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RESEARCH ARTICLE

Efficacy and safety of praziquantel in the treatment of neurocysticercosis in Vietnam

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ABSTRACT

Neurocysticercosis (NCC) is a parasitic infection of the nervous system and is responsible for considerable morbidity and mortality. Praziquantel (PZQ) is one of the antiparasitics mostly used in managing NCC, however, there have been only a few studies on the treatment outcome of this drug. The present study aimed to evaluate the efficacy and safety of PZQ in patients with NCC. Sixty patients with typical characteristics of NCC received three 10-day cycles of PZQ and the interruption between these cycles was 10 days. Additional treatment included antiinflammation (steroids), antiepileptics and analgesics. Clinical and imaging studies were done at baseline and six months after therapy to assess the efficacy of treatment. Laboratory evaluation was done before and after each cycle to investigate laboratory safety profiles. By six months after finishing therapy, all patients had clinical improvement and 75% of them were free of symptoms. The rates of complete, partial or no resolution of cysts on brain magnetic resonance imaging were 61.7%, 28.3% and 10% respectively. The efficacy of therapy was not associated with the number of cysts. There was no difference between the levels of aspartate aminotransferase, alanine aminotransferase, urea and creatinine before and after treatment. Conclusion: Praziquantel is effective and safe in the treatment of patients with neurocysticercosis.

Keywords: Neurocysticercosis; praziquantel; efficacy; safety.

INTRODUCTION

Neurocysticercosis (NCC) is a disease of the central nervous system caused by *Taenia solium* larvae. The disease occurs worldwide, especially in rural areas of low- and middle-income countries with poor sanitation (WHO, 2015). Neurocysticercosis is related to considerable morbidity and mortality. It is the cause of approximately 50000 deaths annually (Prasad & Singh, 2018) and 30% of all epilepsy cases worldwide (WHO, 2022). Furthermore, NCC is also responsible for other neurological manifestations such as chronic headaches, focal neurologic de cits, intracranial hypertension and cognitive decline (WHO, 2022).

Treatment of NCC might include symptomatic, antiparasitic treatment or surgery (Garcia & Brutto, 2014). Antiparasitics with the aim of killing the larvae (cysticerci) have been proven to result in a better course of NCC (Garcia *et al*., 2004; Carpio *et al*., 2008). The two drugs that are most commonly used are albendazole and praziquantel (PZQ). Among them, albendazole is usually preferred due to its availability, lower cost, and favourable pharmacokinetics. For that reason, most studies in this field are applicable to albendazole and only a few studies investigated PZQ (Del Brutto *et al*., 2006; Abba *et al*., 2010). However, albendazole is contraindicated for pregnant or lactating women while PZQ can be used by these patients (Olds, 2003). In addition, PZQ is usually given with shorter regimes (1 to 14 days) compared to those of albendazole (3 to 28 days), therefore, offers some advantages such as shorter hospital stay and better compliance (Abba *et al*., 2010). Furthermore, most studies have observed cyst disappearance in 25% to 37% of cases after albendazole therapy (Carpio *et al*., 1995, 2008; Garcia *et al*., 2014a, 2016) and an alternative regime should be available for patients unresponsive to this drug. In Vietnam, the Ministry of Health allows the prescription of PZQ as a single drug for the management of NCC (MOH, 2004), nevertheless, no reports on treatment outcome of PZQ have been published. This study aims to evaluate the efficacy and safety of PZQ in patients with NCC.

MATERIAL AND METHODS

Ethical consideration

This study was reviewed and approved by the Vietnam National Institute of Malariology, Parasitology and Entomology. All procedures performed in the study were in accordance with the ethical standards of the institute and with the 1964 Helsinki decralation and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Study design

This prospective clinical study was carried out at Specialized Parasitic Clinic, Vietnam National Institute of Malariology, Parasitology and Entomology between January 2017 and December 2020. All patients who visited the Clinic during the studied time and had indicative symptoms/signs of NCC were screened for the disease. To be eligible for inclusion, subjects needed to be more than 5 years old and diagnosed with NCC, willing to complete antiparasitic therapy and follow-up examination after treatment. Exclusion criteria included pregnancy, presence of acute or other parasitic diseases, and active gastric ulcers. Patients having previous neurological disorders, ocular cysticercosis or only calcified cysts in the brain, known allergies to PZQ were also excluded from the study.

