EFFICACY OF IVERMECTIN TREATMENT OF CUTANEOUS GNATHOSTOMIASIS EVALUATED BY PLACEBO-CONTROLLED TRIAL

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Abstract. Previous studies have revealed that ivermectin treatment for gnathostomiasis can reduce parasitic loads in animals and make recurrent subcutaneous swelling subside in 76% of patients. Our study aimed to evaluate the efficacy of ivermectin for cutaneous gnathostomiasis treatment in a placebo-controlled trial. This study was a prospective randomized placebo-controlled study performed at The Bangkok Hospital for Tropical Diseases, Mahidol University, Thailand. Thirty patients with a serologically confirmed diagnosis of cutaneous gnathostomiasis were enrolled. Seventeen patients in the ivermectin treated group received a single dose of 12 mg ivermectin (200 µg/kg bodyweight), while 13 patients in the control group received a single dose of 40 mg of vitamin B1. The follow-up period was 1 year. Of the 17 patients, 7 (41.2%) responded to ivermectin, while no patient responded to placebo. The mean (95% CI) time to the first recurrence of subcutaneous swelling with ivermectin and in the placebo groups were 257 (184-331) and 146 (42-250) days, respectively, (p=0.102). Although this study revealed no significant difference in the mean time to first recurrence of swelling between the ivermectin and placebo groups, there was a trend towards ivermectin efficacy against gnathostomiasis in previous animal and human studies. Further studies with different doses of ivermectin and larger sample sizes, and close monitoring for ivermectin tolerability and treatment response are necessary to confirm an efficacy of ivermectin.

INTRODUCTION

Human gnathostomiasis usually presents as an intermittent migratory subcutaneous swelling (Radomyos *et al*, 1996). It is a parasitic disease frequently encountered in Thailand, Southeast Asia, the Far East, and Mid and South America. Humans are accidental hosts. Swelling is caused by migration of advanced third stage larva of *Gnathostoma spinigerum* through the subcutaneous tissue, causing intermittent migratory swelling. The worm may migrate to vital organs, such as the eyes and central nervous system, causing serious illness. Surgical removal of the worm is considered curative for gnathostomiasis, but it is difficult to locate the parasite. Therefore, it is necessary to search for an effective chemotherapeutic regimen. An efficacious treatment regimen for cutaneous gnathostomiasis has not been well established. Current treatment at the Bangkok Hospital for Tropical Diseases is albendazole, 400 mg twice daily for 14 days or 400 mg once a day for 21 days. However these regimens provide low efficacy and transient elevations of liver enzymes occurs at a dosage of 800 mg daily for 14 days (Inkatanuwat *et al*, 1998). The treatment resulted in cutaneous outward migration of the parasite in only 7.3% and 21%, respectively, in patients treated with twice-daily albendazole for 14 days (Suntharasamai *et al*, 1992) and once or twice daily dose for 21 days (Kraivichian *et al*, 1992). Albendazole resulted in a reduction in the frequency of recurrent subcutaneous swelling when given at a dosage of 400 mg once or twice daily compared to the non-treated group (Kraivichian *et al*, 1992).

Ivermectin is a macro-cyclic lactone causing paralysis of nematodes and arthropods through an influx of chloride ions across the cell membrane (Ottesen and Campbell, 1994). At a dose of 150-200 µg/kg, it reaches a maximum

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concentration at 2.7-4.3 hours with an elimination half-life of 28±10 hours. It is metabolized by the cytochrome p 450 systems in the liver and excreted almost entirely in feces within 12 days (Ett *et al*, 1990). This drug has been shown to be effective for mass treatment of onchocerciasis with a good safety record since 1987 (Pacque *et al*, 1989).

