Ascaris and Growth Rates: A Randomized Trial of Treatment

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Abstract: Three hundred forty-one Tanzanian preschool children were randomly assigned to levamisole or placebo treatment given at three-month intervals. Weights and heights were measured at the tri-monthly treatment visits for a period of one year. Among the 273 children who were seen and weighed at the one-year follow-up visit, the rate of weight gain was 8 per cent greater for those receiving levamisole than for placebo-treated controls (p = .06). In 78 children known to be infected with *Ascaris* at baseline, the rate of weight gain was 21 per cent greater in children treated with levamisole than in those receiving placebo (p = .03). The rate of height gain was no different for treatment and placebo groups. (*Am J Public Health* 69:987-991, 1979.)

Although ascariasis is very common, affecting perhaps one-fourth of humanity,[1] the importance of its effect on the nutritional state of the host remains unclear.[2] Ascariasis has been reported to be associated with anthropometric[3,4] and biochemical[5] indicators of malnutrition in endemic areas, but other studies have failed to confirm these associations.[6,7] Studies of infected children on metabolic wards have demonstrated a malabsorption state, reversible with treatment, for protein,[8-10] fats and carbohydrates,[9,10] and vitamin A.[11] We therefore hypothesized that the periodic administration of an ascaricide as part of well-child care would produce a measurable increase in the growth rates of children in an area where malnutrition and ascariasis were both common.

Subjects and Methods

The site selected for this study was Ubiri village near Lushoto, Tanzania, which is located in a fertile, mountainous area. This village was known to have a high prevalence of malnutrition as well as ascariasis. As no well-child services existed in the village, a mobile clinic was held at three-month intervals. After an initial census, which indicated that there were approximately 600 preschool children, mothers were encouraged to bring their preschool children to the clinic along with a stool specimen. The entire study was reviewed and conducted in conformance with Tanzanian guidelines for the protection of human subjects (see Appendix).

Three-hundred sixty-seven children enrolled in the two initial clinic visits in April and July 1976. They were weighed, while barefoot and lightly clad, on an "Avery" platform balance scale, which was frequently calibrated with a 10 kg standard weight. Length was measured on a horizontal, calibrated board with footpiece and movable headpiece. Each child received routine immunizations and four cups of corn-soy flour.

At the first visit, children over five months of age were allocated to either treatment or placebo groups, using a table of random numbers. There were 341 children ranging from six to 91 months of age; 166 entered the treatment group, and 175 were allocated to the placebo group. Treatment consisted of levamisole ("Ketrax"), which is widely considered a treatment of choice for ascariasis,[12] administered in syrup form at a dosage of 2.5 mg/kg. The drug was given directly by our staff with an oral syringe to insure compliance. Control children received a flavored sucrose syrup.

At follow-up visits every three months, children were weighed and measured as before by a person unaware of their treatment status. Again, a dose of levamisole or placebo was administered along with required immunizations, and each child received four cups of corn-soy flour. Home visits were carried out at the six and 12-month intervals if mothers did not voluntarily bring their children to clinic.

Initial and follow-up stool specimens were preserved

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TABLE 1—Mean Nutritional Status and Prevalence of Ascariasis by Age at Entry into Study (Nutritional Status Expressed as Mean of Observed/Expected Weights)

	Age in Months						
	6-11	12-23	24-35	36-47	48-59	60+	Total
No. children	24	66	69	77	59	46	341
Mean nutritional status	.76	.75	.79	.80	.82	.77	.79
No. stools examined	9	34	40	43	37	19	182
No. positive stools	1	13	19	21	26	17	97
Per cent positive stools	11	38	48	49	70	89	53

with formalin and examined after randomization by a modified formol-ether concentration technique.[13] If positive, and if the quantity of stool was sufficient, quantitative egg counts were performed using the Katoh method.[14]

Growth rates were calculated as the slope of a line determined by the measured weights or heights over the one-year study period using the least squares method. A child was included in the analysis of growth rates if a measurement was obtained at baseline and at the 12-month follow-up visit. Baseline nutritional status was defined as the ratio of observed weight at baseline over the expected weight for age as determined by the median of the National Center for Health Statistics growth charts.[15]

Growth rates for the control and treatment groups were compared, using an analysis of covariance model that included as independent variables the treatment (levamisole or placebo), year of age at start of study, month starting the study (April or July), and baseline nutritional status.

