Original Article

Albendazole and praziquantel combination versus albendazole alone in children with multiple neurocysticercosis: An open labelled randomized controlled trial

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Abstract

Context: The efficacy of the combination of albendazole and praziquantel has not been thoroughly studied in multiple neurocysticercosis in children. **Objective:** To compare the efficacy and safety of albendazole and praziquantel combination versus albendazole alone in the treatment of children with multiple neurocysticercosis in terms of proportion of cysts undergoing complete resolution or calcification at 6-month follow-up. **Materials and Methods:** A total of 52 children, aged 1–14 years, with newly diagnosed two or more active neurocysticercosis were randomized to either group A or B. Group A (n = 26) received albendazole plus praziquantel, and Group B (n = 26) received albendazole alone. At the end of 6 months, a repeat MRI brain was performed to see for the resolution of cysts and was classified as complete resolution, calcified, or persistence of viable and noncalcified cysts. **Results:** The proportion of cysts undergoing complete resolution was higher in Group A (23/60 [38.33%]) than in Group B (19/65 [29.23%]), but the difference was not statistically significant. The proportion of cysts undergoing calcification was also comparable in Group A (20/60 [33.33%]) and Group B (20/65 [30.77%]). Both groups had comparable safety profiles. **Conclusion:** Albendazole and praziquantel combination therapy is as effective as albendazole alone in terms of complete resolution of viable cysts and calcification of cysts.
Trial registration: CTRI/2021/12/038492.

Keywords: Albendazole, neurocysticercosis, praziquantel

Introduction

Neurocysticercosis (NCC) is a common parasitic infestation of the central nervous system. According to the World Health Organization (WHO), it is possibly the most common risk factor for acquired epilepsy worldwide.[1] It refers to infection of the human brain by the larval stage of the helminth *Taenia solium*. Taeniasis is caused by the consumption of cysticercosis-infected pork but can occur in vegetarians too by eating raw vegetables.[2] The disease is widely prevalent in low and middle-income countries and in developed countries too, due to the immigrants from endemic areas and international travellers.[3,4] It is a major cause of epilepsy in the tropics and the most common cause of focal seizures in North Indian children. It is the most common identifiable cause worldwide of new-onset seizures.[5] A study conducted in Southern India among pediatric and adult populations with active epilepsy found that 34% of patients had NCC based on computed tomography and serology.[6] Around 17.3% of individuals had anticysticercus antibodies in a seroprevalence study conducted

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Received: 01-05-2023 **Revised:** 27-11-2023
Accepted: 01-12-2023 **Published:** 14-06-2024

Access this article online

Quick Response Code:

Website: http://journals.lww.com/JFMPC

DOI: 10.4103/jfmpc.jfmpc_733_23

How to cite this article: Rani V, Gehlawat VK, Arya V. Albendazole and praziquantel combination versus albendazole alone in children with multiple neurocysticercosis: An open labelled randomized controlled trial. J Family Med Prim Care 2024;13:2300-4.

in Northern India. Only 8% of the seropositive individuals had a history suggestive of NCC.[7] A study conducted in Northern India showed a 4.5% prevalence of NCC in children attending tertiary care hospitals presenting with acute focal neurological deficit or first episode of seizure.[8]

In a recent consensus statement of the Association of Child Neurology (AOCN), a combination of albendazole with praziquantel is recommended for multiple lesions.[9] The use of anticysticercal therapy is still controversial because of the observed spontaneous resolution of cysts.[10] Specific antiparasitic treatment uses either praziquantel (50 mg/kg/day for 15 days) or albendazole (15 mg/kg/day for 8–30 days).[11,12] However, only 30–40% of patients achieved complete parasite clearance after the first course of treatment.[13,14] Albendazole and praziquantel have different mechanisms of action.[15,16] Previous studies have shown a synergistic cysticidal effect of albendazole and praziquantel combination that was superior to albendazole monotherapy.[17] Considering the paucity of data on the efficacy and safety of albendazole and praziquantel combination therapy in children with NCC, the present study was conducted to compare this combination with albendazole alone in children with multiple NCC.