It has also been shown to be effective in the treatment of many intestinal helminthiases including strongyloidiasis (Aziz *et al*, 1982; Coulaud *et al*, 1983; Kumaraswami *et al*, 1988; De Sole *et al*, 1989; Pacque *et al*, 1989; Shikiya *et al*, 1992; Coutinho *et al*, 1994; Datry *et al*, 1994; Bockarie *et al*, 1998; Kombila *et al*, 1998) and scabies, especially in the elderly and children (Huffam and Currie, 1998; Meinking *et al*, 1995). Severe adverse events noted after using ivermectin treatment included hypotension, breathing discomfort, high fever, hematuria, and abnormal complete blood counts and liver enzymes. However, the laboratory abnormalities were transient and occurred uncommonly (Ett *et al*, 1990).

Ivermectin has been shown to be effective against the larvae of *Gnathostoma spinigerum* in experimental animals (Anantaphruti *et al,* 1992). When infected rabbits were treated with subcutaneous ivermectin, either as a single dose of 0.2 mg/kg or up to 3 doses of 2 mg/kg, these resulted in 74.2% and 84.2% reductions in worm load by 28 weeks of treatment, respectively.

A clinical study of ivermectin to treat human cutaneous gnathostomiasis was conducted with single oral doses of 50, 100, 150 and 200 µg/kg bodyweight. These regimens demonstrated ivermectin was well tolerated (Bussaratid *et al*, 2005). Another study showed that a single dose (200 µg/kg) of ivermectin was effective in the treatment of gnathostomiasis with cure rates of up to 76% during 120 days of follow-up.

This study aimed to assess the safety, tolerability, and efficacy of ivermectin compared to placebo in a randomized placebo-controlled trial.

MATERIALS AND METHODS

This study was carried out prospectively between July 2001 and July 2004 at the Out-Patient Department of the Bangkok Hospital for Tropical Diseases, Mahidol University, Thailand. The study was reviewed and approved by the Ethics Committee on Clinical Research of the Faculty of Tropical Medicine, Mahidol University.

Thirty patients, age 20-65 years, having at least one episode of subcutaneous swelling during the past 12 months with positive antibodies against a specific 24 kDa antigen of *G. spinigerum* third stage larva by immunoblot analysis (Nopparatana *et al*, 1991; Tapchaisri *et al*, 1991) were enrolled with informed consent. Patients were excluded if pregnant, lactating, or if they had taken any anti-parasitic agents during the previous 14 days. Patients with underlying diseases, including pulmonary disease (especially asthma), renal disease (especially hematuria), a history of seizures, liver disease (elevated liver function test), cardiovascular disease (especially tachycardia with a heart rate >100/minute or having an abnormal electrocardiogram at baseline), hematological disorders, such as anemia (hematocrit < 25%), leukopenia (WBC < 3,500/mm^3), or thrombocytopenia (platelet < 100,000/mm^3), and hypotension (blood pressure <90/60 mmHg) were also excluded. After providing informed consent, each patient was randomly assigned to receive a single dose of ivermectin 200 µg/kg (4 tablets of 3 mg ivermectin) or placebo (4 tablets of 10 mg-vitamin B1). Clinical assessment was performed before treatment, on days 7 and 28, at months 3, 6 and 12. The laboratory tests included a CBC, liver enzymes (AST, ALT), BUN, creatinine and urinalysis were performed before treatment and on day 7. If any abnormality occurred, the laboratory tests were repeated on day 28 and at months 3, 6, and 12, or until they returned to normal.

Safety and tolerability

Each patient was observed for immediate adverse reactions for 30 minutes after taking the study drug at the Out-Patient Department. Other symptoms were self recorded for 7 days by each patient using a diary card. The severity of any symptoms was classified as follows. A “mild symptom” was defined as self-limited without needing treatment. A “moderate symptom” was defined as a symptom that was relieved with

medication or an outpatient visit was required. A "severe symptom" was defined as a symptom which led to hospitalization of the patient.

Causality evaluation of adverse events

Adverse events were considered as to whether they were related to the study drug and classified as follows: none, remotely related, possibly related, probably related, and definitely related (Stark *et al*, 1999; Gait *et al*, 2000).