Results

The 341 study children were measured and treated at an average of 74 per cent of possible follow-up visits (four per child) over one year. At the 12-month visit, 282 of the children (82.6 per cent) were seen. The follow-up rates were similar in the levamisole (79.5 per cent) and placebo (84 per cent) groups. The 59 drop-outs at the one-year point include one child who died of measles (levamisole group), 54 whose families were temporarily out of the village that day or had permanently moved, and four whose status was unknown. The children of the families who were temporarily or permanently out of the village at one year were reported by neighbors to be living at the time the family left the village.

As growth rates were calculated only if a measurement was obtained at 12 months, a total of 273 growth rates were obtained for weight and 268 for length.

Baseline Characteristics of Study Children

Nutritional status, expressed as the ratio of observed over expected weight for age, varied only slightly with age, with an overall mean of 0.79 (Table 1). This corresponds to approximately one-half of the study children falling below the third percentile of the National Center for Health Statistics standard.

A total of 182 stools were examined at entry into the study. An increasing prevalence of ascariasis with age is apparent (Table 1). In 26 stools found to be positive for *Ascaris* by the concentration method, the mean quantitative count was 6,300 ova per gram of stool with a range of 400-30,000 ova per gram. Hook-worm ova were seen in 20 of the 182 baseline stools examined; the prevalence being 10 per cent in those assigned to levamisole and 12 per cent in the placebo group. No other helminthic infections were found.

Baseline characteristics of the 341 children randomized to levamisole and placebo treatment groups were similar (Table 2). Treatment groups were also comparable within the subset of 97 children initially positive for ascariasis.

The mean baseline nutritional status for the 97 children known to be infected with *Ascaris* at entry was .79, and for the 85 children known to be negative at entry was .80. Stratification by age also failed to reveal a consistent association between nutritional status and ascariasis (data not shown).

TABLE 2—Baseline Characteristics by Treatment Group (± standard error)

	Total Study Group (N = 341)		Children with Ascariasis at Entry (N = 97)	
	Levamisole (N = 166)	Placebo (N = 175)	Levamisole (N = 45)	Placebo (N = 52)
Mean Weight	10.98 kg (±.26)	11.45 kg (±.25)	12.06 kg (±.44)	12.14 kg (±.42)
Mean Length	85.63 cm (±1.02)	87.56 cm (±.99)	91.06 cm (±1.63)	90.28 cm (±1.55)
Mean Nutritional Status	.79 (±.01)	.79 (±.01)	.79 (±.02)	.79 (±.02)
Mean Age	34.2 months (±1.4)	37.9 months (±1.4)	42.2 months (±2.75)	42.2 months (±2.31)
Ascariasis Positive (%)	51.1	55.3		
Entered in First Session (%)	60.2	54.9	60	52
Followed for Full Year (%)	79.5	84.0	87	85

TABLE 3—Growth Rates in Levamisole and Placebo Groups

Baseline Stool Status	Weight Gain (kg/year)				Length Gain (cm/year)			
	No.	Levamisole	Placebo	% Diff.	No.	Levamisole	Placebo	% Diff.
Ascaris positive	78	2.31	1.91	+21*	79	7.24	7.38	−2
Ascaris negative	68	2.08	1.84	+13	66	7.86	8.00	−2
Unknown	127	1.95	1.97	− 1	123	7.63	7.86	−3
All Children	273	2.08	1.92	+ 8†	268	7.58	7.73	−2

*p = .03
†p = .06

Growth Rates

The rate of weight gain for the treatment group was 2.08 kg/year; for the controls that was 1.92 kg/year (Table 3). There were no differences in length gain between the two groups. In the subgroup of children who were found to have ascariasis at the time of entry into the trial, 78 were followed for 12 months. Within this subgroup the rate of weight gain was 2.31 kg/year with levamisole treatment and 1.91 kg/year with placebo, while length gain was the same for both groups. There were no statistically significant differences in growth rates between treatment groups for children whose baseline stools were either negative for *Ascaris* ova or not obtained.

