindication for treatment with ACTH (active infection, pre-existing hypertension) or zonisamide (known renal stone); (4) parents expressed their inability to come for follow-up; or (5) parents had the plan to initiate or modify pharmacologic or non-pharmacologic interventions during the course of the study.

We restricted the study population to new onset West syndrome between 6 months and 12 months of age as this it is the most typical age of presentation for West syndrome, and also because it is practically challenging to assess adverse events in infants below six months of age. Also, we wanted to avoid enrolment of cases with very late presentation due to diagnostic lag. Children with a suspected neurometabolic disease or degenerative brain disease were excluded as their underlying disease and its progression could influence seizure control and therefore vitiate the outcome(s). More ever these cases are often prescribed megavitamin therapy including pyridoxine which could confound the true effect of zonisamide vs ACTH. Furthermore, we excluded infants with West syndrome underlying tuberous sclerosis complex because vigabatrin is considered by many to be the drug of choice in such cases.

The study was approved by the Ethics Committee of our Institute. The study was registered with the Clinical Trials Registry of India (Reference number CRTI 2013/07/003843).

2.2. Study design

Eligibility for inclusion in the study was assessed during the screening phase. All children who fulfilled the inclusion criteria were eligible for recruitment. The details of the study were explained to the parents and informed written consent was obtained. Detailed clinical evaluation and developmental assessment were done in all the children whose parents gave consent; details were recorded using a structured proforma. Children were randomized to receive treatment either with zonisamide or ACTH, and treatment was initiated within one week of the screening.

Randomization was done by a person not related to patient care in the study, using computer-generated randomization table, and the allocation ratio was 1:1. Allocation to either zonisamide or ACTH was concealed and was done by a person not related to patient care in the study. Sealed opaque envelopes containing group codes were prepared. Envelopes were sequentially numbered and kept in order according to their serial number. Envelopes were opened at the time of randomization, and the patients were allocated to their respective groups.

The drugs studied were: zonisamide and ACTH. Children who were assigned to zonisamide therapy arm, were treated on outpatient basis. Zonisep 25 mg capsules, manufactured by Sun Pharmaceuticals, were used in the study. The initial daily dose of zonisamide was 4–8 mg/kg/day. It was administered in powdered form, (prepared as sachets by pharmacy as per individualised need of child depending upon body weight), orally in two divided doses. Daily dosage was increased by 2–5 mg/kg every three days until the epileptic spasms disappeared or to a maximum daily dosage of 25 mg/kg/day. The ACTH used in the study population was synthetic corticotropin carboxymethylcellulose (Acton Prolongatum, Ferring Pharmaceuticals), which is freely marketed in India and available as 5 mL vial with a concentration of 60 units/millilitre. Initial ACTH therapy was given after hospitalization as per our department protocol. ACTH therapy was given via intramuscular route, 30 IU/day starting dose, as a single morning dose. The dosage was increased by 10 IU every 2–3 days until the spasms disappeared or to a maximum daily dose of 60 IU. Subsequently, slow tapering over 4–6 weeks was done in responders while rapid tapering over 1–2 weeks was

done in non-responders. During ACTH therapy, blood pressure was checked twice a day for two days and then once daily until day 14 and later according to clinical need. Urine was tested for glucose at 48 h and then weekly. Hypertension was diagnosed as blood pressure >95th centile.[12]

2.3. Measurement of effectiveness

The outcome measures related to effectiveness were the cessation of epileptic spasms, improvement in neurodevelopmental scores and hypsarrhythmia scores in the EEG. We measured the proportion of children in each therapeutic arm who had cessation of the epileptic spasms at 2 weeks of initiation of therapy and persistent till 6 weeks clinically and as reported by parents. We followed the consensus recommendations of the West Delphi group.[1] Furthermore, children with partial response (>50% reduction in the number but persistent epileptic spasms at 2 weeks of therapy) were also ascertained by diary review of the frequency of epileptic spasms. Parents were trained to record the number of clusters and epileptic spasms and to maintain the daily diary record.

