THREE DAY ALBENDAZOLE THERAPY IN PATIENTS WITH A SOLITARY CYSTICERCUS GRANULOMA: A RANDOMIZED DOUBLE BLIND PLACEBO CONTROLLED STUDY

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Abstract. A solitary cysticercus granuloma is a benign form of neurocysticercosis. Several reports have suggested albendazole is effective in early resolution of these lesions. A short duration (7 days) albendazole therapy has been found to be effective in treatment. In this study, we evaluated a "three day course" of albendazole in a prospective randomized double- blind trial. Sixty-seven consecutive patients who presented with new-onset seizures and a solitary cysticercus granuloma were randomly allocated to receive either albendazole (15 mg/kg/day for 3 days) or placebo. All patients were treated with antiepileptic drugs. Patients were followed up for 6 months. A repeat CT of the brain was obtained at the end of 6 months of follow-up. The end points were complete resolution of the lesion on CT scan and total seizure control at 6 months follow-up. In the albendazole group complete resolution of lesions was noted in 28 of 33 patients (84.8%), while in the control group only 14 of 34 patients (41.2%) had complete resolution of the lesion (p=0.001). Partial resolution of lesion was seen in 2 patients (6%) in the albendazole group and 4 patients (11.8%) in the control group (p=0.06). The lesion remained unchanged in 9 cases (26.5%) in the control group only. The lesion became calcified in 7(20.6%) and 3(9.1%) patients in the control and albendazole groups, respectively (p=0.187). Seizure recurrence occurred in 3 patients (9.1%) in the albendazole and 1 patient (2.9%) in the control group (p=0.239). The three days course of albendazole was effective in resolving lesions, but there was no significant difference in seizure recurrence rates between the two treatment groups.

Key words: solitary cysticercus granuloma, antiepileptic drug, neurocysticercosis, albendazole

INTRODUCTION

In India, solitary cysticercus granulomas are a common cause of new-onset seizures. Albendazole has been found to be effective in the treatment of such lesion since it hastens their resolution (Garcia *et al*, 2004; Nash *et al*, 2006). Several papers have reported varying duration of albendazole therapy in patients with solitary cysticercus granulomas, with treatments lasting from several days to 1 month,

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with almost similar results (Alarcón *et al*, 1989; Padma *et al*, 1994; Baranwal *et al*, 1998; Alarcón *et al*, 2001; Del Brutto *et al*, 2006; Thussu *et al*, 2008). In this study we have evaluated an ultra-short (three day) course of albendazole therapy.

MATERIALS AND METHODS

Patient population

This study was conducted from November 2007 to October 2008 at the Department of Neurology, Chhatrapati Shahuji Maharaj Medical University, Uttar Pradesh, Lucknow. This is a tertiary medical referral center in the North-Central part of India.

The study population was comprised of patients with new-onset seizures (less than 2 weeks) with solitary cysticercus granulomas in the brain. We did not include patients with other forms of parenchymal (*eg*, cystic) or extra-parenchymal cerebral forms, (*eg*, intraventricular) of neurocysticercosis. In this study 70 consecutive patients were evaluated. Three patients did not give consent to participate in the study, so were not included. The remaining 67 patients were included in the study (Fig 1).

All patients fulfilled the diagnostic criteria of having a solitary cysticercus granuloma. Diagnosis of neurocysticercosis was based on international diagnostic criteria (Del Brutto *et al*, 2001) and Indian criteria for solitary cysticercus granulomas (Rajshekhar *et al*, 1993; Rajshekhar and Chandy, 1997) (Table 1 and Table 2). Written informed consent (from the patient or their legal guardian) was obtained after explaining the procedure and the purpose of the study. The Institutional Ethics Committee approved the study.

