

Oral Dexamethasone versus Prednisolone for Management of Children with West Syndrome: An Open-Labelled Randomized Controlled Pilot Trial

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Abstract

Objective: To compare the efficacy of oral dexamethasone and prednisolone in the treatment of newly diagnosed children aged 3–36 months of West syndrome. **Methods:** An open-labeled, randomized controlled clinical trial with parallel group assignment was conducted among children aged 3–36 months with newly diagnosed West syndrome. They were randomized to receive either oral dexamethasone (0.6 mg/kg/day QID) ($n = 20$) or oral prednisolone (4 mg/kg/day BD) ($n = 20$). Proportion of children who achieved spasm freedom at 2 weeks was the primary outcome. Secondary outcome measures were proportion of children who achieved electroclinical resolution, greater than 50% reduction in spasms frequency, time to cessation of spasms, and adverse effects at 2 weeks. **Results:** The efficacy of oral dexamethasone was comparable to oral prednisolone in terms of proportion of children who achieved spasms cessation (13 [65%] vs. 8 [40%]; $P = 0.21$), electroclinical remission (13 [65%] vs. 8 [40%] $P = 0.21$), greater than 50% reduction of spasms (3 [15%] vs. 7 [35%] $P = 0.65$), and time to cessation of spasms (5.31 [2.81] vs. 4.37 [1.41] $P = 0.39$). Adverse effect profile was also comparable with irritability (18 [90%] vs. 12 [60%] $P = 0.06$) being most common. **Conclusion:** There was no difference in electroclinical remission at 2 weeks between oral dexamethasone and prednisolone in children with infantile spasms in this small pilot trial. Further evaluation is suggested with an adequately powered study and long-term follow-up.

Keywords: Epilepsy, epileptic encephalopathy, infancy, infantile spasms

INTRODUCTION

West syndrome (WS) is a type of epileptic encephalopathy of early infancy and is one of the commonest types of epilepsy in infants and toddlers.^[1] Treatment used for WS includes corticosteroids, vigabatrin, and Adreno-Cortico-Trophic Hormone (ACTH).^[2] ACTH and prednisolone are considered first line for management of infantile spasms (IS) with efficacy ranging from 40 to 70% in achieving reduction of spasms. There is a growing interest in the use of dexamethasone considering its seizure-reducing effect by improvement of blood brain barrier integrity.^[3] However, there is limited experience with use of dexamethasone in WS and other drug-resistant epilepsies in children.^[4-7]

Yamamoto *et al.*^[4] reported reduction of spasms in all five patients with WS on use of liposteroid (dexamethasone palmitate) in dose of 0.25 mg/kg seven times in three months. In a Russian study, injectable dexamethasone has been used in doses of 0.3–0.5 mg/kg with 10 injections per day for 10 days, followed by five injections every alternate day, and five injections every 2 days for management of IS.^[8] Authors observed that 21 of 73 patients who were followed up had persistence of IS. There is anecdotal experience of use of pulse corticoid therapy with dexamethasone (20 mg/m² daily for 3 days once in 4 weeks for five cycles) among seven patients with WS with four of them achieving spasm freedom.^[5] In another study, four children with WS have been treated with dexamethasone palmitate (cumulative dose of 3 mg/kg; 12

doses in a month) with one of them having cessation of spasms with rest two having >50% reduction.^[4] There is another report of dexamethasone (20 mg/m² for 3 days) use in five patients of IS with 80% response rate.^[6]

There are no reports on use of oral dexamethasone in WS. Oral dexamethasone is appealing because of its low cost, ready availability in many countries, ease of administration, and favorable pharmacokinetics. Hence, this pilot study was designed to compare safety and efficacy of oral dexamethasone and prednisolone in management of WS.

METHODS

This open-labeled, randomized control trial was conducted in the Department of Pediatrics and Neurology of a tertiary

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Submitted: 30-May-2022 **Revised:** 02-Jul-2022 **Accepted:** 08-Aug-2022

Published: 31-Oct-2022

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DOI: 10.4103/aian.aian_481_22

care referral center of India. The data were collected from April 2021 to November 2021. Ethical approval from the institutional ethics committee was obtained. Written informed consent was obtained from the parents. All children aged 3–36 months, diagnosed with WS were consecutively enrolled in the study. Children with recognized progressive neurological illness, children with renal, pulmonary, cardiac, or hepatic dysfunction, and severe malnutrition (weight for length and height for less than 3 SD for mean as per WHO growth charts) were excluded from the study. The trial was registered in Clinical Trial Registry of India (CTRI/2021/04/032533).

