Efficacy of Albendazole and Short-Course Prednisolone Treatment in Children with One or Two Ring-Enhancing Lesions of Neurocysticercosis: A Randomized Controlled Trial

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Abstract

Context: Neurocysticercosis is a endemic disease in Nepal causing social and financial burden on society and developmental problem in children. Aims: To determine the efficacy of albendazole plus oral prednisolone in children with 1 or 2 ring-enhancing lesions (by CT) on resolution of lesions and recurrence of seizure. **Setting and Design**: Randomized controlled open trial. **Methods and Materials:** Children with 1 or 2 ring-enhancing lesions <20 mm in diameter on computed tomography scan, likely to have Neurocysticercosis, were assigned to treatment & control groups. Children assigned to the treatment group (n = 50) were given 2.0 mg/kg per day prednisolone orally for 5 days plus 15 mg/kg per day albendazole on third day for 28 days. Anti epileptic drugs were given to both groups {including Control group (n = 51)}. **Statistical Analysis:** The results were analysed with the use of Epi Info version 6.04 and Stata version;7 software. **Results:** The lesions resolved completely or partially in more children in the treated group compared with the control group (p = .04 & p = 0.03). The proportion of children who had seizures was significantly lower in the treated group compared with the control group at 6 months (10% versus 33%; p = .006) and 12 months (14% versus 38%; p = .003). **Conclusion:** Albendazole plus Prednisolone increased resolution of lesions on computed tomography scan and reduced the risk of subsequent recurrence of seizures among children with Neurocysticercosis.

Key words: Prednisolone, Albendazole, Neurocysticercosis and Children.

Introduction

In the developing world, Neurocysticercosis, infection of the central nervous system with Taenia solium larvae is the single most common cause of acquired epilepsy[1]. Inflammatory granulomas of the central nervous system are common in developing countries, where recent studies report that 26% to 72% of hitherto normal children with a first episode of seizure have a ring or disk enhancing lesion on computed tomography (CT)[2-8]. The anticysticercal treatment of single enhancing CT lesions, thought to represent dying cysticerci and thus expected to resolve spontaneously, has been controversial.[7, 9, 10, 11, 12., 13]. Additionally, there is also concern that cysticidal therapy may lead to an enhanced inflammatory response caused by release of larval antigens that can precipitate seizures[12, 14, 15]. On the contrary, there is some experience that Cysticidal therapy may lead to faster resolution of lesions and better seizure control[7, 16, 17, 18, 19]. Between the two randomized controlled trials that evaluated the efficacy of anticysticercal therapy in children with single enhancing lesions, one showed earlier resolution of CT lesions and lower seizure recurrence[20] whereas the other reported no benefit[21]. We conducted this randomized, controlled, open trial to determine the effect of albendazole plus prednisolone in children with seizures and 1 or 2 ring-enhancing lesions on resolution of the lesion as well as seizure recurrence.

Methods

This study was undertaken from January 2004 to May 2007. All patients of either sex, 1year to 14 years of age, with seizures and 1 or 2 ring-enhancing lesions <20 mm in diameter with or without perifocal oedema on CT scan at the Manipal Teaching Hospital, Pokhara, Nepal, were screened for selection in this study. Child and family characteristics and clinical data on type and frequency of seizures, anti-epileptic therapy, presence of interictal headache, vomiting, focal neurologic deficit, or any other neurologic symptoms were recorded on a prestructured questionnaire. Complete clinical assessment was done at the time of enrolment and each follow-up. The side effects of albendazole plus prednisolone treatment and its expected efficacy were explained to parents, and their agreement to let their children participate was obtained before enrolment.

A simple randomization scheme was used for allocation of patients to the treated or control groups. Random assignment code was concealed up to the time of allocation in sealed envelopes labelled with a unique patient number. These envelopes were opened sequentially after consent was obtained to enrol an eligible child. Children assigned to the treatment group were given 2mg/kg/day oral prednisolone for 5 days in 3 to 4 divided doses and 15 mg/kg per day oral albendazole as a single daily dose at night for 28 days,

starting on the third day of prednisolone. Children in the control group were not given prednisolone or albendazole.

Anti-epileptic therapy was given to both the study groups. If an anti-epileptic drug had been started before enrolment, it was continued in appropriate doses if seizures were controlled. Others were given Sodium Valproate in a dose of 15 - 25 mg/kg per day as twice a day dose. The dose was increased to 40 mg/kg per day if seizures recurred. None of the children required addition of a second anti-epileptic drug.