Concomitant therapy

Acetaminophen (paracetamol) was given for pain relieve and serratiopeptidase with or without antihistamines was given to relieve the swelling. There were no antihistamines prescribed during the follow-up period.

Treatment outcome measurement

Patients were followed up for treatment response on days 7 and 28, and months 3, 6, and 12. Treatment outcomes were defined as follows:

Response to treatment was defined as no recurrent subcutaneous swelling during 12 months follow-up or recovery of the gnathostoma larva from the skin either by spontaneous outward migration of the worm through the patient's skin or by minor excision.

Treatment failure was defined as recurrent subcutaneous swelling within 12 months following initiation of treatment. These patients were subjected to alternative antiparasitic treatment (albendazole 400 mg twice daily for 14 days).

Statistical analysis

Sample size calculation. In order to compare a proportion of cases with recurrent swelling after treatment with ivermectin or placebo, the sample size was calculated on the basis of preliminary results (unpublished data). It was found that 8 out of 10 cases with gnathostomiasis had recurrent swelling during 1 year follow-up. It was expected that ivermectin could decrease the proportion of cases with recurrent swelling to 40%. Assuming a 5% level of significance on a 2 sided test with a power of 80% and an expected loss to follow-up within 6 months of 20%, the required sample size was 29 cases for each group (Machin *et al*, 1997).

Data were collected and analyzed using SPSS for windows™ release 11.0 (SPSS Inc Illinois, USA). Baseline characteristics, adverse events and subcutaneous swelling resolution time in patients in the 2 study groups were then compared. Comparability of various variables between the 2 study groups was assessed by the chi-square test or the Fisher's exact test as appropriate for qualitative data, and by the Mann-Whitney *U* test for non-normally distributed qualitative data. Treatment efficacy, as assessed by time to recurrent subcutaneous swellings, was performed using the Kaplan-Meier survival curve and the curves were compared with the log rank test.

RESULTS

Patient characteristics

Thirty patients were enrolled in this trial: 17 in the ivermectin and 13 in the placebo groups. The demographic and baseline characteristics of the patients are shown in Table 1. The two groups were similar in age, weight, sex ratio and peripheral blood eosinophil counts. There was no significant difference between the groups with respect to the number of swelling episodes, resolution time for each swelling episode and sites of swelling before enrollment. The upper extremity was the most common site of swelling in both groups.

Seventy-three point three percent and 75% of patients in the ivermectin and placebo treated groups, respectively, were residents of Bangkok at the time of enrollment. Eighty-one point eight percent and 66.7% of patients in the ivermectin and placebo treated groups, respectively, were from the northern and northeastern regions.

Adverse events

Sixteen patients (94.1%) in the ivermectin group completed a diary card that recorded any adverse events during the first 7 days of treatment. Only 7 patients (53.8%) in the placebo group returned the diary card. The other 6 patients in this group were not available for the diary card interview. The clinical adverse events reported during the first week after treatment are presented in Table 2. The common adverse events in both groups were similar, including malaise, fatigue, dizziness, vertigo, drowsiness, myalgia, palpitations without tachycardia, feel-

Table 1
Clinical and baseline characteristics of patients in the ivermectin and placebo treated groups.

Characteristics	Ivermectin (n=17)		Placebo (n=13)		p-value
	Median (Range)	No. (%)	Median (Range)	No. (%)	
Age (year)	31(20-50)		31 (22-49)		0.644
Sex (male)		6 (35.3)		3 (23.1)	0.691
Body weight (kg)	56 (45-78)		58 (45-77)		0.356
Current Bangkok residence		73.3		75	1.000
Hometown in the North and Northeast		81.8		66.7	0.640
Swelling resolution time for each episode (days)[a]	7 (2-21)		6 (1.5-17.5)		0.138
Number of swelling episodes[b]	3.5 (1-12)		6 (3-72)		0.149
Length of illness (month)	12 (0.25-48)		12 (1-36)		0.545
Eosinophil count (cell/mm^3)	576 (124-2,400)		584 (260-2,254)		0.983
Site of swelling[c]					
Head and face		3 (18.75)		0	
Upper extremities		9 (56.25)		8 (61.6)	0.567
Lower extremities		2 (12.5)		2 (15.4)	
Others[d]		2 (12.5)		3 (23)	