All eligible children were subjected to detailed clinical history and examination. Spasms type, frequency, age at onset, age at diagnosis, frequency of spasms, perinatal details, family history, developmental status, and treatment history were recorded. A baseline electroencephalogram (video-EEG whenever possible) was performed in all children at the time of enrollment for a minimum of 1 h, including at least one sleep–wake cycle.

Eligible children were allotted a study number (JSK), and these numbers corresponded to the order of patients entering the trial who were enrolled consecutively in the study. The random allocation sequence was generated using computer-generated random number table (SL). The eligible participants were randomized in two groups: Oral dexamethasone (0.6 mg/kg/day in four divided doses) and oral prednisolone (4 mg/kg/day in two divided doses). Allocation of treatment group was concealed by preparing a sealed opaque envelope containing group codes (NDV). These envelopes were sequentially numbered and kept in order according to their serial numbers. Envelope was opened after the patient was enrolled in the study and assigned a study number (MD). The assigned study drug was administered (MD) under the supervision (JSK).

Percentage reduction in seizure frequency compared to the baseline was assessed by daily seizure log maintained by parents. At the end of the 2-week study period, the proportion of patients who achieve spasm freedom and more than 50% reduction in spasms frequency in both the groups was recorded. Time to cessation of spasms and the proportion of children with treatment failure were also recorded. A repeat EEG was performed to look for resolution of hypsarrhythmia. Primary electroclinical remission was considered when there was cessation of spasms along with resolution of hypsarrhythmia.^[9]

Considering lack of data on efficacy of dexamethasone, a pilot study was planned with a convenience sample of 20 in each group considering the time constraints and other local logistics. All data collected were entered in Microsoft Excel (MS Excel). Data were analyzed using SPSS 21.0 version. All categorical variables were expressed in numbers (percentage); all continuous variables were expressed as mean (SD) or median (interquartile range). Categorical variables were compared using Chi-square test or the Fischer's exact test. Continuous variables were compared between cases and

controls using the Student's "t" test or Wilcoxon rank sum test. A *P* value of < 0.05 was considered significant.

RESULTS

A total of 47 children were assessed for eligibility, of whom 40 children were randomized to receive either of oral dexamethasone (*n* = 20) or oral prednisolone (*n* = 20) with no follow-up loss till 2 weeks [Figure 1]. The baseline demographic and clinical variables were comparable between the two groups [Table 1]. Majority of the enrolled had perinatal insult and the etiology was comparable between the two groups (15 [75%] and 18 [90%]; *P* = 0.41). Seven children (five dexamethasone group and two prednisolone group) were categorized with presumed genetic etiology as parents were not able to afford clinical exome sequencing. The efficacy of oral dexamethasone compared to prednisolone was comparable in terms of spasms cessation (13 [65%] vs. 8 [40%]; RR [95%CI]: 1.62 [0.86–3.03]; *P* = 0.12). Efficacy in terms of time to cessation of spasms (8 [6.3%] vs. 5.8 [2.5%]; *P* = 0.41), more than 50 percent reduction of spasms (3 [15%] vs. 7 [35%]; RR [95%CI]: 1.31 [0.91–1.89]; *P* = 0.65), and electroclinical remission (13 [65%] vs. 8 [40%]; RR [95%CI]: 1.62 [0.86–3.03]; *P* = 0.12) were comparable

Table 1: Baseline characteristics of enrolled participants (*n* = 40)

Clinical characteristics	Oral dexamethasone (<i>n</i> = 20)	Oral prednisolone (<i>n</i> = 20)	<i>P</i>
Mean (SD)			
Age at onset of spasms (in months)	8.8 (8.32)	5.0 (4.54)	0.81
Time lag in diagnosis (in months)	1.65 (1.72)	2.7 (2.27)	0.11
Number (percentage)			
Male gender [<i>n</i> (%)]	14 (70)	11 (55)	0.51
Female gender [<i>n</i> (%)]	6 (30)	9 (45)	
Spasms frequency at the time of enrolment per day (spasms/day)	24.5 (7.59)	26.0 (6.6)	0.51
Microcephaly [<i>n</i> (%)]	7 (35)	14 (70)	0.06
Perinatal insult [<i>n</i> (%)]			
Perinatal asphyxia	10 (50)	16 (80)	0.79
Neonatal intracranial bleed	3 (15)	1 (5)	
Hypoglycemia	2 (10)	0	
Etiology [<i>n</i> (%)]			
Structural	15 (75)	18 (90)	0.41
Presumed genetic	5 (25)	2 (10)	
EEG findings [<i>n</i> (%)]			
Classical	13 (65)	15 (75)	0.73
Modified	7 (35)	5 (25)	
Anti-seizure medication [<i>n</i> (%)]			
Valproate	18 (90)	14 (70)	0.24
Levetiracetam	9 (45)	12 (60)	0.53
Clonazepam	19 (95)	17 (85)	0.61

between the two groups [Table 2]. Adverse effects profile was although comparable between the two groups in terms of irritability, weight gain/swelling, appetite but number of children who developed irritability were quite higher in oral dexamethasone compared to prednisolone group (18 [90%] vs. 12 [60%] [$P = 0.06$]).

