Impact of Albendazole Therapy on Clinical and Radiological Outcomes at One Month in Patients with Active Solitary Neurocysticercosis Patients

Bhattarai S, Thapa L, Maharjan AMS, Shrestha AM, Shrestha S, Ghimire MR, Upadhyaya S, Thapa M

Department of Neurology

Upendra Devkota Memorial National Institute of Neurological and Allied Sciences,

Bansbari, Kathmandu, Nepal.

Corresponding Author

Suman Bhattarai

Department of Neurology

Upendra Devkota Memorial National Institute of Neurological and Allied Sciences,

Bansbari, Kathmandu, Nepal.

E-mail: suman.bhattarai@hotmail.com

Citation

Bhattarai S, Thapa L, Maharjan AMS, Shrestha AM, Shrestha S, Ghimire MR, et al. Impact of Albendazole Therapy on Clinical and Radiological Outcomes at One Month in Patients with Active Solitary Neurocysticercosis Patients. *Kathmandu Univ Med J.* 2022;77(1):61-5.

ABSTRACT

Background

Cerebral neurocysticerosis is a common parasitic disease of human nervous system but evidence on duration of albendazole therapy and their outcomes in this condition is inadequate

Objective

To evaluate the impact of varying duration of albendazole therapy on the clinical and radiological outcomes at one month in patients with active solitary neurocysticercosis.

Method

This is an interventional study conducted at Upendra Devkota Memorial National Institute of Neurological and Allied sciences, Bansbari over 1 year (2017 March - 2018 February). One hundred eighteen patients with new onset seizure secondary to active solitary cysticercal granuloma either received albendazole therapy for 1, 3, 9 or 21 days with the usual care or only received the usual care. Clinical and radiological outcomes were observed at one month follow-up. The difference in the proportion of the outcome measures between intervention and control groups were assessed using chi-square test.

Result

Our study included 118 patients with male predominance of 61.9%. Albendazole therapy for 3, 9 and 21 days reduced headache by 57.2%, 70.0% and 63.1% respectively which was higher than those with 1-day therapy or without the therapy. This difference in the proportion was statistically significant at p=0.001. Though seizure recurrence also declined but the difference was not significant (p=0.406) between groups. However, at one-month follow-up, majority of patients who received albendazole for 9 days (14, 70%) and 21 days (14, 73.7%) had normal lesion, while most calcified lesion (21, 67.7%) was observed in those who did not receive albendazole therapy. The difference between lesion among the groups was significant ($p < 0.001$).

Conclusion

Albendazole therapy in patients with active solitary neurocysticercosis for 9 days is as effective as 21 days and better than 3 days in headache control and lesion dissolution but seizure control could be achieved irrespective of the treatment.

KEY WORDS

Albendazole, Headache, Lesion dissolution, Neurocysticercosis, New-onset seizure

INTRODUCTION

Neurocysticercosis (NCC) is one of the most frequent parasitic diseases of the human nervous system presenting as a single small enhancing lesion and comprises a dominant social health issue for most of the Indian subcontinent as well as in travellers of industrialized countries returning from endemic zones.[1-4] Solitary cysticercus granuloma (SCG) have traditionally been considered the degenerating form of long-established vesicular cyst that cannot maintain immune evasion and thus is under the host's immune attack. Although management should account earlier degeneration of cysticerci and could then reduce the risk of constant neurological symptoms, there are matters that seizures and other neurological events can be provoked by the inflammatory response to management induced cysticercal degeneration.[3,5] Albendazole has been found to be efficient in the management of such lesions since it expedites their dissolution.[6,7] Several studies have reported variable extent of albendazole therapy in patients with SCG, with treatments varying from days to month, with essentially identical outcomes.[2] Often, natural dissolution of parenchymal cysticerci is seen in serial imaging studies. A systemic review of the literature stated that there is inadequate documentation to clinch that anti-helminthic drug (AHD) treatment is aided with therapeutic advantage in NCC.[8]

We aim to evaluate the impact of varying duration of albendazole therapy (single dose, 3 days, 9 days, 3 weeks) on seizure, headache and lesion after one-month follow-up in patients with an active single cysticercal granuloma.

METHODS

This study was approved from the ethical review committee of Upendra Devkota Memorial National Institute of Neurological and Allied sciences (UDMNINAS). An informed consent was obtained from all the participants. For those under 18 years of age, a proxy consent was obtained from their parents.