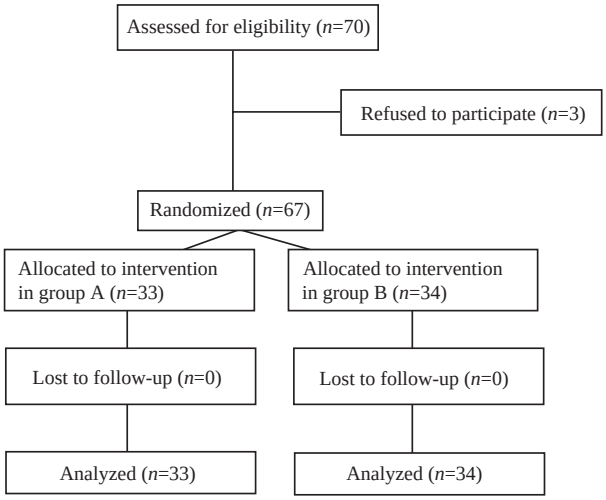


Fig 1–Study flow chart.

Sample size calculation and randomization

A sample size of 33 for each group was determined (90% power for a difference of approximately 20% in the lesion resolution rate between the albendazole and control groups at a significance level of $p<0.05$). Randomization was done after inclusion, with the help of a random number table, into two groups: the albendazole group and a control group.

Initial evaluation

A detailed history was obtained from each patient or an eyewitness. A clinical examination was performed at the time of enrollment and during monthly follow-ups. Patients were followed for 6 months. Seizures were classified according to the classification proposed by the International League against Epilepsy (ILAE). All patients had the following tests performed: complete blood count, erythrocyte sedimentation rate, blood sugar, blood urea nitrogen, creatinine, Mantoux test, chest radiograph and an electroencephalography (EEG) at the time of enrollment. Enzyme-linked immunosorbent assays (ELISA) for

Table 1
Inclusion criteria for solitary cysticercus granuloma and exclusion criteria for the study (Rajshekhar *et al*, 1993; Rajshekhar and Chandy, 1997).

Inclusion criteria

Clinical criteria

1) Patients with new onset seizures of ≤ 2 weeks duration.
2) Minimal or no neurological deficit.
3) No evidence of raised intracranial pressure.

Computed tomographic criteria

1) Solitary contrast enhancing lesion in of the brain.
2) Lesions less than 20mm in diameter.
3) Absence of severe cerebral edema (no midline shift).

Exclusion criteria

1) Patients already or in between received antiparasitic drug or steroids.
2) Patients with systemic diseases such as pulmonary tuberculosis, renal failure or symptomatic secondary epilepsies.

Table 2
International diagnostic criteria for neurocysticercosis (Del Brutto *et al*, 2001).

Absolute

1. Histologic demonstration of the parasite.
2. Cystic lesions showing the scolex on CT or MRI.
3. Direct visualization of subretinal parasites.

Major

1. Lesions highly suggestive of neurocysticercosis.
2. Positive serum EITB.
3. Resolution of cystic lesions after therapy.
4. Spontaneous resolution of single enhancing lesions.

Minor

1. Lesions compatible with neurocysticercosis.
2. Suggestive clinical manifestations.
3. Positive CSF ELISA.
4. Cysticercosis outside the CNS.

Epidemiologic

1. Household contacts.
2. Individuals coming from or living in an endemic areas.
3. Frequent travel to endemic areas.

Definitive

Presence of one absolute criterion .
Presence of two major plus one minor and one epidemiologic criterion.

Probable

Presence of one major plus two minor criteria.
Presence of one major plus one minor and one epidemiologic criterion.
Presence of three minor plus one epidemiologic criterion.

human immunodeficiency virus (HIV) was performed on each patient, none of the patients were HIV positive. Serological tests for neurocysticercosis were not performed.

Treatment

Albendazole was administered orally at a dosage of 15 mg/kg body weight in two divided doses per day for 3 days. Patients were told there was an equal chance to receive albendazole or placebo. Albendazole and placebo tablets were identical in appearance. The blinding was removed after 6 months. Bottles marked-A contained albendazole, bottles marked-B contained placebo tablets. Thirty-three patients received albendazole and 34 patients received placebo (control group).