Materials and Methods

This study was an open-labelled randomized controlled trial (RCT) conducted in the department of pediatrics at a tertiary care centre in northern India from January 2022 to September 2022. The ethical clearance was obtained from the institutional ethics committee**.** The trial was registered in the Clinical Trial Registry of India (CTRI/2021/12/038492). Participants aged 1–14 years having multiple NCC were enrolled from pediatric wards after obtaining written informed consent from parent/legal guardians. Children with a single lesion or more than five lesions at diagnosis, with extraparenchymal lesions including intraocular or intraventricular NCC, with encephalopathy or signs of raised intracranial pressure, with intellectual disability, global developmental delay, or coexisting neurodegenerative/neurometabolic pathology, children with renal, pulmonary, cardiac or hepatic dysfunction or who had received antiparasitic drugs in preceding 3 months were excluded from the study.

Baseline data, including demographic details, history and examination, were recorded according to a preset proforma. Type, duration of seizure, dietary pattern, perinatal details, family history, developmental status, and treatment history, including number, nature, duration, and dosage of antiseizure medications, were noted. Magnetic resonance imaging (MRI) findings, including the number and location of NCC and the status of perilesional edema, were recorded in the case record form.

Eligible children were randomized using computer-generated random number tables in either of the two groups. Group A received albendazole (15 mg/kg/day, maximum up to 800 mg/d) for 28 days and praziquantel (50 mg/kg/d) for 14 days, and Group B received albendazole (15 mg/kg/day maximum up to 800 mg/d) for 28 days. Children of both groups were given a short course of oral dexamethasone (0.6 mg/kg/day in 3 divided doses) for 5–7 days, which was started 2 days before starting the antiparasitic therapy. Antiepileptic drugs (phenytoin, sodium valproate or carbamazepine) were also given for seizure prophylaxis as per the availability in the hospital and treating unit protocol.

All children were followed up twice weekly for the initial 4 weeks, then monthly for the next 5 months. All parents were given a contact phone number and were advised to report immediately if the seizure recurred. At each visit, all children were evaluated for seizure recurrence, change in seizure type, development of raised intracranial pressure, appearance of any neurologic abnormality, focal neurologic deficit, compliance to therapy and its related complications.

At the end of 6 months, an MRI brain was repeated to assess the proportion of patients with completely resolved viable and noncalcified cysts, reduction in the number of viable cysts and cysts undergoing calcification. The need for a second course of the same antiparasitic treatment was decided as per repeat MRI findings. The proportion of patients who had seizure recurrence, along with the median time of its recurrence, was recorded.

All data collected were entered in Microsoft Excel (MS Excel). Data were analyzed using the Statistical Package for the Social

Table 1: Baseline parameters of children in the 2 study groups

Characteristics	Group A (*n*=26)	Group B (*n*=26)
Age[a]	7 (2,13)	8 (2,13)
Male gender	17 (65.3)	10 (38.4)
Type of seizure		
Primary generalized	8 (30.7)	6 (23)
Focal with awareness	14 (53.8)	15 (57.6)
Secondary generalized	3 (11.5)	3 (11.5)
Focal without awareness	1 (3.8)	2 (7.6)
Seizure duration (min)[a]	8.5 (5,14.2)	10 (4.2,21.5)
Seizure frequency[a,b]	1 (1,2)	2 (1,2)
Predominant lobe involved		
Frontal	2 (7.6)	4 (15.3)
Parietal	14 (53.8)	10 (38.4)
Occipital	1 (3.8)	0 (0)
Temporal	4 (15.3)	3 (11.5)
Number of viable cysts		
Two	21 (80.7)	18 (69.2)
Three	2 (7.69)	3 (11.5)
Four	3 (11.5)	5 (19.2)
Total number of viable cysts	60	65
Antiseizure medication		
Phenytion	14 (53)	14 (53)
Valproate	8 (30)	8 (30)
Carbamazepine	2 (8)	3 (12)
Levetiracetam	2 (8)	1 (4)

Values are expressed as *n* (%) or [a]median (interquartile range [IQR]). All $P>0.05$. [b]before therapy

Sciences (SPSS) 21.0 version. The proportion of cysts undergoing complete resolution or calcification and children with seizure recurrence were compared using the Chi-square test or the Fischer exact test. A *P* value of < 0.05 was considered significant.