A single centre, intervention study was conducted at UDMNINAS, Kathmandu, Nepal from March 2017 to February 2018. Patients received either usual care (anti-epileptic medication, steroid) with albendazole therapy (intervention) or only usual care without albendazole therapy (control).

All the patients with new-onset seizures secondary to active SCG; diagnosed by Del Bruto's "Revised diagnostic criteria and degrees of diagnostic certainty for neurocysticercosis" in the brain with an active NCC lesion in MRI brain/CT scan brain, new onset seizure were included.[9] Those with calcified granuloma, ocular NCC, ventricular NCC, previous known seizures and those who were pregnant were excluded.

The intervention group was treated with albendazole (800 mg/day) with usual care. There were four intervention groups. Group-1, group-2, group-3 and group-4 received the therapy for 1, 3, 9 and 21 days. The comparator or control group was those who did not receive any albendazole therapy. Patients in both intervention and control groups received usual care.

The primary outcome of the study was seizure control at one-month follow-up post-randomization for control group and post-completion of respective albendazole therapy for the intervention groups. The secondary number was headache. Seizure and headache control was assessed from patient's interview. We also analysed the lesion dissolution by repeat CT scan/MRI brain at one-month follow-up.

The data was entered and analysed using IBM-SPSS version 25.0. The change in the proportion of seizure and headache at one-month was assessed using chi-square test. The same test was used to compare the proportion of lesion dissolution across the groups at one-month follow-up.

RESULTS

Our study included 118 patients with new onset seizure secondary to SCG and was treated with anti-epileptics, steroids and with or without albendazole.

Table 1 shows baseline demographic and clinical data of participants in four intervention group and control group. The table shows that there was no significant difference in any of the characteristics between those who did not receive albendazole therapy and those who received albendazole for varying duration. Those who did not receive albendazole therapy were 26.3% while 22.9% received albendazole therapy for 1 day, 17.8% for 3 days, 16.9% for 9 days and 16.9% for 21 days. All the patients, irrespective of the group, had a seizure while headache was also common in all the groups.

Table 2 shows the difference in seizure and headache after varying duration of albendazole therapy and no albendazole therapy. Though there was decline is seizure the differences between the groups was not significant (p=0.406). In contrast to that a statistically significant decline in the headache (p=0.001) was observed between the groups. Albendazole therapy for 3, 9 and 21 days reduced the headache by 57.2%, 70% and 63.1% which was higher than the control (54.7% reduction).

Table 3 shows the difference in the number of patients with lesion dissolution in various groups. It can be observed that there was a statistically significant difference in the proportion of patients with lesion. Majority of the patients had either normal scan (35.6%) or calcified lesion (44.9%). Majority of normal lesion was observed in patients who received albendazole for 9 days (14, 70%) and 21 days (14, 73.7%), while most calcified lesion (21, 67.7%) was observed in those who did not receive albendazole therapy.

Table 1. Baseline demographic and clinical data (n=118)

Characteristics		Group					P-value
		Intervention (Albendazole therapy)				Control (n=31)	
		1 Day (n=27)	3 days (n=21)	9 days (n=20)	21 days (n=19)		
Age in years (mean±SD)		31.7±16.2	29.5±15.6	25.8±15.3	32.2±18.4	32.9±16.2	0.602
Sex (male)		14(51.9)	11(52.4)	12(60.0)	16(84.2)	20(64.5)	0.192
Seizure		27(100)	21(100)	20(100)	19(100)	31(100)	NA
Headache control		20(74.1)	14(66.7)	16(80.0)	13(68.4)	26(83.9)	0.582
Mantoux test	0-5 mm	27(100)	21(100)	18(90.0)	30(96.8)	30(96.8)	0.261
	> 5 mm	0	0	2(10.0)	1(3.2)	1(3.2)	
Abnormal in 1h VEEG		11(40.7)	11(52.4)	8(40.0)	10(52.6)	14(45.2)	0.865
Number of AED	< 2	16(59.3)	14(66.7)	10(50.0)	11(35.5)	11(35.5)	0.154
	≥ 2	11(40.7)	7(33.3)	10(50.0)	20(64.5)	20(64.5)	

Numbers are n(%) except for age.
NA: As all patients in each group had seizure, it is a constant and therefore, no statistics can be computed.
All p-value obtained from Pearson χ^2-test except ANOVA test for age.