Children with evidence of tuberculosis by chest radiography, a positive Mantoux test, or a history of contact with a patient with tuberculosis were excluded. Children with intraocular cysts or with multiple lesions (>2), disk or calcified lesions, Intraventricular cysts, or hydrocephalus on CT scan were also excluded from the study. Children with neurological deficit, signs of increase intracranial pressure & papiloedema were also excluded from the study.

Follow-up and Outcome Variables

A single radiologist blinded to treatment assignment and to the clinical outcome performed evaluation of CT lesions at baseline and 6-month follow-up scans. The site, type, size of lesion and degree of perifocal oedema were recorded, along with any change compared with the previous scan. The effect of therapy on the CT lesions was categorized as beneficial if the lesions disappeared, were reduced in size by >50%, or were calcified

All patients were evaluated 15 days after enrolment for side effects of albendazole plus prednisolone, which included seizures, headache, vomiting, and visual problems. Recording the missed doses since last visit monitored adherence to treatment.

Study children were evaluated at 6 and 12 months after enrolment to determine efficacy of treatment. Data on recurrence, frequency, and type of seizures were recorded. Seizure recurrence was assessed on the basis of history from parents at the follow-up visits. Follow up was done every monthly up to 6 months and then 3 monthly up to 12 months of enrolment.

Statistical Analysis

The results were analyzed with the use of Epi Info version 6.04 and Stata version;7 software (Stata Corp, College Station, Tex). The proportions of children who had recurrence of seizures and improvement in the CT lesions in the treatment group were compared with those in the control group. Difference in proportions and their 95% confidence intervals are presented.

Results

Baseline characteristics

110 patients, out of whom parents of 9 patients refused to participate, met eligibility criteria. The remaining 101 children were randomly assigned to treatment (n = 50) and control groups (n = 51). The number of children lost to follow-up was similar in the two study groups: 2(4 %) and 6 (12 %) at 12 months follow-up. The two study groups were similar for most baseline characteristics (Table I) results for Neurocysticercosis. The majority (84%) of enrolled children had a single lesion on CT scan, and most (97%) had perifocal oedema. The characteristics of the lesion on CT scan were similar in both groups.

Table 1: Baseline Characteristics Of Patients In The Treatment (Albendazole Plus Prednisolone) And Control Groups.

Characteristics	Treatment Group(50)	Control Group(51)
Mean age in month	94	92
Males (%)	27(54)	28(55)
Types of seizures n (%)		
Generalized (%)	11(22)	10(20)
Partial (%)	37(74)	36(72)
Multiple (%)	1(2)	2(4)
Partial to generalized seizure (%)	1(2)	2(4)
Mean no. of seizure (SD)	2.6(2.9)	2.8(2.7)
Valproate therapy (%)	48(96)	46(90)
Headache (%)	22(44)	18(35)
Vomiting (%)	5(10)	3(6)
History of taking pork(%)	30(60)	28(55)
Lesions on CT		
Single (%)	41(82)	44(86)
Double (%)	9(18)	7(14)
Right side (%)	28(56)	24(47)
Left side (%)	22(44)	27(53)
Parietal lobe (%)	34(68)	31(61)
Frontal lobe (%)	13(26)	16(31)
Temporal lobe (%)	2(4)	3(6)
Occipital lobe (%)	1(2)	1(2)
Abnormal EEG (%)	13(26)	11(21.5)

Adverse effects during first two weeks of treatment

In the 15 days' follow-up after enrolment, the proportion of children with headache, vomiting, or visual problems were not significantly different between the two study groups. There was a trend toward decrease in seizures during the initial period of treatment in the albendazole plus prednisolone group compared with the control group (3.0% vs. 14.0%; p = .09).