All patients were treated with antiepileptic drugs (sodium phenytoin, carbamazepine or oxcarbazepine) at a dose appropriate for their body weight. In situations of antiepileptic drug toxicity, appropriate dose adjustments or drug replacements were made. Antiepileptic drug levels were not performed. The end points of the study were complete resolution of the lesions on CT scan and the absence of seizures after 6 months of follow-up.

Neuroimaging

A contrast enhanced computed tomography (CT) scan of the head was performed on a single slice spiral CT scanner (General Electric, USA) using 5 mm axial sections. The CT scan was done at the time of inclusion in the study and at 6 months. A follow-up CT scan was performed with the same machine with cuts taken at the same levels, to reduce the chances of missing a lesion. All CT scans were examined by a radiologist who was blinded to the treatment arms.

Follow-up

The patients maintained a diary of seizure recurrences and adverse effects of the drugs and brought this to each follow-up. They were also instructed to report immediately if there was persistence or development of new symptoms of raised intracranial pressure or progression of neurological deficits.

Statistical analysis

Data were described as proportions for categorical variables, mean (±SD) and medians for continuous variables. The analysis was done using Pearson and chi-square statistics for categorical observations and the *t*-test to compare continuous variables with normal distribution; unequal variances were adjusted. In case of non-normal distribution and/or graded data the Wilcoxon rank-sum (Mann-Whitney) test was used to test for significance between two groups, and the Wilcoxon sign rank test was used to check for significance within the treatment group. The data were analyzed using the statistical package Stata 9.2, College Station, Texas, USA. A p-value<0.05 was considered significant.

RESULTS

Patient characteristics

The treatment groups were comparable in all respects. Sixty-seven patients (43 males and 23 females) completed the study. The age of the patients ranged from 4.5 to 45 years. The mean age was 18.05 ± 10.28 years in the albendazole group and 15.99 ± 8.36 in the control group. The mean durations between onset of seizures and enrollment in the albendazole and control groups were 7.55 ± 4.56 and 8.32±4.24 days, respectively (Table 3).

Seizure characteristics

Forty-one patients (61.2%) had partial seizures with secondary generalization,

Table 3
Clinical characteristics of patients with solitary cysticercus granulomas.

Variables	Albendazole (*n*=33)	Control (*n*=34)	Total % (*n*=67)
Age of onset (years) (Mean±SD)	18.05±10.28	15.99±8.36	
Sex			
Male	23	20	43 (64.2)
Female	10	14	24 (35.8)
Duration of illness (Days) (Mean±SD)	7.55±4.56	8.32±4.24	
Types of seizures			
Simple partial	7	8	15 (22.4)
Complex partial	0	4	4 (6.0)
Partial with generalization	22	19	41 (61.2)
Generalized	4	3	7 (10.5)
Seizure pattern			
Single	14	9	23 (34.3)
Multiple	16	21	37 (55.2)
Cluster	3	4	7 (10.5)
Todd's palsy	6	3	9 (13.4)

15 had simple partial seizures and 7 had primary generalized tonic clonic seizures. Thirty-seven patients (55.2%) presented with multiple seizures and 7 patients (10.5%) with seizures in clusters. Other features, such as headaches and Todd's palsy, were seen in 14 (21%) and 9 (13.5%) of patients, respectively (Table 3). Twenty patients had abnormal electroencephalography.