Data collection

The data of demographic, clinical, laboratory findings of the patients were collected using a case record form. Clinical data included a detailed history of the disease and symptoms/signs at hospital admission. Laboratory data included results of brain magnetic resonance imaging (MRI), blood biochemistry assays and screen tests for common infections in Vietnam. Serum enzyme-linked immunosorbent assay (ELISA) for cysticercosis, strongyloidiasis, fascioliasis, amebiasis, and toxocariasis was performed using Cortez Diagnostics Inc. (USA) according to the manufacturer's instructions. Fecal exams were done with participants' stool samples to find intestinal helminths or protozoans.

The treatment: Patients with viable cysts on MRI received three 10-day cycles of PZQ at a daily dose of 30 mg/kg in two divided doses and the interruption between these cycles was 10 days (MOH, 2004). All patients were given antiinflammation (steroids) while antiepileptics and analgesics were prescribed as needed. The dose of prednisone (steroid) was 1.5 mg/ kg/day (75 mg for those weighing 50 kg or more) for 8 days, then 50 mg/day for 1 week and finally 25 mg/day for 1 week. The dose of phenytoin (antiepileptics) was 5 mg/kg at night daily.

Follow-up: Biochemical parameters were examined before and after every course to determine the laboratory safety profile of therapy. The effectiveness of treatment was evaluated by clinical evaluation and MRI six months after finishing therapy.

Definition: The diagnosis of NCC was based on epidemiological, clinical and laboratory criteria (MOH, 2004). Patients who met epidemiologic criteria were those living in endemic areas or having a history of raw vegetable consumption. Clinical criteria were considered for patients having chronic headaches, focal neurologic deficits, late-onset seizures, cognitive decline, or intracranial hypertension. Laboratory criteria included (1) typical cysts discovered by biopsy; (2) pathognomonic lesions, i.e., cysts with "hole-with-dot" appearance on MRI, (3) parasites detected after funduscopic examination and (4) specific antibodies against *T. solium* cysticerci in serum determined by ELISA. The distribution of cysts on the brain was designated as cortex/subcortex, hemisphere, subarachnoid, and intraventricular. The stages of cysts were vesicular (1) (Figure 1), colloidal (2), granular (3), and calcified (4) (Figure 2) (Zhao *et al*., 2015). The efficacy of therapy was evaluated based on clinical and radiological criteria. Clinical criteria for cure, improvement or failure were total disappearance, significant improvement or no significant improvement in symptoms/signs. Criteria for the changes on MRI were complete, partial or no resolution applied for patients being free of active (stage 1, 2 or 3) cysts, showing a significant resolution (disappearance or calcification in > 50% of cysts) or no resolution of cysts (changes in less than 50% of cysts) (Kalra *et al*., 2003; Pandey *et al*., 2020). The normal range for liver enzymes (aspartate aminotransferase (AST) and alanine aminotransferase (ALT) was 1–35 U/L (Walker *et al*., 1990). Mild elevation was defined as the level of these enzymes being higher than normal levels but less than five times the upper limit of normal value while the severe elevation was applied to a level higher than 15 times the upper limit. The reference range of urea was 1.8 - 7.1 mmol/L, creatinine was 44-97 µmol/L for females and 53-106 µmol/L for males (Walker *et al*., 1990).

Statistical analysis

Data was analyzed by SPSS 22.0 (IBM Company). The normally distributed continuous variables like age, biochemical parameters were presented as means ±SDs and compared by paired sample t-test. Categorical variables were expressed as case number (n) and percentages and compared by Chi-square test. The accepted level of significance was two-tailed $P< 0.05$.

RESULTS

During the studied time, there were 85 patients diagnosed with NCC and indicated for using PZQ. Nineteen patients were excluded from the study because of concurrent infection with other parasites (eleven with roundworms and eight with hookworms)

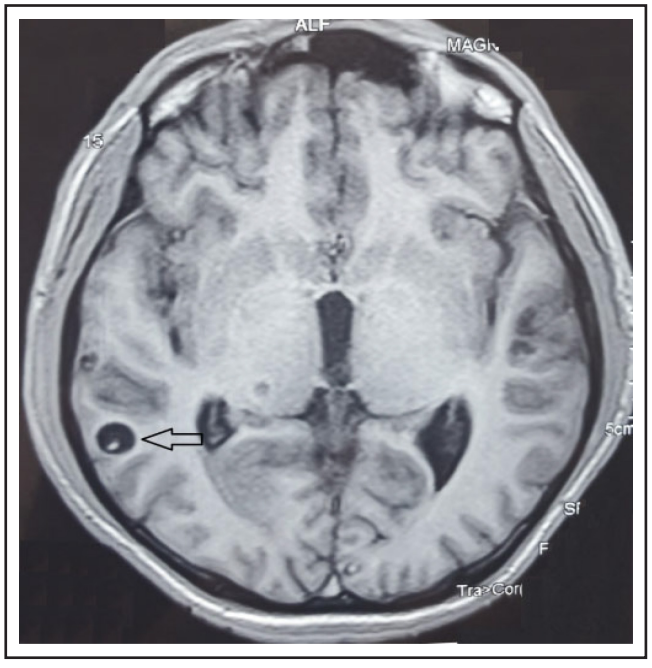

Figure 1. Vesicular cyst (arrow) in the brain parenchyma.