EEG scores were used to determine the proportion of children who had a resolution of hypsarrhythmia, as determined by 30-min sleep EEG done at baseline, days 14–21 and days 42–49 of initiation of therapy. EEG scoring was done by a consultant pediatric neurologist, who was blinded to group allocation. Hypsarrhythmia scoring was done using the Jeavons scoring system.[13] The scoring system has been designed to give highest scores to utterly chaotic tracings and least scores to highly organized epileptic records. Using the EEG scoring system, a completely hypsarrhythmic record scores 13–30 points; modified hypsarrhythmia scores 9–12 points; an epileptic record of centrencephalic type and a focal epileptic record scores 2–8; a normal or non-specific record scores 0 or 1 point, respectively.[13]

To assess improvement in the development quotient, the Development assessment scale for Indian Infants (DASII), was administered at baseline, days 28–35 and days 90–104 of initiation of treatment. The DASII consists of various standardized items for assessment of mental and motor development. While mental scale ascertains cognitive, personal and social skills, the motor scale determines gross and fine motor development.[14]

2.4. Tolerability

The outcome measures related to drug safety included the adverse effect profile of the drugs in the study and number of withdrawals from the study. A daily diary was maintained by parents to record the treatment given, any treatment missed, and adverse effects. The diary records were reviewed on follow-up visits. Adverse effects were elicited at each visit by questioning the caregiver using a pre-structured questionnaire about the child's status and through direct observation. All adverse events reported or observed were recorded, along with the date and time of onset and cessation, plus assessments of severity and the likelihood of their being related to treatment.

Patients who received zonisamide therapy were followed-up in the outpatient department weekly for initial two weeks and then at 4, 8 and 12 weeks of initiation of therapy or more frequently according to clinical need. Patients who received ACTH therapy were followed-up after discharge from hospital in the outpatient department at 2, 4, 8 and 12 weeks of initiation of therapy or more frequently according to clinical need. Both-postal address and telephone number (whenever available) were carefully recorded so that patients who failed to visit on follow-up could be contacted. Compliance was also assessed by monitoring of consumption of medication doses. Patients not taking medication for any reason (<80 percent compliance) during follow-up were labelled as trial deviates but were followed-up for final assessment.

2.5. Statistical analysis

This pilot study had a convenient sample size of consecutive total 30 infants with West syndrome with 15 in each group. Analysis was done after completion of study. The primary analysis of safety and effectiveness was done on an intention-to-treat basis. It included all patients who were randomized to receive treatment. The data were analysed using the SPSS statistical package, version 22. Kolmogorov-Smirnov and Shapiro-Wilk tests were used to test for normality distribution of continuous variables. On exploration, the continuous variables did not follow normality distribution; therefore, non-parametric tests were performed. Fisher's exact test was used to test the association between categorical outcome variables. Mann-Whitney *U* test was used to compare continuous outcome variables between both groups. P value was two-sided, and the significance level of <0.05 was considered as statistically significant.

3. Results

3.1. Baseline characteristics of the patients

Between July 2012 and June 2013, a total of 82 infants with West syndrome were screened for eligibility (Fig. 1). Of those 82 infants, 52 were excluded. All 30 consecutive infants who were found eligible were assigned to zonisamide or ACTH after randomization. 15 infants were assigned to zonisamide group and 15 infants to ACTH group. All 30 infants were included in the final analysis.

The median age of children included in the study was 8.5 (IQR 6.8–11) months. Of the 30 infants, 27 (90%) were boys, and 3 (10%) were girls. In our study, 27 infants (90%) had an onset of epileptic spasms after 3 months of age. The median treatment lag in months was 2 (IQR 1–6) in the zonisamide group and 2 (IQR 1–5) in the ACTH group ($p = 0.80$). In our study, 27 infants (90%) had structural aetiology, and 3 (10%) had non-structural aetiology. The baseline characteristics of both groups are shown in Table 1. Both treatment groups were found comparable except that the median age at presentation and onset of epileptic spasms were earlier in the zonisamide group. This skewed distribution could be due to a chance phenomenon with a small sample size as allocation was randomized.

3.2. Effectiveness outcome measures

The proportions of children with cessation of epileptic spasms within 2 weeks of initiation of therapy and persistent till 6