Follow-up Stool Examinations

At least one stool was obtained during the follow-up period for 54 (56 per cent) of the 97 children initially positive for *Ascaris* at baseline. Of those receiving levamisole, 32 per cent were positive at follow-up, compared with 63 per cent of those receiving placebo (Table 4).*

Discussion

In this study, preschool children receiving periodic doses of levamisole gained weight more rapidly than those who received placebo. This effect in the overall group was of marginal statistical significance; however, this group contained both infected and non-infected children. One would expect that the greatest effect of treatment would be within the group of initially infected children, and that it would be manifested primarily in weight gain rather than length gain, as the latter is a less sensitive indicator of nutritional changes. The fact that the difference in growth rate was greatest and statistically significant only in the subgroup of initially infected children supports the hypothesis that treatment causes an increase in growth rate.

In a study finding a statistically significant difference in outcomes, it is important to consider whether the magnitude of the observed differences is biologically important. In this study, the children who were initially infected gained weight approximately 20 per cent faster than control children. As the median of standard growth curves represents a cumulative weight gain approximately 20 per cent greater than the third percentile, the difference seen between treatment groups in this study is indeed meaningful.

Several alternative explanations of the differences in growth rate were considered. Although the design of the study was double blind, mothers could have realized what treatment their child received by the passage or non-passage of worms in the stool after treatment. However, to cause bias this knowledge would have had to affect the child's weight, which is unlikely, or to have influenced the mother in whether she brought her child for follow-up. The follow-up rates were in fact similar for both treatment groups, and virtually all cases lost to follow-up were because the family was out of the village on the clinic day.

Bias in assessment of weight and length was unlikely, as the person doing the measurement was unaware of treatment groups; hundreds of children were measured in a day, and there was little chance to converse with mothers and perhaps uncover treatment status. Moreover, weight and length are relatively objective measurements.

Age, baseline nutritional status, and session starting were significant indicators of growth rate and thus could have been confounding factors if they were also related to treatment group. However, the distribution of these factors between treatment groups was similar. Furthermore, adjustment for these factors was made in the final analysis of covariance model. Adjustment actually caused a slight increase in the differences between treatment groups compared to the crude growth rates as shown in Table 2.

To our knowledge, the only similar trials have been conducted in India.[7, 16] In both of these studies, children were not randomly assigned to treatment or placebo, but rather, all preschool children in two villages were treated, with children of other villages serving as controls. One of these stud-

TABLE 4—Proportion of Follow-Up Stools with *Ascaris* Ova in Children Positive at Baseline

Follow-up Stool	Levamisole	Placebo
Positive	7 (32%)	20 (63%)
Negative	15 (68%)	12 (37%)
TOTAL	22	32

$\chi^2 = 4.9$, $p < .05$

*If more than one stool was obtained per child, only the first one was used in this analysis.

ies reported a greater increase in weight after one year in the levamisole group which was statistically significant. A preliminary report after only three months from the other Indian study showed no differences in growth rates between levamisole and untreated villages. Latham, et al,[17] have reported that Kenyan children with ascariasis exhibit increases in weight and skinfold thickness when treated with levamisole, but this study did not have an untreated control group. Controlled trials of antihelminthics in *Ascaris*-infected chicks and weanling pigs have shown more rapid weight gain in treated animals.[18-20]

The baseline data in this study show no difference in nutritional status between infected and non-infected children. Other cross-sectional data from the United States, India, and Kenya[5-7, 17] have likewise failed to demonstrate an association between ascariasis and anthropometric indicators of nutritional status. However, cross-sectional studies of this association are limited by the fact that in an *Ascaris*-endemic community, there may be frequent movement from infected to non-infected status and vice versa.[21] This was seen in our data, where 37 per cent of *Ascaris*-positive children treated with placebo were negative when examined during the follow-up period (Table 4), and 50 per cent of the 22 children initially negative and treated with placebo were later found to be positive. Since nutritional status reflects the cumulative experience of children over a long period, and a single stool examination apparently is not an accurate way to classify a child's long-term infection status, the lack of association between these two variables in cross-sectional studies is not surprising.