Results

A total of 52 children were enrolled [Figure 1]. The baseline demographic data, clinical characteristics, and radiological findings, including the number of viable cysts per patient, were comparable in both groups [Table 1]. Only one child in Group A was lost to follow-up, and the data were analysed by intention to treat. The proportion of viable cysts undergoing complete resolution and the proportion of viable cysts getting calcified at 6-month MRI were comparable in both groups [Tables 2 and 3]. None of the patients had complete resolution of all the cysts. Two (7.69%) patients in Group A had seizure recurrence in the next 6 months as compared to 3 (11.54%) in Group B. The difference in seizure recurrence in both groups was also statistically insignificant. No adverse drug reaction was observed in either of the groups during the study period.

Discussion

The present study has shown that the complete resolution of cysts and calcification of cysts was comparable in both the albendazole and praziquantel group and the albendazole alone group. On MRI performed at 6 months, in the albendazole + praziquantel group, a total of 38.33% cysts were completely resolved, and in the albendazole alone group, 29.23% cysts were completely resolved. We found that a total of 33.33% of cysts were calcified in the albendazole + praziquantel group, and 30.77% of cysts were calcified in the albendazole alone group.

Traditionally, multiple NCC has been treated with albendazole alone for a duration of 28 days, and up to 31–91% of lesion resolve within 6 months.[18] The current recommendations suggest the use of albendazole (15 mg/kg/d) and praziquantel (50 mg/kg/d) for 10–14 days for more than two viable cysts. In the study conducted by Garcia *et al.* (2014)[19] among adult patients with NCC, the proportion of patients with complete cyst resolution in MRI at 6 months was significantly higher, that is, 64% in the albendazole (ABZ) + praziquantel (PZQ) combination group as compared to 37% in the standard ABZ group ($P = 0.014$). In the same study no significant difference was found ($P = 0.792$) in seizure frequency in 180 days after starting dual therapy (46%) versus albendazole monotherapy (39%). The Garcia *et al.* (2016)[20] study also concluded that complete cyst clearance was higher in the ABZ+PZQ group (75%) as compared to those in the ABZ group (25%), no serious side effects were found within the entire study population. Guo *et al.*[21] (2003) also reported higher cysticidal efficacy in 90 patients in the albendazole and praziquantel group. Kaur *et al.*[17] evaluated the efficacy and safety of albendazole (15 mg/kg/day for 7 days) combined with a single dose of praziquantel (75 mg/kg/day on day 1) versus albendazole alone in children with single lesion NCC and they found higher