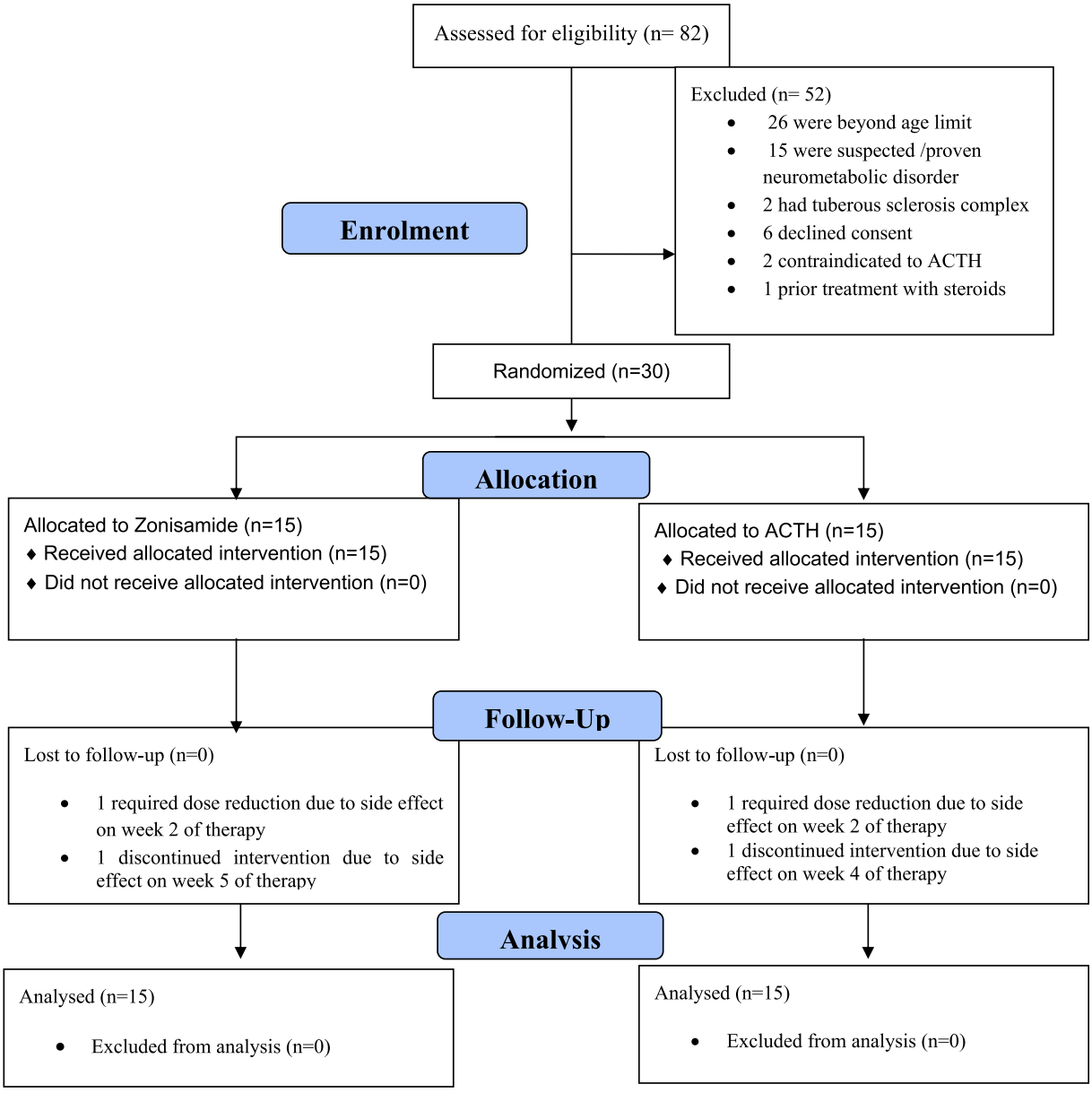

Fig. 1 – Enrolment, randomization and analysis of patients.

weeks were low in both groups, and the difference was not statistically significant [zonisamide 4/15 (27%) vs. ACTH 6/15 (40%), P-value 0.70] (Table 2A). Similar results were observed regarding the resolution of hypsarrhythmia at 14 days of initiation of therapy [zonisamide 3/15 (20%) vs. ACTH 5/15 (33%), P-value 0.68]. However, at 6 weeks of therapy, the ACTH group had a higher resolution of hypsarrhythmia [zonisamide 5/14 (36%) vs. ACTH 10/14 (71%); P-value 0.14]. This difference was not statistically significant, probably due to inadequate power in the study but this is clinically relevant. The median EEG scores which were comparable at baseline, however, improved significantly in the ACTH group at 2 weeks and 6 weeks of therapy. Median developmental scores as assessed by DASII were comparable at baseline, 1 month and 3 months of therapy (Table 2B).

3.3. *Tolerability*

Table 3 shows the adverse effect profile of patients in both groups. In the zonisamide group, predominant adverse effects were lethargy and irritability. One child required dose reduction and one required withdrawal of medication due to significant loss of appetite. In the ACTH group, hypertension was the predominant adverse effect. Children who developed hypertension were treated with oral amlodipine, and the dose was titrated according to the response. One child required the

Table 1 – Baseline characteristics of the patients.

