RESEARCH PAPER

Fourteen Days vs 28 Days of Albendazole Therapy for Neurocysticercosis in Children: *An Open Label Randomized Controlled Trial*

ANKIT SINGLA,[1] SEEMA LEKHWANI,[2] NARAIN DAS VASWANI,[1] JAYA SHANKAR KAUSHIK,[4] SUREKHA DABLA[3]

From Department of [1]Pediatrics, [2]Biochemistry and [3]Neurology, Pt BD Sharma Postgraduate Institute of Medical Sciences, Rohtak, Haryana; and [4]Department of Pediatrics, All India Institute of Medical Science, Guwahati, Assam.

Correspondence to: Dr Jaya Shankar Kaushik, Additional Professor, Department of Pediatrics, All India Institute of Medical Sciences, Guwahati, Assam 781 101. jayashankarkaushik@gmail.com

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Background: There is a paucity of literature to support 14-days albendazole therapy for neurocysticercosis (NCC).

Objective: To compare the efficacy of 14-day and 28-day albendazole therapy in the management of children with newly diagnosed active NCC.

Study design: Open-labelled randomized controlled trial

Participants*:* Children aged 1-14 years with newly diagnosed active neurocysticercosis.

Intervention: Albendazole (15 mg/kg/day) for either 14 days or 28 days.

Outcome: The primary outcome measure was proportion of children with radiological resolution of active lesion at 6-month follow up. Secondary outcome measures were proportion of children with seizure recurrence, duration to seizure recurrence and calcification on follow up imaging.

Results: 65 children with newly diagnosed NCC were randomized to receive albendazole therapy for 14 days (*n*=32) or 28 days (*n*=33). The proportion of children with complete resolution was comparable between the two groups [6 (18.8%) vs. 9 (27.3%); OR (95%CI):0.61 (0.19 to 1.98); *P*=0.56]. Similarly, proportion of children with seizure recurrence [5(15.6%) vs 2(6.1%); OR (95%CI): 2.87(0.51-16.0); *P*=0.26] and proportion of children with calcification on follow-up imaging [26(81.2%) vs 23(69.7%); OR (95%CI): 1.88 (0.59-5.99); *P*=0.39] were also comparable. There were no major side-effects noted during the study.

Conclusion: 14-day treatment with albendazole therapy is as effective as 28-day treatment in achieving radiological resolution at six-month follow up. However, high rate of calcification in both the groups indicates need for further evaluation with an adequately powered study and longer follow up

Keywords: Duration, Seizure recurrence, Calcification.

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Neurocysticercosis (NCC) is a common parasitic infestation of the central nervous system and is possibly the most common risk factor for acquired epilepsy worldwide [1]. Antiparasitic treatment with albendazole increases the radiological clearance and is known to reduce the recurrence of seizures [2,3]. There is wide heterogeneity in clinical practice regarding the duration of albendazole treatment ranging from 7 days, 14 days to 28 days for single and/or multiple NCC. In a study by Johnson, et al. [4], it was observed that long term clinical, radiological, and cognitive outcome in children with single neurocysti-cercosis was comparable among those who received 7-days and 28-days of albendazole therapy. The limited number of adult and pediatric studies on 14-days duration of albendazole therapy have revealed 69-95% resolution of radiological lesion at 6-month follow up [5-7].

In a recent consensus statement of Association of Child Neurology (AOCN) [8], 10-14 days of albendazole therapy is recommended for management of single viable NCC and combination of albendazole with praziquantel for more than one lesion. Further, the AOCN guideline clearly mentions that the quality of evidence is strong for use of albendazole therapy for management of NCC, but not for the duration of therapy. Considering the paucity of data on short-term efficacy of 14-days albendazole therapy, the present study was conducted to compare the efficacy of 14-days vs 28-days course of albendazole therapy in children with newly diagnosed active neurocysticercosis.

Invited Commentary: Pages 908-9.