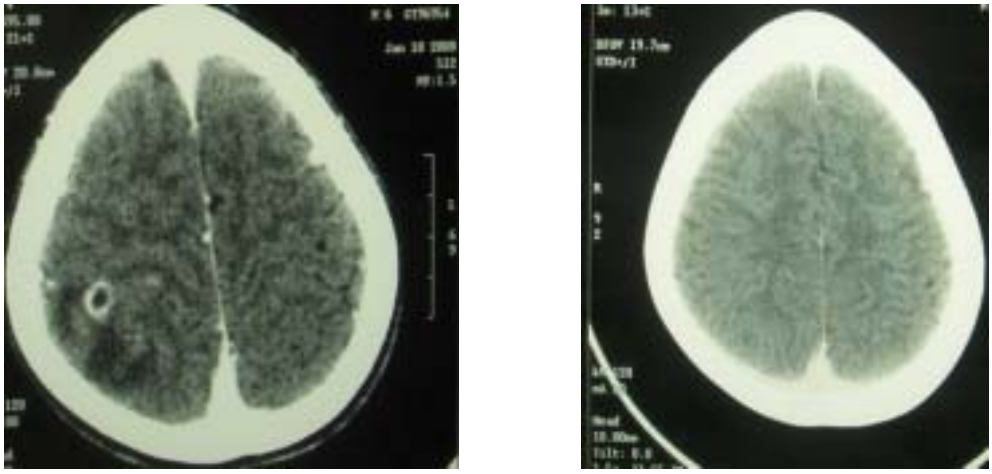
Radiological features

The most common site of solitary cysticercus granuloma was the parietal lobe (53 cases; 79%) followed by the frontal lobe (9 cases; 13.4%). In 44 cases (66%), lesions were of ring enhancing type with or without eccentric dots, followed by 15 cases (22.4%) in which lesions were of the disc enhancing type. All patients had perilesional edema. The mean size of lesions was 9.0±1.8 mm in the albendazole group and 8.3±2.6 mm in the control group. The largest lesion was 14 mm diameter (Table 4). No significant differences were observed in any of the imaging parameters between the albendazole group and the control group.

Lesion disappearance

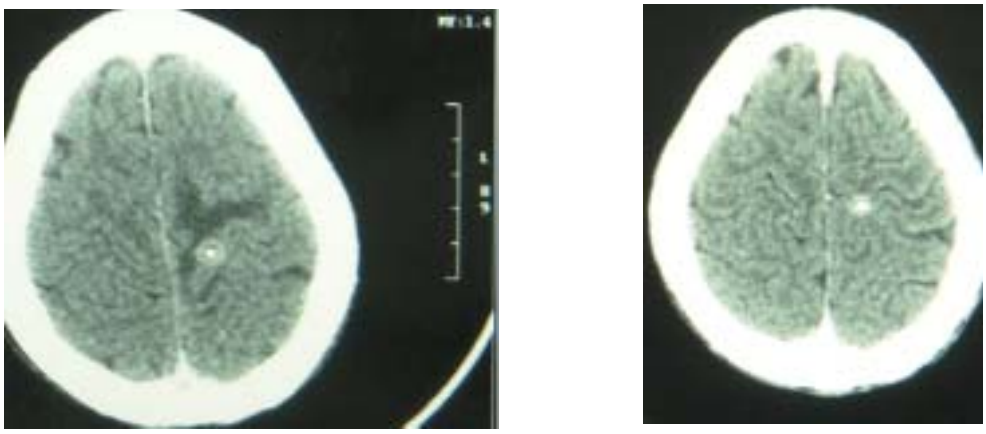
A repeat CT scan of the head, at 6 months showed a disappearance of lesions in 28 of 33 patients (84.85%) in the albendazole group and 14 of 34 patients (41.18%) in the control group. This difference was statistically significant ($p < 0.001$) (Fig 2).

Partial resolution of the lesions was seen in 2 of 33 (6.1%) and 4 of 34 cases (11.8%) in the albendazole and control groups, respectively (p=0.06). Lesions persisted unchanged in 9 patients (26.5%) in the control group only (p=0.02). Lesion calcification was seen in 3 patients (9.1%) in the albendazole group and 7 patients (20.6%) in the control group (p=0.187) (Fig 3). The overall outcome in terms of disappearance (complete resolution)



(a) (b)

Fig 2–Cranial computed tomography showing: (a) a ring enhancing lesion; (b) complete disappearance of the lesion after 6 months.



(a) (b)

Fig 3–Cranial computed tomography showing: (a) a ring enhancing lesion; (b) CT scan after 6 months showing calcification of the lesion.

was approximately twice as high in the albendazole group as in the control group; the difference was statistically significant ($p \leq 0.001$).

