

GROWTH REDUCTION AMONG PRIMARY SCHOOL-CHILDREN WITH LIGHT TRICHURIASIS IN MALAYSIA TREATED WITH ALBENDAZOLE

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Abstract. We studied asymptomatic primary schoolchildren in northeastern Malaysia with light to moderate trichuriasis to determine the effect of albendazole treatment on growth rates and TNF-alpha levels. Thirty-seven schoolchildren aged 6-7 years with stool samples positive for *Trichuris trichiura* and negative for other geohelminths and protozoa were randomized to receive albendazole 400 mg or a placebo daily for 2 days. Anthropometric parameters at baseline, 3, 6 and 12 months were compared between the 2 groups. The placebo group had a significantly greater increase in height ($p=0.04$) than the albendazole treatment group. There were no significant differences in urinary TNF-alpha levels ($p=0.8$) between the 2 groups and no significant changes between baseline and 1 month post-treatment levels. Further studies are needed to determine the etiology of this apparent association between the albendazole treatment group and the delay in growth rate at 6 months post-treatment.

Keywords: *Trichuris trichiura*, albendazole, growth, schoolchildren, Malaysia

INTRODUCTION

Intestinal geohelminth infections are common in the developing world. There have been numerous studies of the potential effects of these infections on nutrition and growth among children with disparate results (Forrester *et al*, 1998; Stephenson *et al*, 1989; Taylor-Robinson *et al*, 2007). Treating children with heavy trichuriasis has obvious benefits for growth, but the

benefits of treating light to moderate infections is unclear. Children with *Trichuris* dysentery syndrome have been shown to have elevated levels of the cytokine TNF-alpha, a potential mediator of the constitutional symptoms of this disease (Cooper, 2009; Duff *et al*, 1999). Therefore, we conducted this study to determine the effect of treating trichuriasis among children in Malaysia and to study TNF-alpha levels in these children.

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MATERIALS AND METHODS

We examined the stool of 242 ethnic Malay children aged 6-7 years attending a rural primary school (Sekolah Rendah

Kebangsaan Tawang, Kelantan, Malaysia) in northeastern Peninsular Malaysia for the presence of helminth eggs and protozoa cysts. Thirty-seven children (15.3%) had stool samples positive for *Trichuris trichiura* infection and negative for other common intestinal geohelminths (*Ascaris lumbricoides* and hookworms) and protozoa (*Entamoeba* spp). The stool samples were examined using a modified Stoll's concentration technique (Garcia and Bruckner, 1998) to improve the chances of detecting *T. trichiura*. Some of the stool samples were preserved in 10% formalin prior to examining for helminth eggs and protozoa cysts. Children with overt dysenteric symptoms or other overt illnesses were excluded from the study.

The 37 children with confirmed *T. trichiura* infection only were included in the study. All the subjects underwent anthropometric measurements at baseline. The height in centimeters was measured using a measuring tape affixed to a wall. The weight in kilograms was measured using a calibrated digital weighing machine (Seca, Birmingham, UK). The weight for age (WAZ), height for age (HAZ) and weight for height (WHZ) were calculated using EPI info, version 6.04c (EPINUT component) (CDC, Atlanta, GA) and expressed as a Z score compared to baseline weight. Urine samples for TNF-alpha were collected and transported in dry ice and then stored at -30°C. The TNF-alpha assay was performed by a laboratory technician, blinded to the study group, using a commercially available kit (Endogen Human ELISA TNF-Alpha, Thermo Fisher Scientific, Rockford, IL) (Aggarwal and Reddy, 1994).

The 37 subjects were randomized to either a treatment group and given albendazole (GlaxoSmithKline, Brentford, Middlesex, UK) 400 mg for 2 days or a

placebo group and given a placebo tablet daily for 2 days, using randomization software (Urbaniak and Plous, 2012). Both the active drug and placebo were repackaged by a pharmacist (JAS) blinded to the study groups. All doses of albendazole and placebo tablets were consumed in the presence of an investigator. The height and weight of each subject were repeated at 3, 6 and 12 months after treatment. Comparisons were made between the treatment and placebo groups for growth parameters at baseline, 3 months, 6 months and 12 months. Urine samples were again collected at one month post-treatment for the TNF-alpha assay.