METHODS

This open-labeled, randomized controlled trial was conducted from February 2020 to March 2021, in the Department of Pediatrics, Neurology and Biochemistry of a tertiary care, referral center of India. Ethics approval was obtained from the Institutional Ethics Committee. The trial was registered in the Clinical Trial Registry of India (CTRI). After taking written informed consent from the parents,

consecutive children aged 1-14 years, newly diagnosed with active neurocysticercosis were enrolled. Neurocysticercosis was diagnosed based on Revised Del Brutto criteria for Neurocysticercosis [9]. The lesion was considered to be NCC when either scolex was demonstrable, or the lesion was thin walled, cystic, less than 2 cm, in typical location of grey matter and white matter junction or basal ganglia [8]. The lesion was considered active when MRI demonstrated T2 hyperintensity in the core of the lesion. Children who had received albendazole or diagnosed with neurocysti-cercosis in the preceding three months, those with intellectual disability, recognized progressive neurological illness, renal, pulmonary, cardiac, or hepatic dysfunction, were excluded from the study.

A detailed history, including demographic details, type and duration of seizure, dietary pattern, perinatal details, family history, developmental status and treatment particulars, was taken. Examination was done according to a pre-designed proforma. Imaging details including number and location of NCC with or without presence of perilesional edema were also recorded.

Block randomization was done using variable block size of 2, 4 and 6 using computer-generated random number tables in two groups: Albendazole (15 mg/kg/day in two divided doses; maximum daily dose being 800 mg) for 14 days and 28 days. Sequentially numbered, opaque, sealed envelopes containing group codes were prepared. Envelop was opened at the time of randomization, and the patient was allocated to their respective group. Children of both groups received short course of oral dexamethasone (0.6 mg/kg/day) for 5-7 days, which was commenced two days prior to albendazole therapy and continued for 3-5 days after starting albendazole. Any of the antiepileptic drugs - phenytoin, carbamazepine or valproate was continued for seizure prophylaxis, as per the treating unit protocol.

All children were followed up for a minimum duration of 6 months. At the end of six-month study period, a repeat MRI Brain/CECT head was performed. Lesion on follow up MRI was classified as complete resolution (no residual lesion), calcified lesion (presence of blooming on GRE images) and resolution of active lesion (when T2 hyperintense core in the lesion has become isointense or hypointense). The primary outcome of the study was proportion of children with resolution of active lesion and secondary outcome was proportion of children with seizure recurrence and duration to seizure recurrence. Parent reported adverse effects were recorded.

Assuming that proportion of children with resolution of NCC lesions at 6 months with 14 days therapy would be 68% and 79% with 28 days therapy of albendazole [5,10], taking a power of 80%, alpha error of 5% and 0.3 as the margin on risk difference under two tailed test, sample size of 73 in each group was computed, However, owing to logistic constraints, a convenience sample size was adopted.

Statistical analysis: All data collected were entered in Microsoft Excel (MS Excel). Data were analyzed using SPSS 21.0 version. Intention-to-treat analysis was done. Proportion of children with resolution of active lesion and those with seizure recurrence were compared using Chi-square test or the Fischer exact test. Time to seizure recurrence were compared using the student '*t*' test or Wilcoxon rank sum test. A *P* value of <0.05 was considered significant.

RESULTS

A total of 65 children were enrolled (**Fig. 1**). The baseline demographic, clinical and radiological characteristics of enrolled children in both the groups were comparable. (**Table I**) The proportion of children with complete resolution, seizure recurrence and calcification on follow-up neuroimaging, were comparable between the groups. However, the mean (SD) duration to seizure recurrence was significantly longer with 14-day treatment [46.4 (7.9) days] as compared to 28 days treatment [22.5 (14.9) days]; (*P*=0.03) (**Table II**). There were no reported clinical adverse events in both the groups. Predictors for calcification of lesion like age, duration of albendazole therapy and number