Table 2. Changes in seizure and headache from baseline to one-month follow-up after intervention with albendazole therapy of varying duration compared to control (n=118)

Outcomes	Group					P-value
	Intervention (Albendazole therapy)				Control (n=31)	
	1 Day (n=27)	3 days (n=21)	9 days (n=20)	21 days (n=19)		
Seizure	6(22.2)	7(33.3)	9(45.0)	4(21.1)	11(35.5)	0.406
Headache	7(26.0)	12(57.2)	14(70.0)	12(63.1)	17(54.9)	0.001*

*significant at $p < 0.05$; P-value obtained from χ^2-test.

Table 3. Difference in lesion after intervention with varying duration of albendazole therapy compared to control (n=118)

Characteristics		Group					P-value
		Intervention (Albendazole therapy)				Control (n=31)	
		1 Day (n=27)	3 days (n=21)	9 days (n=20)	21 days (n=19)		
Lesion	Normal	3(11.1)	8(38.1)	14(70.0)	14(73.7)	3(9.7)	
	Calcified	12(44.4)	11(52.4)	5(25.0)	4(21.1)	21(67.7)	<0.001*
	Active	12(44.4)	2(9.5)	1(5.0)	1(5.3)	7(22.6)	

* significant at $p < 0.05$; P-value obtained from χ^2-test.

DISCUSSION

SCG is the most frequent form of parasitic infestation seen in Nepal and Indian subcontinent and travellers from developed countries to endemic zone.[10-13] Antiepileptic therapy with steroids and albendazole is the mainstay treatment for adults and children with seizure secondary to NCC.[14] Although the g ranuloma shows spontaneous resolution with time, complete resolution can take anywhere from few weeks to several years.[15]

Our study showed that new onset seizure secondary to neurocysticercosis was more common among male population (61.9%); with mean age of patients being 29.9% (range 3-66 year). Similar findings with proportion of women ranged from 29.7% to 47.2%, and the mean age of patients at the baseline ranged from 7.4 to 24 years.[4,13,16,17]

In our study, all of the patients enrolled presented with new onset seizure secondary to single granulomatous NCC. All of the patients were treated with anti-epileptic drugs and corticosteroids. Out of them 26.3% of patients received no albendazole therapy; 22.9% received single dose of albendazole, 17.8% received 3 days of albendazole therapy while 16.9% received nine days and 21 days of albendazole therapy respectively.

Our study showed headache in 75.4% of population. In contrast, study by Carabin et al. showed headache in symptomatic epilepsy secondary to neurocysticercosis in 27.7% cases.[18] Headache control was statistically significant seen in 22.9% of population (p=0.001); majority (48.1%) with single dose of albendazole followed by no albendazole (33.3%).

At 1 month of follow-up, 31.3% of patients had seizure recurrence. In our study, 24.7% had seizure recurrence with no albendazole. Similar rates of recurrence were observed in different studies with rate of control ranging from 3-47% with or without steroids with varying duration of follow-up ranging from 1 month to 12 months while 25.9% had seizure recurrence with single dose of albendazole.[19] Our study showed 17.3 % of populations had seizure recurrence with 3 days of albendazole while 9.1% seizure recurrence was observed in study by Chaurasia et al. 13.6% of population had seizure recurrence with 9 days and 18.5% with 21 days of albendazole therapy.[2] Varying rate of seizure recurrence, ranging from 8 to 22.6% was observed in different studies in patients receiving albendazole for 1-4 weeks with varying duration of follow-up.[20-26]

Even though the granulomatous lesion shows natural dissolution with time, complete dissolution might vary from a few weeks to several years.[15] In our study there is statistically significant difference in lesion dissolution between control and those who received albendazole for 3 days, 9 days and 3 weeks suggesting that 9 days of albendazole therapy had similar response to 3 weeks of albendazole therapy in terms of lesion dissolution ($p<0.001$) compared to 3 days of albendazole ($p=0.038$). In similar studies, lesion dissolution ranged from 19-88% at varying duration of follow-up CT scan at 1 month to 12 months in patients without albendazole therapy.[2,19,20-25,27-31] Patients receiving albendazole therapy for 3 days had lesion dissolution in 85%.[2] Patients receiving albendazole therapy ranging from 7 days to 4 weeks had lesions dissolution in 20-74% in follow-up CT scan or MRI at varying duration of 1 month to 12 months.[19,20,22-27]

Various meta-analyses have reported that anthelminthic therapy with albendazole and corticosteroids with different combinations (Conservative treatment, anthelmintics versus corticosteroids, combination of anthelmintics and corticosteroids versus conservative treatment, and combination of anthelmintics and corticosteroids versus corticosteroids) have improved the seizure-free rate and hastened the dissolution of the granuloma.[32-34]

CONCLUSION

Our study showed that 9 days of albendazole therapy is as effective as 3 weeks and better than 3 days, single dose or no albendazole in terms of lesion dissolution. Even single dose of albendazole therapy had significant control in headache with no significant response in seizure recurrence.