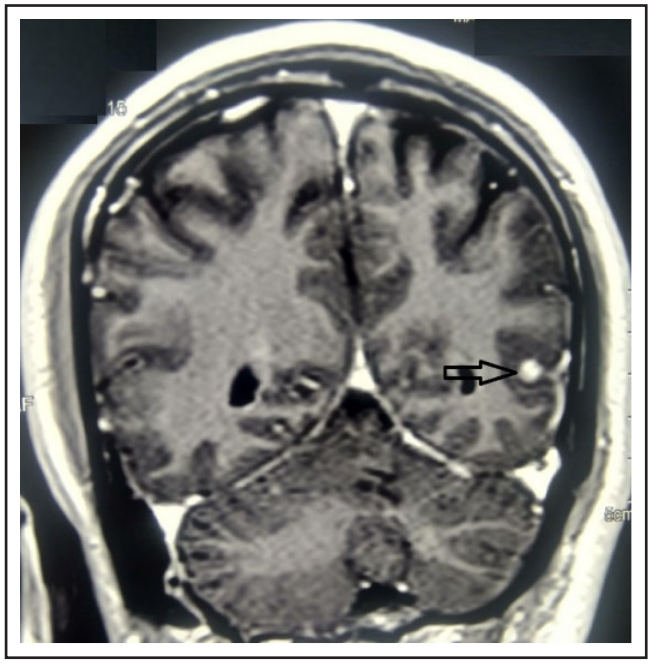

Figure 2. Calcified cyst (arrow) in the brain parenchyma.

or neurological disorders (three with chronic headaches). Three patients refused to participate and finally, 60 patients were enrolled.

Baseline data for all patients are provided in Table 1. The age range was 20–83 (mean 52.28± 12.97) years. The highest incidence was among the 41–50-year age group (33.3%) and only 7 (11.7%) of the patients were less than 30 years old. The rate of males/females was 2.75/1. The most common manifestation was headache (86.7%) and followed by seizure and other neurological symptoms. There were only 5 (8.3%) patients having a history of defecating proglottides and 2 with subcutaneous cysts.

Cysts were distributed in many regions but mostly in the cortex/subcortex region (68.3%). Most patients had 1 – 10 cysts but 2 patients had numerous cysts. The cysts were mainly of stage 1 or 2 and many patients had cysts of different stages. The average values of biochemical parameters were in normal ranges but 22 (36.7%) and 20 (33.3%) patients had elevated AST or ALT respectively (Table 2). No tapeworm eggs or proglottids were found in feacal samples of the patients.

By six months after finishing therapy, clinical improvement was reported in all patients and 75% of them were free of symptoms/signs. On MRI, 90% of patients showed a significant improvement of cysts and 61.7% were free of active cysts. There were 6 (10%) patients who had no significant changes in cystic lesions. The response to treatment was not statistically associated with the number of cysts. Comparison of outcomes between the parenchymal and extra parenchymal NCC was not performed because of the low number of patients with extra parenchymal cysts (Table 3).

After therapy, the average levels of parameters indicating the damage of the liver or kidneys were all within normal ranges and not significantly higher than the baseline values. The levels of urea after three cycles of PZQ were lower than those before the cycles (Table 4). Clinically, some patients showed manifestations suggesting side effects of drugs including dizziness, headache, fatigue, nausea and abdominal discomfort. All these symptoms were mild and transient and no patients had to stop therapy.