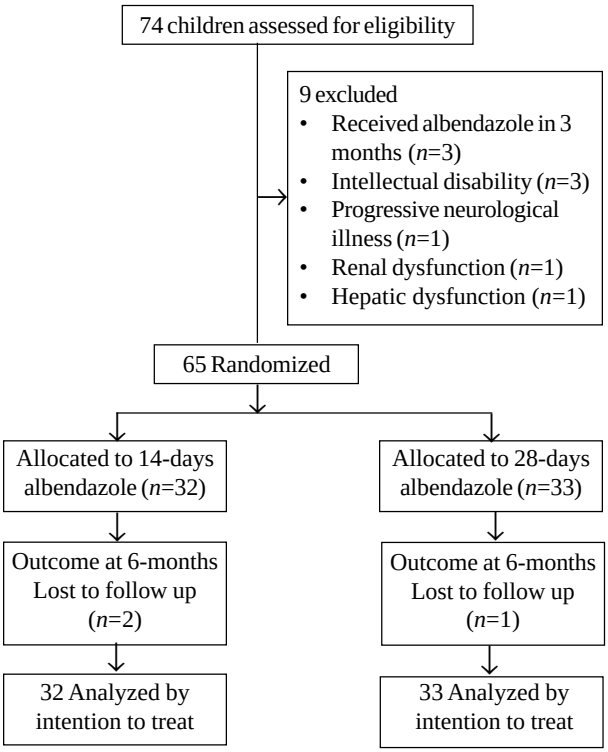

Fig. 1 Study flow chart.

Table I Characteristics of Children With Neurocysticercosis Treated With Two Albendazole Regimens (*N*= 65)

Characteristics	*14-days group (n=32)*	*28-days group (n=33)*
Age[a]	8 (6.5, 11)	7 (4, 10)
Male gender	21 (65.6)	19 (57.6)
Type of seizure		
Primary generalized	10 (31.2)	7 (21.2)
Focal with awareness	16 (50)	22 (66.7)
Secondary generalized	5 (15.6)	2 (6.1)
Focal without awareness	1 (3.1)	2 (6.1)
Seizure duration (min)[a]	8 (4.7, 18.5)	10 (5, 20)
Seizure frequency[a,b]	1 (1, 1)	2 (1, 3)
Seizure-therapy interval (d)[a,c]	7.5 (3, 26)	13 (2, 144)
Predominant lobe involved		
Frontal	10 (31.3)	6 (18.2)
Parietal	17 (53.1)	23 (69.7)
Occipital	2 (6.3)	1 (3)
Temporal	3 (9)	3 (9.1)
Number of lesion[d]		
One	26 (81.2)	28 (84.8)
Two	5 (15.6)	4 (15.1)
Anti-seizure medication		
Phenytoin	16 (50)	19 (57.6)
Valproate	13 (39.6)	10 (30.2)
Carbamazepine	3 (9.4)	2 (6.1)
Levetriacetam	0	2 (6.1)

Values are expressed as no. (%) or [a]median (IQR). All P>0.05. [b]before therapy; [c]Interval between seizure and initiation of therapy; [d]three lesions in 1 child in each group.

of lesions, were assessed by logistic regression analysis for possible association. None of these variables could independently predict the development of calcification.

DISCUSSION

This randomized controlled trial revealed comparable rates of complete resolution of lesion and proportion of children developing calcification between children receiving 14-days and those receiving 28-days of albendazole therapy. We found that that only 18.7% (*n*=6) children in 14-days treatment group and 27.3% (*n*=9) in 28-days treatment group had complete resolution of the lesion, while all the remaining children developed calcification of lesion at 6-month follow up.