Characteristics	Zonisamide group (n = 15)	ACTH group (n = 15)	P*
Median age at presentation in months (IQR)	8 (6–9)	10 (8–11)	0.05
Male Gender (%)	15 (100%)	12 (80%)	0.22
Number of children with onset of epileptic spasms <3 months of age (%)	2 (13%)	1 (7%)	>0.99
Median age at onset of epileptic spasms in months (IQR)	5 (4–7)	7 (6–8.5)	0.05
Number of children with structural aetiology (%)	15 (100%)	12 (80%)	0.22
Median treatment lag in months (IQR)	2 (1–6)	2 (1–5)	0.80
Median EEG score at baseline (IQR)[a]	18 (16–20)	16 (14–17)	0.20
Median Developmental score as assessed by DASII-Motor scale at baseline (IQR)[b]	50 (48–56)	54 (50–56)	0.11
Median developmental score as assessed by DASII-Mental scale at baseline (IQR)[b]	50 (42–52)	50 (50–52)	0.21

Abbreviation: IQR, Interquartile range; ACTH, adrenocorticotropic hormone; DASII- Development assessment for Indian infants.
*P value < 0.05 considered as significant. Medians were compared with Mann-Whitney *U* test and frequencies were compared with Fisher's exact test.
[a] Score ranges from 0 to 30 with higher score indicates higher EEG abnormalities.
[b] Score ranges from 9 to 67 for motor scale & 14–163 for mental scale with higher score indicates better performance.

Table 2A – Comparison of control of epileptic spasms in zonisamide versus ACTH group.

Outcome	Zonisamide (n = 15)	ACTH (n = 15)	p*
Proportion of children with cessation of epileptic spasms at 2 weeks and persistent cessation till 6 weeks of therapy (%)	4/15 (27%)	6/15 (40%)	0.70
Proportion of children with >50% reduction but persistent epileptic spasms at 2 weeks of therapy (%)	8/15 (53%)	4/15 (27%)	0.26

Abbreviation: *P value < 0.05 considered as significant. Frequencies were compared with Fisher's exact test.

Table 2B – Comparison of EEG & developmental scores as outcome measures in zonisamide versus ACTH group.

Outcome	Zonisamide group (n = 15)	ACTH group (n = 15)	p*
Proportion of children with resolution of hypsarrhythmia at 14 days of therapy	3/15 (20%)	5/15 (33%)	0.68
Proportion of children with resolution of hypsarrhythmia at 6 weeks of therapy	5/14 (36%)	10/14 (71%)	0.14
Median EEG score at 14 days of therapy (IQR)[a]	16 (10–20)	10 (7–12)	0.008
Median EEG score at 6 weeks of therapy (IQR)	14.5 (6.8–18)	7.5 (4–13)	0.03
Median Developmental score as assessed by DASII-Motor scale at 1 month of therapy (IQR)[b]	54 (50–56)	56 (50–58)	0.17
Median Developmental score as assessed by DASII-Mental scale at 1 month of therapy (IQR)[b]	50 (42–54)	52 (50–54)	0.15
Median Developmental score as assessed by DASII-Motor scale at 3 months of therapy (IQR)	56 (52–59)	58 (53–62)	0.27
Median Developmental score as assessed by DASII-Mental at 3 months of therapy (IQR)	50 (40–54)	53 (52–56)	0.05

Abbreviation: IQR, Interquartile range; *P value < 0.05 considered as significant. Medians were compared with Mann-Whitney *U* test and frequencies were compared with Fisher's exact test.
[a] Score ranges from 0 to 30 with higher score indicates higher EEG abnormalities.
[b] Score ranges from 9 to 67 for motor scale & 14–163 for mental scale with higher score indicates better performance.

withdrawal of ACTH due to gastroenteritis, probably unrelated to therapy.

4. Discussion

The present study is the singular study of children with West syndrome to compare oral zonisamide with ACTH in a randomized controlled manner. The observed responses, i.e., cessation of epileptic spasms and resolution of hypsarrhythmia were poor in both the groups. This could perhaps be related to long treatment lag in both the groups. The median hypsarrhythmia scores at 2 weeks and 6 weeks of therapy were significantly better with the ACTH group. The treatment effect on neurodevelopmental outcome did not show any meaningful difference between the two groups at 1 month and 3 months of therapy. However, zonisamide therapy appeared safe and tolerable and might be a potential therapeutic option.

In our study, there was a striking male preponderance observed in the children diagnosed with West syndrome; 90% of the enrolled cases were boys. Male preponderance among infantile spasms population was observed in a previous study from our department[15] and has also been reported in other studies from India.[16,17] Kaushik et al. reported 81% male preponderance in their cohort of 148 children with West syndrome from Northern India.[16] Similarly, Gulati et al. reported male: female ratio of 3.1:1 in their series of 310 children with West syndrome.[17] It was attributed to probable gender-biased referral and treatment-seeking behaviour of parents.