Efficacy of albendazole plus prednisolone treatment

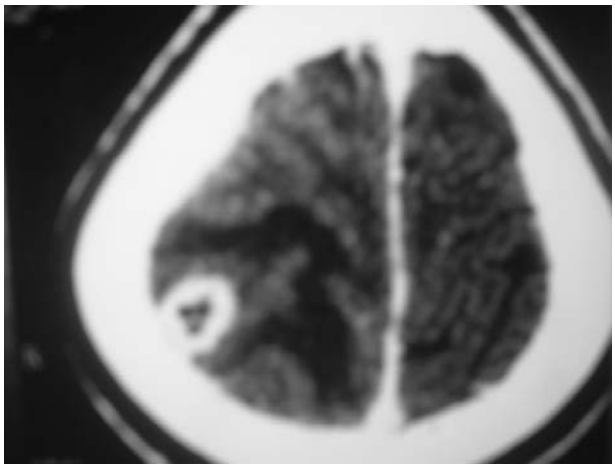
After the first CT scan, repeat CT scan at 6 months after enrolment could be obtained in 93 children (92.0%), after a mean duration of 178 (SD 34) days in the treatment group and 166(SD 36) days in the control group. Changes in CT scans after 6 months of treatment is depicted in Table-2 with p value. Total resolution, Partial resolution, calcification and no changes in lesions in CT scan both in the control & treatment group revealed significant difference in both total and partial resolution group only ($p< 0.05$).

Table 2: Comparison of Both the Control & Cases After 6 Months & 12 Months of Follow-Up.

Characteristics	Treatment group(48)	Control group(45)	Difference in proportions(95% CI)	*p*- value
CT findings after 6 months				
Complete resolution of lesion	14(29%)	9(20%)	9% (3% to 27%)	0.04
Partial resolution	20(41.5%)	7(15.5%)	26 %(9 to 38%)	0.03
Calcification of lesions	4(8.2%)	10(22.2%)	-14%(-24% to -6%)	0.06
No changes in lesion	10(20.8%)	19(42.2%)	-21%(-37%to-19%)	0.09
Incidence of seizure recurrences				
0-6 months post enrolment	5(10%)	15(33%)	- 23 %(- 35% to – 6%)	0.006
0-12 months post enrolment	7(14%)	17(38%)	-24%(- 38% to – 3%	0.003

Worsening of findings in the scan, defined as appearance of new lesions, was not seen in any treatment or control group. During the 6-month post enrolment period, a significant reduction was observed in seizure recurrence, when only 5 (10%) of children in the treatment group had any seizures compared with 17 (33%) children in the control group (p = 0.006). The proportion of children who had a seizure in the 12 months' follow-up period after enrolment was also significantly lower in the treatment group (14.0%vs38.0%, *p*= 0.003).

Fig 1: CT Scan With Contrast in a Child Showing Racemose Type of Neurocysticercosis.Fig



Discussion

The main findings of this study are that albendazole plus prednisolone significantly increased the complete or partial resolution of the CT lesion and reduced the risk of seizures during 12 months of follow-up in children who had seizures and 1 or 2 ring-enhancing lesions of Neurocysticercosis on CT scan. The other study conducted exclusively in children found cysticidal therapy to be beneficial in resolution of the lesion in children with single ring-enhancing lesions[20], our findings are consistent with this study.

Patients have clinical symptoms rather than an abnormal CT scan, and therefore some contend that an assessment of clinical outcome is a better measure of efficacy of treatment. As seizures are the most frequently occurring symptom, seizure recurrence may represent one clinical outcome that can be defined and quantified. After 12 months of follow-up in our study, a significantly higher proportion of patients in the control group had recurrence of seizures compared with the treated group (38.0% versus 14.0%; $p < 0.05$). The previous trial in children also reported a trend toward reduction in seizure recurrence (31% in placebo vs. 13% in the treated group), but this difference was not statistically significant[20]. Garg RK et al also reported a decrease in seizure recurrences in childhood Neurocysticercosis having 1 to 2 ring enhancing lesions (n=12% vs.=48%) in prednisolone treated group[22].

Some previous reports cited adverse reactions such as increased severity of seizures, worsening of pre-existing intracranial hypertension and even death during the initial period of treatment[17, 20]. However, we did not find higher incidence of seizures, headache, vomiting, or visual problems in the treated children during the initial twoweeks of therapy. One study from India also reported short-term prednisolone therapy helps in rapid resolution of solitary cysticercus granuloma in-patients with new-onset seizures and resolution of lesions is associated with improved seizure-related prognosis, which was similar to our study[23].

We do not believe that the lack of blinding of the treating physician or patient affected the results of this study, since one of our primary outcome variables lesion on CT scan-was evaluated by the radiologist, who was blinded to the treatment group and to clinical outcome.

Conclusion

In conclusion, albendazole plus prednisolone treatment in children with 1 or 2 ring-enhancing lesions on CT scan due to neurocysticercosis resulted in early resolution of CT lesions and less recurrence of seizures up to 12 months of follow-up. Multicenter studies with long-term follow-up are required to confirm these findings and determine the effect of cysticidal therapy on seizures beyond 12 months of therapy.

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