[a] Number of patients: ivermectin group (n=13), placebo group (n=12)
[b] Number of swelling episodes during the past year, number of patients: ivermectin group (n=14), placebo group (n=12)
[c] Number of patients: ivermectin group (n=16), placebo group (n=13)
[d] Others defined as swelling not confined to the same part of the body

Table 2
Adverse events reported within 7 days of treatment.

Adverse events	No. (%) of patients		p-value
	Ivermectin n=16 (100)	Placebo n=7 (100)	
Malaise	6 (37.5)	4 (57.1)	0.650
Fatigue	3 (18.8)	0	0.526
Dizziness	4 (25)	3 (42.9)	0.626
Vertigo	5 (31.3)	5 (71.4)	0.169
Drowsiness	7 (43.8)	6 (85.7)	0.089
Myalgia	6 (37.5)	2 (28.6)	1.000
Palpitations without tachycardia	1 (6.3)	1 (14.3)	0.526
Feeling breathing	1 (6.3)	2 (28.6)	0.209
Difficulty without dyspnea			
Nausea	3 (18.8)	2 (28.6)	0.621
Vomiting	1 (6.3)	0	1.000
Anorexia	3 (18.8)	0	0.526
Constipation	3 (18.8)	2 (28.6)	0.621
Diarrhea	0	1 (14.3)	0.304
Abdominal pain	3 (18.8)	0	0.526
Itch	4 (25)	2 (28.6)	1.000
Localized rash	3 (18.8)	0	0.526
Generalized rash	0	1 (14.3)	0.304
Subcutaneous swelling	2 (12.5)	1 (14.3)	1.000

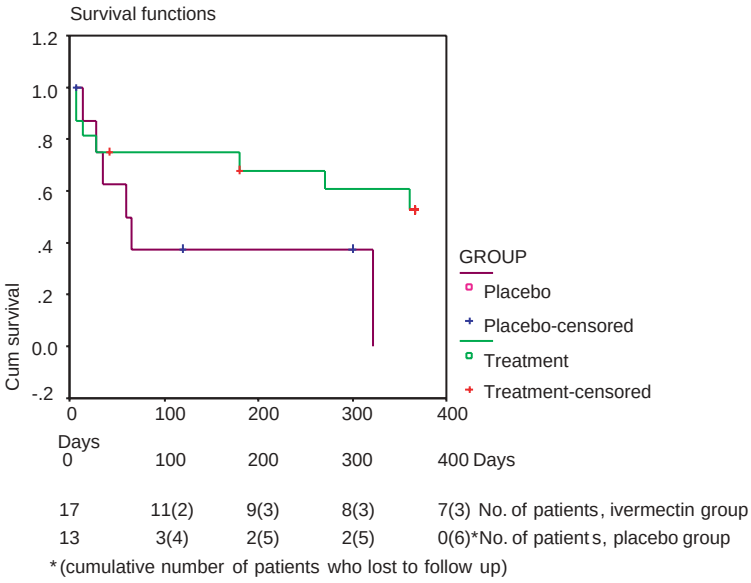

Fig 1–Kaplan-Meier curves of time to recurrence of subcutaneous swelling during 1 year follow-up of patients in a placebo-controlled trial with ivermectin.

ing of breathing difficulty, nausea, vomiting, anorexia, constipation, diarrhea, abdominal pain, itch, and rash, but no significant differences were observed.