DISCUSSION

The present pilot study provides a preliminary evidence on comparable efficacy of oral dexamethasone and high dose oral prednisolone in the treatment of newly diagnosed

children with WS. There was no difference in proportion of children with electroclinical remission, spasm freedom, greater than 50% reduction, and time to spasm freedom between oral dexamethasone and oral prednisolone groups in this under-powered pilot study. The adverse effect profile were also comparable between the two groups with majority of children having irritability, weight gain, and increase appetite.

Steroids may accelerate central nervous system (CNS) myelination and dendritic formation and, thus, may shorten a hypothetical period of vulnerability to IS.^[10] Steroids may also act as a direct anticonvulsant via GABAergic or

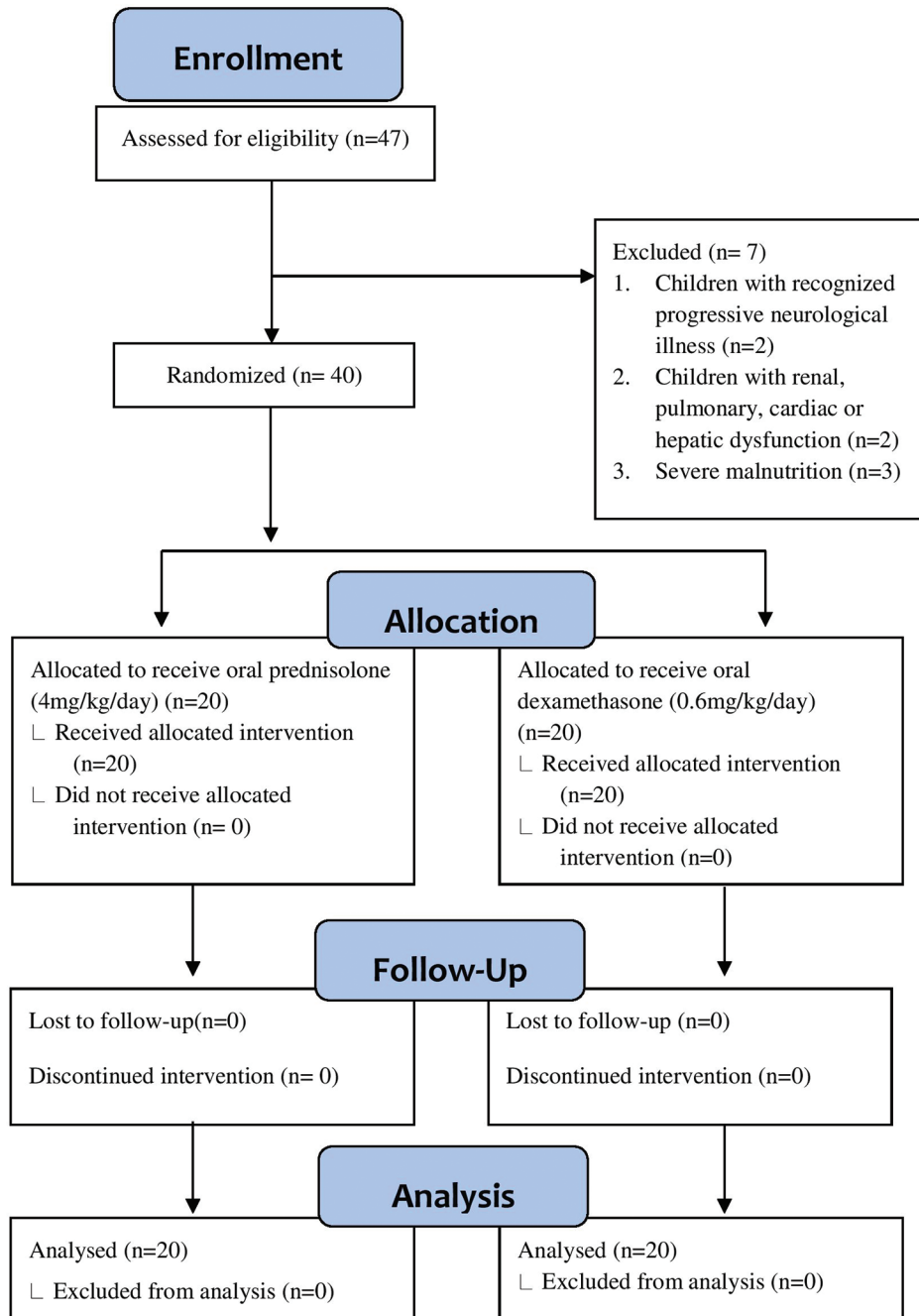


Figure 1: Study flow

Table 2: Outcome measures of enrolled participants (n=40)

Final outcome measures	Oral dexamethasone (n=20)	Oral prednisolone (n=20)	OR (95% CI)	P
Number of children with clinical spasms cessation [n (%)]	13 (65)	8 (40)	2.78 (0.77, 10.1)	0.21
Time to cessation of spasms in days [mean (SD)] [SE (95% CI)]	5.31 (2.81)	4.37 (1.41)	0.71 (-2.36-0.48)	0.39
Number of children with more than fifty percent reduction in spasms [n (%)]	3 (15)	7 (35)	0.32 (0.07, 1.51)	0.65
Number of children with electroclinical remission [n (%)]	13 (65)	8 (40)	2.78 (0.77, 10.1)	0.21
Adverse effects [n (%)]				
Irritability	18 (90)	12 (60)	6 (1.08, 33.3)	0.06
Weight gain/swelling	15 (75)	11 (55)	2.45 (0.64, 0.39)	0.32
Increased appetite	6 (30)	6 (30)	1.0 (0.25, 3.86)	1.0
Decreased appetite	4 (20)	2 (10)	2.25 (0.36, 13.9)	0.65
No change in appetite	10 (50)	12 (60)	0.66 (0.19, 2.33)	0.52

other mechanisms. Dexamethasone is known to protect blood brain barrier from damage as measured by serum S100beta and Evans blue brain extravasation in rat model of acute seizure.^[3] Liposteroids (dexamethasone palmitate) have been traditionally used in management of rheumatoid arthritis and there are anecdotal reports of its efficacy in WS.^[4,7] However, this often requires hospital admission for intravenous administration. It has been demonstrated that bioavailability of oral dexamethasone is sufficient in children and has been suggested as an alternative for intravenous administration.^[11] In infective neurological conditions and in those with malignancy, dexamethasone has been preferred over prednisolone considering better CNS penetration.^[12] These reports prompted the authors to explore the role of oral dexamethasone and compare it with traditional high dose prednisolone in children with WS.