ACKNOWLEDGEMENT

I would like to acknowledge to all of the participants who agreed to participate in this study and to the Upendra Devkota Memorial National Institute of Neurological and Allied Sciences which allowed me to complete the study.

REFERENCES

1. Osvaldo M. Takayanagui. Neurocysticercosis. *Arq Neuropsiquiatr*. 2013 Sep;71(9B):710-3.
2. Chaurasia RN, Garg RK, Agarwal A, Kohli N, Verma R, Singh MK, et al. Three day albendazole therapy in patients with a solitary cysticercus granuloma: a randomized double blind placebo controlled study. *Southeast Asian J Trop Med Public Health.* 2010 May;41(3):517-25.
3. Takayanagui OM. Therapy for neurocysticercosis. *Expert Rev Neurother*. 2004 Jan;4(1): 129-39.
4. Zhao BC, Jiang HY, Ma WY, Jin DD, Li HM, Lu H et al. Albendazole and Corticosteroids for the Treatment of Solitary Cysticercus Granuloma: A Network Meta-analysis. *PLoS Negl Trop Dis*. 2016 Feb 5;10(2):e0004418.
5. Singh G, Sander JW. Anticysticercal treatment and seizures in neurocysticercosis. *Lancet Neurol*. 2004 Apr;3(4):207-8.
6. Garcia HH, Pretell EJ, Gilman RH, Martinez SM, Moulton LH, Del Brutto OH, et al. Cysticercosis Working Group in Peru. A trial of antiparasitic treatment to reduce the rate of seizures due to cerebral cysticercosis. *N Engl J Med*. 2004 Jan 15;350(3):249-58.
7. Nash TE, Singh G, White AC, Rajshekhar V, Loeb JA, Proano JV, et al. Treatment of neurocysticercosis: current status and future research needs. *Neurology.* 2006 Oct 10;67(7):1120-7.
8. Carpio A, Kelvin EA, Bagiella E, Leslie D, Leon P, Andrews H, et al. Effects of albendazole treatment on neurocysticercosis: a randomised controlled trial. *J Neurol Neurosurg Psychiatry*. 2008 Sep;79(9):1050-5.
9. Del Brutto OH, Nash TE, White AC Jr, Rajshekhar V, Wilkins PP, Singh G, et al. Revised diagnostic criteria for neurocysticercosis. *J Neurol Sci*. 2017 Jan 15;372:202-10.
10. Coyle CM, Mahanty S, Zunt JR, Wallin MT, Cantey PT, White AC Jr. et al. Neurocysticercosis: neglected but not forgotten. *PLoS Negl Trop Dis*. 2012; 6(5):e1500.
11. DeGiorgio CM, Sorvillo F, Escueta SP. Neurocysticercosis in the United States: review of an important emerging infection. *Neurology*. 2005; 64(8):1486.
12. Garcia HH, Gonzalez AE, Rodriguez S, Tsang VC, Pretell EJ, Gonzales I, et al. Neurocysticercosis: unraveling the nature of the single cysticercal granuloma. *Neurology*. 2010; 75(7):654-8.
13. Ojha R, Shah DB, Shrestha A, Koirala S, Dahal A, Adhikari K, et al. Neurocysticercosis in Nepal: a retrospective clinical analysis. *Neuroimmunol Neuroinflammation.* 2015;2(3):167-70.
14. Baird RA, Wiebe S, Zunt JR, Halperin JJ, Gronseth G, Roos KL. Evidence-based guideline: treatment of parenchymal neurocysticercosis: report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology.* 2013 Apr 9;80(15):1424-9.
15. Rajshekhar V. Rate of spontaneous resolution of a solitary cysticercus granuloma in patients with seizures. *Neurology*. 2001; 57(12):2315–7.
16. Singhi P, Ray M, Singhi S, Khandelwal N. Clinical spectrum of 500 children with neurocysticercosis and response to albendazole therapy. *J Child Neurol*. 2000 Apr;15(4): 207-13.
17. Morgado C, Gomes LB, de Campos JG. Neurocysticercosis. An imaging analysis of 35 cases. *Acta Med Port*. 1994 May;7(5):269-75.
18. Carabin H, Ndimubanzi PC, Budke CM, Nguyen H, Qian Y, Cowan LD, et al. Clinical manifestations associated with neurocysticercosis: a systematic review. *PLoS Negl Trop Dis.* 2011 May;5(5):e1152.