Seizure outcome

Overall, seizure recurrence was seen in 3 patients (9.1%) in the albendazole and 1patient (2.9%) in the control group; this difference was not statistically significant (p=0.239).

Side effects

One patient had carbamazepine induced a rash which subsided after removal of the offending drug.

DISCUSSION

Rajshekhar (2001) studied the rate of spontaneous lesion resolution in 210 patients and found only 18% of granulomas

Table 4
Imaging characteristics of solitary cysticercus granulomas.

Variables	Albendazole (*n*=33)	Control (*n*=34)	Total % (*n*=67)
Site			
Parietal	27	26	53 (79.1)
Frontal	5	4	9 (13.4)
Temporal	0	1	1 (1.5)
Occipital	1	3	4 (6.0)
Lesion morphology[a]			
Ring	22	22	44 (65.7)
Disc	8	7	15 (22.4)
Target	3	5	8 (11.9)
Size of lesions (mm)	9.03±1.81	8.26±2.64	

[a]According to enhancement pattern on computed tomography

had spontaneously resolved by 3 months, and 67% by 1 year. Several studies of anticysticidal therapy have been found effective in producing early resolution of solitary cysticercus granulomas (Baranwal *et al*, 1998; Garcia *et al*, 2004; Nash *et al*, 2006; Thussu *et al*, 2008). In our study we demonstrated even a three day treatment of albendazole was equally effective in patients with a solitary cysticercus granuloma. Albendazole produced complete resolution of the lesions in significantly high proportions of patients.

The published literature suggests the role of anticysticidal therapy in the early resolution of solitary cysticercus granuloma and seizure recurrence has been variable. Out of published randomized double-blind studies, only 2 studies addressed similar treatment issues. In one study(Padma *et al*, 1994), the authors reported albendazole was not beneficial in terms of disappearance of lesions. The cause for this negative result might have been a long duration of symptoms before enrollment (mean ~11.4 months) and the loose definition of a positive outcome (intervention was considered successful even if only the edema surrounding the lesion diminished more than 25% on the CT scan). This explains the high rate of positive outcomes in their albendazole and placebo groups (94% and 77%, respectively). Another recent study(Thussu *et al*, 2008) showed a positive result in terms of early resolution of solitary cysticercus granulomas. They observed 95.6% resolution of lesions with albendazole and 70% resolution in the placebo group with a 2 week duration of treatment.

In addition to our study, several studies in the past have shown that even shorter duration of treatment is equally effective. Authors of one such study divided the patients into 3 arms: a 3day course, a 1week course and placebo. The resolution rates were 56, 67 and 7%, respectively. There were no statistically significant differences in outcome between those treated for 3 days and those treated for 1 week (Alarcón *et al*, 2001). Another study done by the same group of authors showed there was no statistically significant difference in outcome between those

treated for 3 days and those treated for 4 weeks with albendazole (Alarcón *et al*, 1989). A similar short duration treatment study done by Sotelo *et al* (1988) showed the effective role of albendazole over placebo.

In our study seizure recurrence was seen in 3 patients (9.1%) in the albendazole group and 1 patient (2.9%) in the control group; this difference was not statistically significant. Calcification was noted in 3 of 33 patients (9.1%) in the albendazole group and 7 of 34 patients (20.6%) in the control group (p=0.187). Clinical outcome is variable. Controlled trials suggests that in patients with single or multiple parenchymal brain enhancing lesions who present with a short duration of seizures had a better seizure outcome following cysticidal therapy than those who present with a longer duration of seizures and multiple cystic lesions (Carpio *et al*, 1995; Baranwal *et al*, 2001; Gogia *et al*, 2003; Garcia *et al*, 2004; Singhi *et al*, 2004).

In conclusion, this study has shown a three day course of albendazole therapy is associated with rapid resolution of solitary cysticercus granulomas, but there were no significant differences in seizure outcomes between the albendazole and control groups.

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