Traditionally, neurocysticercosis has been treated with 28 days of albendazole therapy and many of the studies have demonstrated 31-91% resolution of lesion at 6 months [11-13]. The few studies that have looked for resolution of lesion at 3-4 months have demonstrated 75-91% of resolution [6,14]. Type of neuroimaging (MRI or CT), and timing of neuroimaging plays a crucial role in deciding the resolution of lesion. In a study by Singhi, et al. [15], 42% and 39% of patients had resolution at 1 month follow up and 77% and 79% at 3 months follow up, when treated with 1 week and 4 weeks of albendazole, respectively. Complete resolution of lesion with 28-day albendazole therapy was seen in 27.3% in our study as compared to 75-91% resolution seen in previous Indian studies, at 3-6 months follow up [11,12,15]. In contrast, majority of our patients had calcification of the lesion rather than complete reso-lution. Presence of one or more than one active NCC lesion, presence of perilesional edema, time lag between clinical presentation and treatment initiation could be some of possible factors for lower rates of resolution and higher rates of calcification in the present study. Variable period of follow-up and variation in the choice of neuroimaging in previous studies could possibly contribute to this wide discrepancy.

In a study by Kaur, et al. [16], incidence of seizure recurrence was 9.6% and 3.4% at 6-month follow up in 7-day and 28-day albendazole group, respectively. Though, seizure recurrence in our study was comparable to previous studies, long term follow up would have answered the risk of epilepsy, especially with three-fourth of the lesions calcifying.

Calcified neurocysticercosis has an important role in pathogenesis of seizure and resulting morbidity in neurocysticercosis. In a study from Peru, 220 patients with parenchymal neurocysticercosis from three randomized controlled trials were assessed and it was observed that 38% of these patients had calcification of lesion [17]. They observed that predictors of calcification included those where the cyst size is larger than 14mm, cysts with perilesional edema, patient with seizure recurrence beyond 24 months, and those who received higher dose of

Table II Outcome Among Enrolled Patients in 14-Days and 28-Days Albendazole Treatment Arms (*N*=65)

Outcome measure	*14-days group (n=32)*	*28-days group (n=33)*	*OR (95% CI)*	*P value*
Complete resolution	6 (18.8)	9 (27.3)	0.61 (0.19-1.98)	0.56
Seizure recurrence	5 (15.6)	2 (6.1)	2.87 (0.51-16.0)	0.18
Time to seizure recurrence (d)[a]	46.4 (7.9)	22.5 (14.9)	–	0.03
Calcification	26 (81.2)	23 (69.7)	1.88 (0.59-5.99)	0.39

Values are expressed as no. (%) or [a]mean (SD).

WHAT IS ALREADY KNOWN?

- There is robust evidence for albendazole therapy in neurocysticercosis but not on the duration of therapy.

WHAT THIS STUDY ADDS?

- 14-day treatment with albendazole is as effective as 28-day treatment in achieving radiological resolution at six-month follow up.

albendazole regimen. In the present study, rates of calcification were comparable between the two groups and none of the variables predicted the rates of calcification.

Limitations of the study include small sample size, underpowered owing to convenience sampling. Other limitations include unmasked inter-ventions, lack of serial scans at one-to-three month interval, non-measurement of size of neurocysticercosis lesion, and recording only parent reported adverse effect profile with no laboratory monitoring. A longer follow-up, beyond 6 months could have predicted the risk of seizure recurrences.

Fourteen-day albendazole therapy was found to be safe and effective therapeutic option among children with three or less than three lesions with proportion of children achieving resolution of lesion, being comparable to those receiving 28 days therapy. These preliminary findings may support the existing revised guidelines advocating 14 days treatment for single active neurocysticercosis. However, high rate of calcification noted in the present study in both the groups indicates need for further evaluation with an adequately powered study and long-term follow-up, before 14-day albendazole treatment can replace 28-day albendazole treatment of neurocysticercosis in children.

Ethics clearance: An institutional ethical approval was obtained before the commencement of the study.
Contributors: JSK, NDV, SL, SD: concept and design of the study; AS, NDV, JSK: drafting the manuscript and review of literature; JSK, SD, SL: critical review of the manuscript for intellectual content and final approval of the version to be published. All authors approve of the final version.
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