19. Baranwal AK, Singhi PD, Khandelwal N, Singhi SC. Albendazole therapy in children with focal seizures and single small enhancing computerized tomographic lesions: a randomized, placebo-controlled, double blind trial. *Pediatr Infect Dis J*. 1998; 17(8):696-700.

20. Garg RK, Potluri N, Kar AM, Singh MK, Shukla R, Agrawal A, et al. Short course of prednisolone in patients with solitary cysticercus granuloma: a double blind placebo controlled study. *J Infect*. 2006; 53(1):65-9.

21. Gogia S, Talukdar B, Choudhury V, Arora BS. Neurocysticercosis in children: clinical findings and response to albendazole therapy in a randomized, double-blind, placebo-controlled trial in newly diagnosed cases. *Trans Roy Soc Trop Med Hyg*. 2003; 97(4):416-21.

22. Singhi P, Jain V, Khandelwal N. Corticosteroids versus albendazole for treatment of single small enhancing computed tomographic lesions in children with neurocysticercosis. *J Child Neurol*. 2004; 19(5):323-7.

23. Sharma SR AA, Kar AM, Shukla R, Garg RK. Evaluation of role of steroid alone and with albendazole in patients of epilepsy with single-small enhancing computerized tomography lesions. *Ann Indian Acad Neurol.* 2007; 10:39-43.

24. Thussu A, Chattopadhyay A, Sawhney IM, Khandelwal N. Albendazole therapy for single small enhancing CT lesions (SSECTL) in the brain in epilepsy. *J Neurol Neurosurg Psychiatry*. 2008; 79(3):272-5.

25. de Souza A, Thennarasu K, Yeshraj G, Kovoor JM, Nalini A. Randomized controlled trial of albendazole in new onset epilepsy and MRI confirmed solitary cerebral cysticercal lesion: effect on long-term seizure outcome. *J Neurol Sci*. 2009; 276(1–2):108–14.

26. Kalra V, Dua T, Kumar V. Efficacy of albendazole and short-course dexamethasone treatment in children with 1 or 2 ring-enhancing lesions of neurocysticercosis: a randomized controlled trial. *J Pediatr*. 2003; 143(1):111–4.

27. Padma MV, Behari M, Misra NK, Ahuja GK. Albendazole in single CT ring lesions in epilepsy. *Neurology*. 1994; 44(7):1344-6.

28. Mall RK, Agarwal A, Garg RK, Kar AM, Shukla R. Short course of prednisolone in Indian patients with solitary cysticercus granuloma and new-onset seizures. *Epilepsia*. 2003; 44(11):1397-401.

29. 29. Prakash S, Garg RK, Kar AM, Shukla R, Agarwal A, Verma R, et al. Intravenous methyl prednisolone in patients with solitary cysticercus granuloma: a random evaluation. Seizure. 2006; 15(5):328–32.

30. Kishore D, Misra S. Short course of oral prednisolone on disappearance of lesion and seizure recurrence in patients of solitary cysticercal granuloma with single small enhancing CT lesion: an open label randomized prospective study. *J Assoc Phys India*. 2007; 55:419-24.

31. Singla M, Prabhakar S, Modi M, Medhi B, Khandelwal N, Lal V. Short-course of prednisolone in solitary cysticercus granuloma: a randomized, double-blind, placebo-controlled trial. *Epilepsia*. 2011; 52(10):1914–7.

32. Otte WM, Singla M, Sander JW, Singh G. Drug therapy for solitary cysticercus granuloma: a systematic review and meta-analysis. *Neurology*. 2013; 80(2):152–62.

33. Del Brutto OH, Roos KL, Coffey CS, Garcia HH. Meta-analysis: Cysticidal drugs for neurocysticercosis: albendazole and praziquantel. *Ann Intern Med*. 2006; 145(1):43–51.

34. Abba K, Ramaratnam S, Ranganathan LN. Anthelmintics for people with neurocysticercosis. *Cochrane Database Syst Rev*. 2010;(3):CD000215.