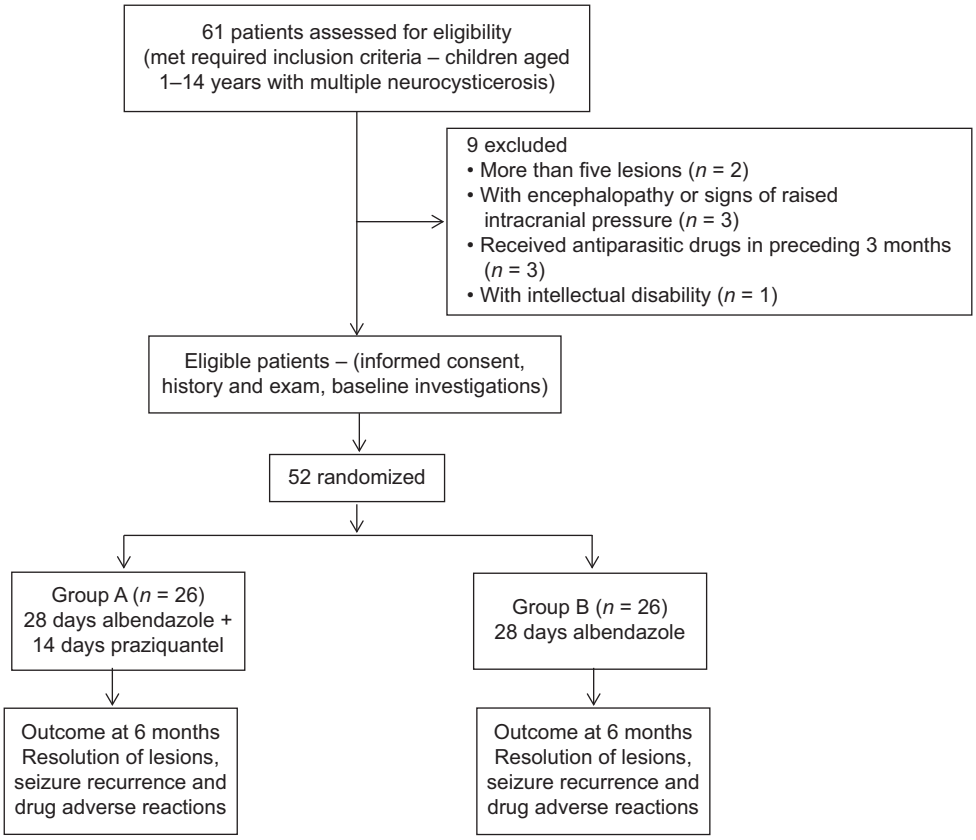

Figure 1: Study flow chart

Table 2: Number of cysts completely resolved in ABZ + PZQ and ABZ alone groups in MRI performed at 6 months

Number of cysts completely resolved per patient	ABZ + PZQ (*n*=26)	ABZ alone (*n*=26)	*P*
0	10 (38.46%)	8 (30.77%)	0.028*
1	9 (34.62%)	17 (65.38%)	
2	7 (26.92%)	1 (3.85%)	
Total	26 (100%)	26 (100%)	
Total Number of cysts completely resolved	23/60 (38.33%)	19/65 (29.23%)	0.282†

ABZ=Albendazole, MRI=Magnetic resonance imaging, PZQ=Praziquantel

Table 3: Number of cysts that got calcified in ABZ + PZQ and ABZ alone groups in MRI performed at 6 months

Number of cysts getting calcified per patient	ABZ + PZQ (*n*=26)	ABZ alone (*n*=26)	*P*
0	9 (34.62%)	9 (34.62%)	1*
1	14 (53.85%)	14 (53.85%)	
2	3 (11.54%)	3 (11.54%)	
Total	26 (100%)	26 (100%)	
Total Number of cysts that got calcified	20/60 (33.33%)	20/65 (30.77%)	0.282†

ABZ=Albendazole, MRI=Magnetic resonance imaging, PZQ=Praziquantel

complete resolution of lesions with the combination therapy. However, the differences were not statistically significant.

In the present study, no significant adverse effects were observed in both groups. Kaur *et al.*[17] found that both ABZ and PZQ were well tolerated in the study population. However, three children in the ABZ + PZQ group and two in the ABZ group developed headaches on days 3 to 4 of treatment, which lasted for 1 to 2 days.

In the pathogenesis of seizure and morbidity related to seizure in NCC, the calcified lesion has an important role. In a study conducted by Bustos *et al.*[22] in 2021, 220 patients with parenchymal NCC from three RCTs were assessed, and they concluded that calcification of lesions was observed in 38% of patients. The predictors of calcification included were those with cyst size more than 14 mm, presence of perilesional edema, patients with recurrence of seizure beyond 24 months, and patients who received a high dose of albendazole regimen. In the present study, the proportion of calcification was comparable in both groups, although predictors of calcification were not evaluated.

The strength of the present study includes a robust study design, which provides credibility to our result. The present study was an open-labelled RCT. RCTs provide the highest level of evidence. The inclusion of a homogenous population with all patients who had multiple (2–5) cysticercus lesions increased the external validity of the study. To allow the comparability of results with other studies, standard outcome parameters were chosen as per previous studies. A sufficient follow-up of 6 months, minimal follow-up losses and performance of repeat imaging on all who followed up were some of the other strengths of the present study. This study is of high relevance for the practice of primary care providers and family physicians as NCC is a major cause of epilepsy in the Indian population; both pediatric as well as adult and primary care providers should be well versed with the treatment guidelines and updates.

Limitations of the present study include a small sample size and the inability to mask the interventions. Hence, the results of the present study need to be interpreted in the context of limited sample size. We followed patients for a period of 6 months; a longer follow-up could have predicted the risk of seizure recurrences and epilepsy.

Conclusion

In the present study, no child had shown complete resolution of all viable and noncalcified cysts at 6 months follow up. Although the complete resolution of cysts and calcification of cysts was higher in the albendazole + praziquantel group, no statistically significant difference was found between the groups. Both groups had comparable safety profile and no adverse drug reaction was observed in either of the group during the study period. Further studies with larger sample sizes and longer follow-up periods are required to extrapolate this result to a larger population.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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