Two patients (one female and one male) in the ivermectin treated group had asymptomatic microscopic hematuria (10-15 cells/ high-power field) on day 7. The female patient had a normal urinalysis on day 28 after treatment, but the male patient had no follow-up urinalysis done. However, he was healthy and asymptomatic throughout the 1-year follow-up period. There were no abnormal urinalysis findings in the placebo group. Other laboratory findings, including CBC, liver enzymes, and renal function test were within normal limits for both groups.

Treatment outcome

By the end of 1 year follow-up, of the 17 patients in the ivermectin treated group, 7 (41.2%) cases responded to treatment, 7 (41.2%) cases did not respond to the treatment and the remaining 3 (17.6%) cases were lost to follow-up. Of the 13 patients in the placebo group, 7(53.8%) cases did not respond to treatment and 6 (46.2%) cases were lost to follow-up.

There were 4 and 1 patients in the ivermectin and placebo treated groups, respectively, were followed up for longer than 365 days. One patient in the ivermectin and another patient in the placebo group had recurrent subcutaneous swelling on days 7 and 60, respectively. The other 3 patients in the ivermectin treated group had no recurrent subcutaneous swelling for 400 days of follow-up. These 3 patients had a baseline frequency of recurrent subcutaneous swelling ranging from about 1.5 to 5 times per 6-month period.

The mean (95% CI) time to the first recurrent subcutaneous swelling in the ivermectin treated group [257 (184-331) days] was longer than the placebo group [146 (42-250) days], but no significant difference between the 2 groups was observed (p= 0.102).

Four patients in the ivermectin treated group and 7 patients in the placebo group were enrolled while having active subcutaneous swelling. In the patients receiving ivermectin, the median (range) swelling resolution time for each episode before treatment [7 (2-21) days] was not significantly different from that observed after treatment [6 (6-6) days] (p=0.066). For those who received placebo, the swelling resolution time for each episode before and after treatment was not significantly different [6 (1.5-17.5) days versus 7 (1.5-8) days, p= 0.233]. The mean swelling resolution time for each episode before enrollment in the ivermectin treated group was not significantly different from the placebo group [7 (2-21) days versus 6 (1.5-17.5) days, p=0.138] (Table1).

It was noted that the first recurrence of subcutaneous swelling observed in both groups were localized at or adjacent to the baseline sites of swelling.

DISCUSSION

Surgical removal of the worm is considered as a curative treatment for human gnathostomiasis, but it is rather difficult to locate the parasite. Therefore, the alternative approach is to search for an effective chemotherapeutic regi-

men. Albendazole treatment resulted in cutaneous outward migration of the worm in only 7.3-21% in 2 previous studies (Kraivichian *et al*, 1992; Suntharasamai *et al*, 1992).

In our randomized placebo-controlled trial, only 17 and 13 patients were enrolled in ivermectin and placebo groups, respectively. The target sample size could not be reached due to expiration of study medication in June 2003. Therefore study enrollment was terminated then.

Ivermectin did not show a statistically significant difference in the therapeutic effect over placebo (analyzed by the log rank test). Ivermectin may be either ineffective or effective under different conditions for human gnathostomiasis.

Serum or blood levels of the study drug may affect the treatment outcome. Factors influencing therapeutic blood levels of the study drug include the patient's bodyweight, pharmacodynamics, pharmacokinetics, and volume of distribution of the study drug. This study showed that in the ivermectin group, the patients' bodyweights among the successfully treated and failed treatment groups were not statistically different (p= 0.217). Pharmacodynamics, pharmacokinetics, and volume of distribution may depend on individual host variation and drug dosage. In a previous 6-month follow-up study using 50-200 mg of ivermectin single dose for the treatment of cutaneous gnathostomiasis, it was found that 2 of 4, and 3 of 5 patients receiving ivermectin 50 and 200 µg/kg bodyweight, respectively, responded to treatment (Bussaratid V, unpublished data). Further studies with larger sample sizes are needed before any conclusion can be made.