The study was designed to have a power of 80% with an alpha value of 0.05. Seventeen subjects were required for each group (treatment and control) to detect a 0.8 kg difference in weight and a 0.8 cm difference in height. All statistical analysis was performed using SPSS version 10.0.1 (SPSS, Chicago, IL). A Student's *t*-test was used to test for differences unless the data had a non-normal distribution, in which case the Mann-Whitney test was used. The Shapiro-Wilk test was used to test for normality of distribution.

Ethical approval for the study was obtained from the Human Research and Ethics Committee, Universiti Sains Malaysia (USM) for this study. The study was also approved by the Ministry of Education of Malaysia. Informed consent was obtained from the parents of all children who participated in the study.

RESULTS

None of the 37 subjects had *Trichuris* dysentery syndrome. The treatment and placebo groups were comparable in age, gender, anthropometric parameters and intensity of infection (Table 1).

Table 1
Baseline characteristics of study subjects.

Characteristics		Albendazole (n=18)	Placebo (n=19)
Age (months)	Median (range)	88.2 (79.2; 102.0)	88.8 (79.2; 102.0)
Sex	Male	9	10
	Female	9	9
Family income ^a	n (%)	16 (43.2)	17 (45.9)
Eggs per gram (x 10 ³)	Median (range)	8.2 (0.8; 70.0)	8.6 (2.4; 78.6)
Height (cm)	Mean (SD)	112.7 (6.2)	115.7 (5.7)
Weight (kg)	Median (range)	17.9 (15.8; 27.2)	19.6 (15.4; 34.6)
WHZ (Z score)	Median (range)	-0.4 (-1.9; 2.0)	-0.3 (-1.7; 4.0)
WAZ (Z score)	Median (range)	-1.7 (-2.8; 0.6)	-1.4 (-2.8; 1.6)
HAZ (Z score)	Mean (SD)	-2.1 (0.9)	-1.6 (0.8)

SD, standard deviation; WHZ, weight for height Z score; WAZ, weight for age Z score; HAZ, height for age Z score.

^aFamily income less than RM 500 or USD 150

The *t*-test was used where the parameter is expressed as a mean and the Mann-Whitney test was used where the parameter is expressed as a median.

There were no dropouts at 3 and 6 months but 4 subjects (3 treatment and placebo) were lost to follow-up at 12 months and were not included in the analysis. The only statistically significant difference in the anthropometric parameters between the two groups was an improved raw height in the placebo group compared to the albendazole treated group at 6 months ($p=0.04$, Table 2). There was a trend towards a similar difference in HAZ between the two groups at 6 months that did not reach statistical significance (Table 2). The difference in height and HAZ score between the 2 groups disappeared by 12 months (Table 2).

Urinary TNF-alpha levels did not differ between the two groups at baseline (Table 3) or at 1 month post-treatment ($p = 0.8$).

DISCUSSION

The treatment of trichuriasis in Malay

primary school children with light to moderate infection did not have any growth benefits. There was also no evidence the infection at this intensity caused a systemic inflammatory response measurable by urinary TNF-alpha level. These findings suggest mild to moderate trichuriasis infection does not cause a significantly measurable inflammatory response or impair growth.

Previous randomized controlled studies showing a beneficial effect for treating trichuriasis have been conducted among populations with a high prevalence of concomitant hookworm infection (Stephenson *et al*, 1989; Mahendra Raj, 1998; Albonico *et al*, 2008). There is little data on the effect of treating light to moderate trichuriasis in populations with low hookworm prevalence. One mechanism by which hookworm infection may contribute to growth impairment is chronic intestinal blood loss (Elias *et al*, 1997). In northeastern Peninsular Ma-

Table 2
Differences in anthropometric measurements after randomization of treatment.