The present study demonstrated electroclinical remission in 65% (13/20) of children who received oral dexamethasone that is numerically higher than 40% (8/20) children who received high dose prednisolone that does not reach statistical significance. The short-term efficacy in terms of cessation of spasms for high dose steroids have ranged from 40 to 70%.^[13-16] Few studies on liposteroids in various regimens have demonstrated that one out of four children, four out of five, and four out of seven children have achieved spasm freedom.^[4,6,7] However, there are no comparable data for efficacy of oral dexamethasone in IS. The efficacy in terms of >50% reduction in seizure frequency and time to cessation of spasms was also comparable among the two groups. Adverse effect profile was comparable in the two groups, but when looking at the numerical figures, there is a higher proportion of irritability and weight gain in dexamethasone group.

To the best of our knowledge, this is the first randomized controlled clinical trial comparing oral dexamethasone to high dose steroids in treatment of children with WS. The limitations include small sample size, inclusion of children up to the age of 36 months (concern of overlap with Lennox-Gestaut syndrome), and assessment of short-term efficacy at 2 weeks. Considering limitations in the present study, future studies

are recommended with adequately powered sample size and assessment of long-term outcome. The enrolled patients of WS in the present study had predominant structural etiology with significant time lag in seeking treatment that may limit the generalizability of study findings in other clinical settings. Those with presumed genetic etiology could not afford genetic testing owing to financial constraints that is also acknowledged as one of limitations of the present study.

To conclude, this single-institution, pilot, open-labeled randomized controlled trial demonstrated that oral dexamethasone has comparable efficacy and safety to conventional high dose prednisolone in the management of children with WS. Hence, in practice, it will be difficult to implement the routine use of oral dexamethasone as an alternative to oral prednisolone for treatment of children with WS till further data on the same is available.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Ethical approval

An institutional ethical approval was obtained before the commencement of the study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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