Although difficult to prove in living patients, multiple infestations or re-infestation with the gnathostoma larva, may be attributed to failure of treatment. This study found all, except 2 events, of the first time recurrent subcutaneous swellings observed occurred without risk of re-infestation.

Outcome measurement in the study relied on clinical recurrence, which is not specific for cutaneous gnathostomiasis. In Thailand, the etiology of localized angioedema includes gnathostomiasis, allergic reaction, insect bite reaction or Well's syndrome. In certain parts of Africa, loiasis or so-called calabar swelling is another possible etiology. The disadvantages in our study included lack of an immediate clinic visit for each episode of recurrent subcutaneous swelling. Therefore, retrospective interview could not accurately determine the cause of the subcutaneous swellings. Serological tests available at the time of study cannot be used for monitoring treatment response or re-infestation with new gnathostoma larva. Anti IgG against specific 24kDa gnathostoma larva antigen observed by immunoblot analysis may remain positive for years, irrespective of treatment received. (Bussaratid V, unpublished data). In addition, ELISA for serum IgG detection using crude antigen extract of third stage larvae of *Gnathostoma spinigerum* shows cross reaction with other common parasitic infestations in Thailand (Suntharasamai *et al*, 1985; Dharmkrong-At *et al*, 1986; Soesatyo *et al*, 1987; Tada *et al*, 1987; Maleewong *et al*, 1988).

A high drop-out rate in both the study groups may affect the treatment success curves. The large percentage of patients lost to follow-up may underestimate failure and overestimate the remission rate.

A previous study by Kraivichian and colleagues (2004) revealed that the swelling resolution time for each episode in 61.54% of patients receiving a single dose of 200 µg/kg ivermectin was 3 days (n=13, range 3-40 days). This study showed that the median (range) swelling resolution time for each episode after ivermectin treatment was 6 (6-6) days, n=4.

There was no change in medical practice with time during this study. Immunoblot analysis for anti-IgG has been the gold standard for serodiagnosis until present (Kraivichian *et al*, 2004; Bussaratid *et al*, 2005). The treatment of choice has been controversial. Albendazole has been the first antiparasitic agent of choice.

No serious adverse events were reported for a single 200 µg/kg dose of ivermectin to treat human gnathostomiasis both in this and previous studies (Kraivichian *et al*, 2004; Bussaratid *et al*, 2005). There was no statistically significant difference in the occurrence of clinical adverse events between the two groups. Although

it was found that fatigue, vomiting, anorexia, and abdominal pain, and localized rash were reported only in the ivermectin treated group, there was not enough evidence to exclude other possibilities that may relate to the adverse events.

Most clinically adverse events reported in both groups were mild, except for 3 patients in the ivermectin group and 1 patient in the placebo group. The 3 patients in the first group reported moderate vertigo, drowsiness, or myalgia. A patient in the latter group reported moderate generalized rash. These symptoms with moderate severity were considered remotely related to the treatment by investigators as the symptoms were pre-existing or present on days 5 to 6, excepted for vertigo occurring on day 2, which was possibly related to the treatment.

Although breathing difficulty has been previously observed in patients receiving ivermectin for onchocerciasis (De sole *et al*, 1989; Pacque *et al*, 1989), our study found no such case. Our patients reported only a feeling of breathing discomfort without dyspnea, tachypnea, or cyanosis. Palpitations were reported from patients in both groups but no tachycardia or dysrythmia was observed at the time the symptom presented.

Asymptomatic microscopic hematuria, an adverse laboratory event, was found in one male and one female patient. One patient had laboratory proof of recovery. We were not able to conclude that the hematuria in these 2 patients was related to causes other than ivermectin. Hematuria after use of ivermectin has been reported, but it was transient and occurred uncommonly (Njoo *et al*, 1993).

In summary, more information on the tolerability and efficacy of ivermectin on human gnathostomiasis is required to consider the use of ivermectin for human gnathostomiasis. Further clinical trials with safety assessment are necessary.

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