Anthropometric parameters	Albendazole	Placebo	<i>p</i> -value
Change at 3 months from baseline	<i>n</i> = 18	<i>n</i> = 19	
Weight (kg) Median (range)	0.6 (0.0; 2.2)	0.6 (0.0; 2.4)	0.8
Height (cm) Mean (SD)	2.0 (0.6)	2.4 (0.9)	0.1
WHZ (Z score) Mean (SD)	-0.01 (0.3)	-0.05 (0.4)	0.4
WAZ (Z score) Median (range)	0.2 (0.0; 0.8)	0.2 (0.0; 0.6)	0.8
HAZ (Z score) Mean (SD)	0.4 (0.1)	0.4 (0.2)	0.2
Change at 6 months from baseline	<i>n</i> =18	<i>n</i> =19	
Weight (kg) Median (range)	1.0 (0.4; 4.2)	1.6 (-0.2; 3.2)	0.09
Height (cm) Mean (SD)	3.5 (0.9)	4.1 (0.7)	0.04*
WHZ (Z score) Mean (SD)	0.01 (0.3)	-0.04 (0.3)	0.6
WAZ (Z score) Mean (SD)	0.4 (0.2)	0.5 (0.2)	0.4
HAZ (Z score) Mean (SD)	0.6 (0.2)	0.7 (0.1)	0.08
Change at 12 months from baseline	<i>n</i> =15	<i>n</i> =18	
Weight (kg) Median (range)	2.6 (1.2; 7.2)	2.5 (1.2; 6.6)	0.8
Height (cm) Mean (SD)	6.2 (1.2)	6.3 (1.1)	0.7
WHZ (Z score) Mean (SD)	0.5 (0.6)	0.1 (0.6)	0.08
WAZ (Z score) Median (range)	1.0 (0.6; 2.3)	0.8 (0.5; 1.6)	0.4
HAZ (Z score) Mean (SD)	1.1 (0.2)	1.1 (0.2)	0.9

n, number of subjects; SD, standard deviation.

*Significant *p*-value <0.05

The *t*-test was used where the parameter was expressed as a mean and the Mann-Whitney test was used where the parameter was expressed as a median.

Table 3
Urinary TNF-alpha levels at baseline and 1 month post-treatment.

Time collected	Urinary TNF-alpha concentration (pg/ml) ^a		<i>p</i> -value
	Albendazole (<i>n</i> =18)	Placebo (<i>n</i> =19)	
Baseline (x 10 ⁻²)	19.0 (19.0; 19.1)	19.0 (19.0; 19.1)	0.4
1 month after randomization	19.0 (18.9; 19.1)	19.0 (18.9; 19.1)	0.8

^aMedian (range)

laysia, trichuriasis does not cause occult gastrointestinal blood loss in the absence of overt *Trichuris* dysentery syndrome (Mahendra Raj, 1999).

The paradoxical finding in this study that subjects treated with albendazole

have a delay in vertical growth at 6 months is interesting but must be interpreted with caution. It is possible this constitutes a type 1 error. A previous study showed an adverse effect on growth among children with light trichuriasis treated with

1,200 mg of albendazole but not with a 400 mg dose (Forrester *et al*, 1998). In our study we used a dose of 800 mg, suggesting treating light infection with albendazole may have an adverse effect on growth. A direct toxic effect from albendazole is a potential explanation, as could the speculation that light trichuriasis may confer an advantage to the host. In this study by 12 months post-treatment there were no differences between the study groups. Stool examinations were not repeated in the current study; however, it is common for reinfection to occur (Jia *et al*, 2012).

Light *Trichuris* infection did not elicit a systemic inflammatory response as measured by urinary TNF-alpha. This is in contrast with children having *Trichuris* dysentery syndrome (MacDonald *et al*, 1994). The absence of inflammatory response gives an advantage to the parasite and host. Without a systemic inflammatory responses measured by TNF-alpha, the host does not have impaired growth, maintains adequate nutrition needed by the parasite and results in a reduced host immunological response (Th2 mediated) which might otherwise have resulted in expulsion of the parasite (Duff *et al*, 1999; Stephenson *et al*, 2000; Ierna *et al*, 2009).

A recent study among patients with inflammatory bowel disease found infecting with the eggs of *Trichuris suis* reduces disease activity, a beneficial effect thought to be mediated by modulation of the host immune response (Summers *et al*, 2003, 2005). It is tempting to postulate that in areas of the world where the risk of potentially serious bacterial or protozoal intestinal infection is high, mild trichuriasis may favorably modulate the inflammatory response to such infections and confer an advantage to the host (Fiasse and Latinne, 2006).

In conclusion, there is no evidence that treatment of light to moderate trichuriasis in primary school children in north-eastern Peninsular Malaysia confers a growth benefit, nor is there evidence mild to moderate trichuriasis incites a systemic inflammatory response. While admittedly speculative, it is possible mild *T. trichiura* infections may confer an advantage to the host in the ecological setting of this study.

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