DISCUSSION

Demographic data

This prospective study involved 60 patients who were diagnosed with NCC and accepted enrolment. The diagnosis of NCC was based on Vietnamese criteria (MOH, 2004) that are more or less identical to those suggested by Del Brutto *et al*. (2001, 2016). As a result, our patients had typical characteristics of NCC. The mean age of 52.28 years and the predominance of males (73.3%) or farmers (53.3%) in our patients were similar to those in published studies (Huang *et al*., 2019; Son *et al*., 2019). The most common manifestations were headache (86.7%), seizure (51.7%) which have been described elsewhere in patients with NCC (Huang *et al*., 2019; Son *et al*., 2019). The high percentage of Kinh patients in this study (50%) is due to the fact that the Kinh ethnic group comprise about 86 percent of the national population in Vietnam (Thanh, 2019). On brain MRI, cysts were distributed in many locations but mainly in the cerebral

Table 1. Characteristics of the patients at baseline (n=60)

	Characteristic	N,% or $\underline{X}$ ± SD
Demographic information		
Age (*year*)		52.28 ± 12.97
Gender	Female	16 (26.7)
	Male	44 (73.3)
Ethnicities	Kinh	38 (63.3)
	Tay	7 (11.7)
	Thai	7 (11.7)
	Other *	8 (13.3)
Occupation	Farmers	32 (53.3)
	Other †	28 (46.7)
Clinical findings	Headache	52 (86.7)
	Seizure	31 (51.7)
	Fainting	12 (20.0)
	Memory loss	9(15.0)
	Limb numbness	7(11.7)
	Vomiting, nausea	3(5.0)
	Gait problems	5(8.3)
	Limb weakness	4(6.7)
	Defecating proglottides	5(8.3)
	Subcutaneous cysts	2 (3.3)
	Blurred vision	1(1.7)

* other ethnicities: Dao, Day, H'mong, Ha Nhi, Khang, Nung, Xinh Mun…
† other occupation: workers, officials, free traders, housewives…

Table 2. Laboratory findings at baseline

		N,% or $\underline{X}$ ± SD
Characteristics of cysts on MRI*		
Location	Parenchyma	60 (100)
	Extra parenchyma	4 (6.7)
	Hemisphere	35 (53.8)
	Cortex/subcortex	41 (68.3)
	Cerebellums	5 (8.3)
	Other	4 (6.7)
Number	1 cyst	19 (31.7)
	2 – 4 cysts	17 (28.3)
	5 – 10 cysts	22 (36.7)
	Numerous	2 (3.3)
Stage	Vesicular (1)	53 (88.3)
	Colloidal (2)	18 (30.0)
	Granular (3)	8 (13.3)
	Calcified (4)	2 (3.3)
Biochemical parameters	AST (U/L)	34.03 ± 20.48
	ALT (U/L)	33.16 ± 23.43
	Urea (mmol/L)	5.76 ± 1.79
	Creatinine (mmol/L)	81.94 ± 13.96

* Some patients had cysts of different stages and in different location.

Table 3. Efficacy of the treatment (n=60)

		Whole group		By number of cysts			
		N	%	1 cyst	2-4 cysts	≥ 5 cysts	*P*
Clinical efficacy	Complete cure	45	75.0	15	12	18	0.846
	Partial cure	15	25.0	4	5	6	
	Inefficacy	0	0	0	0	0	
Results on MRI	Complete cure	37	61.7	12	11	14	0.506
	Partial cure	17	28.3	5	3	9	
	Inefficacy	6	10.0	2	3	1	

Table 4. Levels of biochemical parameters before and after therapy (n=60)

	Course	Before	After	*P**
AST (U/L)	1	34.03±20.48	31.47±21.60	0.250
	2	29.79±10.78	29.48±13.70	0.774
	3	30.00±11.76	31.83±15.00	0.212
ALT (U/L)	1	33.16±23.43	34.16±29.61	0.747
	2	28.23±10.75	28.96±14.45	0.615
	3	30.13±11.95	29.12±13.69	0.478
Urea	1	5.76 ± 1.79	5.34 ± 1.20	**0.030**
(mmol/L)	2	5.31 ± 1.30	4.92 ± 1.21	**0.004**
	3	5.31 ± 1.19	5.04 ± 1.16	**0.019**
Creatinine	1	81.94 ± 13.96	82.30± 3.78	0.761
(mmol/L)	2	78.66 ± 13.19	79.97±12.29	0.233
	3	79.10 ± 11.38	77.83±11.22	0.063

*Comparisons between before and after each course of same group, paired sample t-test.

hemisphere (83.3%) and cortical/subcortical (68.3) regions that were similar to the results of previous studies (Huang *et al*., 2019).