Our study observed a median treatment lag of 2 (1–6) months in the zonisamide group and 2 (1–5) months in the ACTH group. This high treatment lag in comparison with data

Table 3 – Summary of adverse effect profile.

	Zonisamide (n = 15)	Adrenocorticotropin (n = 15)
Nature of the adverse effect and the proportion of children with the adverse effect	Lethargy (8/15) Irritability (5/15) Gastroenteritis (2/15) Dryness of skin and mouth (1/15) Loss of appetite (1/15)** Metabolic acidosis (1/15)*	Hypertension (14/15) Weight gain (5/15) Cushingoid (3/15) Irritability (3/15) Infection (2/15)** Hyperpigmentation (1/15)*

*One case required dose reduction and **one case required discontinuation of drug due to adverse effect in each group.

from developed countries is important because it adversely affects therapeutic response.[18] A prolonged treatment lag is often reported from developing countries and is likely due to high diagnostic lag. Kaushik et al. reported lead time of 7.9 months (SD 7.4) in their cohort.[16] Pre-existing developmental delay of children, educational status of the parents and qualification of the first practitioner visited are important determinants of treatment lag.[19,20]

In the present study, treatment response was poor in both groups. The efficacy of ACTH was 40% at 6 weeks of initiation of therapy. It is a lower responder rate than 87% reported by Baram et al.[3] and 76% reported by UKISS study group.[21] This could be due to preponderance of structural aetiology, significant treatment lag and a different dose protocol of ACTH in our cohort of patients. The median age at presentation and onset of epileptic spasms were later in the ACTH group than that of zonisamide group. Although this must have arisen by chance, probably because of the small numbers recruited, it could possibly be responsible for the poor response to ACTH seen in this study. However, our results were similar to 37% responder rate reported by Wanigasinghe J and colleagues who used the same ACTH preparation but with a lower dose protocol.[22] Our study showed that zonisamide was effective in only 4 of 15 (27%) children in term of cessation of epileptic spasms at 6 weeks of therapy. Furthermore, 8 of 15 (53%) children had >50% reduction, but persistent epileptic spasms at 2 weeks of therapy with zonisamide compared with 4 of 15 (27%) children in the ACTH group. However, the results are comparable with previous studies of zonisamide monotherapy which ranged from 30 to 33%.[5,11] A high number of cases with structural aetiology and a long treatment lag may account for poor response to therapy in the zonisamide group. It is noteworthy that the efficacy of zonisamide is less than that of oral prednisolone, as reported in UKISS study.[18] Oral prednisolone is also a cheap and oral therapeutic option. The cost of ACTH and the associated requirement of hospitalization has a higher financial impact on the family than that of oral zonisamide or oral steroids therapy.

In our study, oral zonisamide treatment with rapid titration of drug dosage was well tolerated. Safety measured in terms of tolerability and withdrawal from the study had no significant difference in comparison with ACTH group. Our results are in concordance with observations by Yum and Ko.[6] There was a high incidence of hypertension in the ACTH group, which was probably related to the high-dose of ACTH used.

Our study findings should be interpreted with consideration to a few inadvertent limitations. Being a pilot and small number study, it is not sufficiently powered. The reasons for small sample size were a relative rarity of the condition along with stringent inclusion criteria. We did not perform therapeutic drug monitoring for zonisamide levels as it has limited clinical utility. Our study lacks data on subsequent relapses and long-term outcome due to a short follow-up.

In conclusion, with limitations of the design, this study suggested an inferior efficacy regarding the cessation of spasms and resolution of hypsarrhythmia with both ACTH and zonisamide therapy. The reasons are multifactorial; a large treatment lag, the preponderance of structural aetiology, and a different ACTH regime and preparation perhaps had important contributions. However, zonisamide regimen of 4–25 mg/kg/day appeared to be tolerable and safe for infants aged 6–12 months with West syndrome and might be a therapeutic option. Furthermore, adequately powered, long-term follow-up, randomized controlled, blinded trials are needed to determine the long-term efficacy and safety of oral zonisamide in infants with West syndrome.

Author contribution

DA, JKS, and PS conceptualised the study. DA collected data. JKS was involved in EEG scoring. PM was involved in psychometric assessments. DA and JKS wrote the first draft of the manuscript; PS and all co-authors contributed in a critical review of manuscript writing. DA and JKS share the first authorship for the work described in this paper. PS is the guarantor for this study.

Ethics approval

The study design was approved by the institute ethics committee.

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Conflict of interest

None.

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