Several mechanisms exist whereby ascariasis may cause malnutrition: 1) the parasites may actually ingest and metabolize nutrients eaten by their host; 2) they may cause nutrient loss through the production of their ova, which are not available for host usage; and 3) the parasites may cause a malabsorption of nutrients through some disruption of normal intestinal processes. The latter two mechanisms were studied by Venkatachalam, et al,[8] who concluded that the loss of protein through ova production was negligible, but that a mean fecal nitrogen loss of 1.3 gm/day occurred in children with ascariasis, which reduced to .7 gm/day when the ascariasis was treated. Tripathy, et al,[9, 10] have demonstrated a substantial malabsorption of fat and carbohydrate as well as protein, which improved with eradication of the worms. Small bowel biopsies in several of the children showed flat villi which reverted to normal after the worms were expelled. Jejunal abnormalities have also been demonstrated by Maxwell, et al,[22] and Lagundoye[23] in patients with ascariasis.

The worm burdens exhibited by the children in this study, although assessed by a small number of egg counts, would probably be characterized as light to moderate. Counts of over 150,000 ova per gram are commonly seen in ascariasis, even in the southern United States.[24] Levamisole did produce a significant reduction in *Ascaris* prevalence in stools obtained at follow-up visits, although less than the 90 per cent or more cure rates seen in short-term trials.[12] This can probably be attributed in part to our treatment interval; because the time from ingestion of *Ascaris* ova to the onset of egg production is approximately two months, there was ample time for re-infection to occur.

The low prevalence of hookworm infection and absence of trichuriasis in spite of high prevalence of ascariasis in the study population may appear unusual. However, this is consistent with other unpublished surveys conducted by the University of Dar es Salaam in the relatively cool, mountainous area of Lushoto. In the surrounding lowlands, both hookworm and trichuris are more common, and the prevalence of ascariasis is much lower.

Although ascariasis is often considered to be a cause of malnutrition in children,[1, 25] data to support this contention are sparse. The results of this trial are consistent with a causal association between ascariasis and malnutrition. Periodic ascaricide treatment may be a practical adjunct in nutrition programs in selected areas, as the cost of the drug is less than $.25 per year per child. However, further studies which extend the treatment period beyond one year and consider the optimal drug choice and treatment interval are indicated before recommending that periodic ascaricide treatment be carried out routinely in young children. In the meantime, this study supports the desirability of treating children known to have ascariasis.

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APPENDIX
Protection of Human Subjects

As this study was funded and conducted within Tanzania, Tanzanian regulations for the protection of human subjects were followed. The study proposal was reviewed first at the level of the Faculty of Medicine, and subsequently by the Research and Publication Committee representing all Faculties of the University of Dar es Salaam. After determining that the study was scientifically appropriate and that human subjects were not put at risk because of the research, funding was allocated and the study was formally approved by the Vice-Chancellor of the University acting on behalf of the Prime Minister's Office. It was felt that meaningful individual written informed consent could not be obtained in the context of this study, and this is not a requirement in Tanzania.

In the conduct of the study, the official established Tanzanian "10-cell" system of communication was used. It was explained to the village chairman and 10-cell leaders that the investigators were from the University of Dar es Salaam and were conducting a study of a method to promote the growth of children. It was explained that all children would received full well-child care, including immunizations and a food supplement and, in addition, one of several treatments which were being studied. Mothers were requested to bring their preschool children to a special clinic for this study. The information was passed on to households by the 10-cell leaders, and reinforced by direct contact by the investigators whenever possible.

As the families and children were not institutionalized, enrollment and follow-up in the study required continued active participation. At the end of the trial period all children received levamisole treatment.

On the basis of the findings in this study, the authors have developed a proposal for a similar trial extending over two years and using piperazine as well as levamisole. This study has been reviewed by the Peter Bent Brigham Hospital Human Subjects Committee. The committee determined that human subjects will not be at risk because of the study and approved the proposal subject to approval in Tanzania, acknowledging that individual written informed consent will not be obtained. Approval has also been obtained in Tanzania.