Efficacy of praziquantel

The primary and secondary outcomes of this study were treatment efficacy (clinical and radiological improvement six months' post-treatment) and laboratory safety profile, respectively. Results of the study suggest that PZQ have good efficacy against NCC. All patients showed clinical improvement and 90% had resolution of cysts on MRI. Determination of clinical efficacy of antiparasitic treatment in NCC is difficult because some symptoms, such as seizures, can be present long after clearance of cystic lesions in the brain (Garcia & Del Brutto, 2003). However, our result of clinical evaluation is encouraging and collaborating with those in the literature. The high rate of clinical cure (75.0%) in our studies was similar to a rate of 78.1% that was reported by Robles *et al*. (1987). The overall clinically improvement rate in the present study was 100% and was in concordance with previous studies. According to the studies done in China, 3–5 courses of PZQ achieved the control of epileptic seizures in 95 % of cases (Wu *et al*., 2013) and the clinically effective rate was 93.0% (Fu *et al*., 1988). On MRI examination, the complete resolution rate of cystic lesion was also high (61.7%) and in range of efficacious rates reported in previous observations (from 53% to 70%) (Robles *et al*., 1987; Fu *et al*., 1988; Sotelo *et al*., 1988; Corona *et al*., 1999; Wu *et al*., 2013). Nevertheless, not all patients had changes in cystic lesions and radiological inefficacy was noted in 10% of participants. It is concluded that antiparasitic treatment is partly effective and destroys about 60–80% of cysts so a proportion of patients will still have viable cysts in their brain (Garcia *et al*., 2014b). The proportion of radiological inefficacy reported in our study follows the trend described previously (from 6.7% to 21.9%) (Robles *et al*., 1987; Fu *et al*., 1988; Corona *et al*., 1999). Other approaches to treatment may be needed for these patients.

In the current study, the efficacy of therapy was not associated with the number of cysts (Table 3). Studies evaluating the association between the number of cysts and treatment outcomes in the literature have inconsistent results. The better efficacy of anthelmintics in patients with fewer cysts has been shown (Carpio *et al*., 1995). Nevertheless, Garcia *et al*. (2016) observed a better outcome of treatment in patients with multiple cysts compared to those with single (or two) cysts. The absence of association between treatment outcome and the number of cysts in the present study could be due to the effects of other variables causing the heterogeneity in the response to treatment (cyst viability, size or host immunity) (Cárdenas *et al*., 2014; Monk *et al*., 2021). Therefore, proper characterisation of patients is very important before planning the treatment of NCC (Garcia *et al*., 2014b).

Safety of praziquantel

Considering the safety profile, our results suggested that three 10-day courses of PZQ at a dose of 30 mg/kg/day^{-1} did not result in remarkable damage to the liver or kidneys. As shown in Table 4 there were no significant increases in the levels of liver enzymes, urea and creatinine after all three courses. Data regarding the safety of PZQ is scarce and has mainly focused on clinical manifestation (Hong 2018b) so our laboratory findings appear to extend current knowledge on this topic. Other published studies have demonstrated that PZQ can result in mild and self-limiting elevations of serum aminotransferase levels and no long-term adverse effects have rarely been reported (Hong *et al.,* 2018a). The unalterable levels of urea and creatinine after therapy in the current study were consistent with those from another study (Hong *et al.*, 2018a). In the present study, clinical manifestations of adverse effects relating to PZQ were not included in the analysis. The reason for this was neurological manifestations such as dizziness, headache, seizures could be related to the anticidal effects but not to adverse reactions of PZQ. In addition, these manifestations may be alleviated by using corticosteroids simultaneously with PZQ, as in our patients, so it is difficult to determine the exact cases with side effects (Fu *et al.,* 1988). Some digestive manifestations including nausea or abdominal discomfort were probably due to the concomitant steroids. A previous study showed that a higher dose of PZQ (100 mg/kg daily for 10 days) was well tolerated and without severe adverse reactions (Bittencourt *et al.,* 1990).

There are some limitations to our study. The duration of follow-up (six months) in the current study may not be long enough to investigate the long-term outcome of therapy. Some authors suggest a follow-up duration of two years (Qavi *et al*., 2016), but the persistence of cystic lesions six months after therapy is an indication of another course of anti-parasitic treatment (White *et al.*, 2018). The lack of a control group makes delineating the natural course of NCC from those modified by therapy difficult. Nevertheless, this could be not accepted from the clear benefit of PZQ for patients with NCC. The comparison of efficacy between patients with different distribution of cysts was not accessible based on the limited number of patients with extra parenchymas cysts.

CONCLUSION

Three 10-day courses of praziquantel seem to be efficacious and safe in patients with neurocysticercosis. Assessment of treatment outcome by brain MRI six months after therapy is needed because not all patients have complete resolution. Further studies to explore the cause of the heterogeneous effect of praziquantel are necessary to develop treatment strategies for patients with neurocysticercosis who do not respond to this antiparasitic drug.

Conflict of interest:

The authors declare that they have no conflict of interest.

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