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Original Article

Efficacy of mebendazole and levamisole, alone or in combination, for soil-transmitted helminthiasis

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Abstract

Background The World Health Organization (WHO) recommends four, single-dose drugs (albendazole, levamisole, mebendazole, and pyrantel pamoate) for management of soil-transmitted helminthiasis (STH). Previous studies have shown varied and inconsistent outcomes of these STH treatments.

Objective To compare the efficacy of mebendazole and levamisole, alone or in combination, for the treatment of STH.

Methods An open randomized controlled trial was conducted in Secanggang, North Sumatera from August to October 2009. School-aged children with STH infection were randomized into three groups. Group I received a single dose of mebendazole (500 mg); group II received a single dose of levamisole (2.5 mg/kg); and group III received a single dose of mebendazole-levamisole combined. Stool samples were collected at baseline, and the 1st, 2nd, 3rd, and 4th weeks after treatment and examined by the Kato-Katz technique. Statistical analyses were Kruskal-Wallis test for cure rate and Analysis of Variance (ANOVA) test for egg reduction rate.

Results STH was diagnosed in 197 children with the following parasite species: *Ascariasis* (96 children, 48.7%), *Trichuriasis* (58 children, 29.4%), and mixed infection (43 children, 21.8%). We found no hookworm infection in any of our subjects. Groups I and III had significantly higher efficacy (P=0.0001) against STH (egg reduction rate 99.3% and 99.9%; cure rate 92.2% and 98.4%, respectively) at 4th week of treatment.

Conclusion A single dose of mebendazole alone and combined with levamisole have better efficacy compared to a single dose of levamisole for the treatment of STH. The highest efficacy of these treatments is noted at the 4th week after drug administration. **[Paediatr Indones. 2014;54:9-14.]**.

Keywords: *soil-transmitted helminth, mebendazole, levamisole, combination*

Soil-transmitted helminths (STH) are a group of parasitic nematode worms causing human infection through contact with parasite eggs or larvae that thrive in the warm and moist soil of the world's tropical and subtropical countries. Of particular worldwide importance are *Ascaris lumbricoides, Trichuris trichiura, Necator americanus, and Ancylostoma duodenale*.[1]

In 1999, the WHO estimated that these infections represented more than 40% of the disease burden from all tropical diseases, excluding malaria.[2-4] An estimated 4.5 billion individuals might be infected with *A. lumbricoides*, close to 800 million with *T. trichiura*, and more than 700 million with hookworm.[5] School-aged children in developing countries bear the greatest health burden due to helminth infections.[6] Factors influencing the prevalence of STH are hygiene, sanitation, socioeconomic level, educational level, and ecosystem differences.[6,7] In Indonesia, the prevalence of STH remains high at

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60-90%, and is related to the location and cleanliness of the environment.[6]

Four, single-dose antihelminthic drugs, albendazole, levamisole, mebendazole, and pyrantel pamoate, are available for the treatment of STH infections in pharmacological-based control programs.[8,9] These drugs are recommended by the WHO.[9]

The objective of this study was to compare the efficacy of mebendazole and levamisole, alone or in combination, for the treatment of STH.

Methods

We conducted an open randomized controlled trial in Secanggang, North Sumatera from August until October 2009. Subjects were primary school-aged children infected with STH. The inclusion criteria for subjects were primary school aged children, infected with STH, and had not taken antihelminthics for at least the one month prior to the study. Patients were excluded if they refused to swallow the antihelminthic or submit stool specimens after treatment, or had diarrhea, cough, or fever.

Prior to treatment, each participant underwent anthropometric assessment and completed a questionnaire on socioeconomic and hygiene status. Participants were randomly assigned following a simple randomization procedure (random table) into three groups. Group I received single-dose mebendazole (500 mg); group II received single-dose levamisole (2.5 mg/kg); and group III received single-dose mebendazole-levamisole combined.

Subjects' stool specimens were collected and examined at baseline, and on the 1st, 2nd, 3rd, and 4th weeks after treatment. Outcome measures were cure rate and egg reduction rate. Subjects were considered to be cured when no worm eggs were found in their stool specimens. All adverse reactions were recorded. Written consent was obtained from subjects' parents. This study was approved by the Medical Ethics Committee of the University of North Sumatra Medical School.

We used SPSS version 14.0 for data processing. Statistical analyses were carried out by *Kruskal-Wallis and Analysis of Variance* (ANOVA) tests. Differences were considered to be statistically significant at P values <0.05, and 95%CI.

Results

We performed stool examinations on 415 primary school-aged children, of whom 197 had STH infections. We enrolled and randomly assigned them into three groups. Group I (67 children) received single-dose mebendazole 500 mg, group II (65 children) received single-dose levamisole 2.5 mg/kg, and group III (65 children) received single-dose mebendazole-levamisole **(Figure 1).**

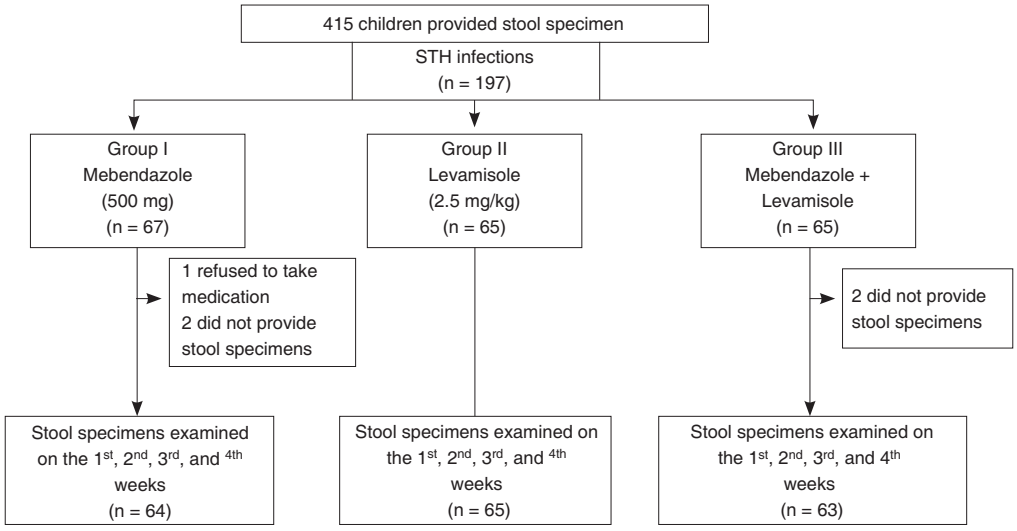

Figure 1. Study profile

The prevalence of STH infections was 47.5%, comprised of 48.7% ascariasis, 29.4% trichuriasis, and 21.8% mixed infection. We found no hookworm infection. The baseline characteristics of each group were similar. Number of males and females in all groups was almost the same. The average age of subjects was 9.3 years, with the percentage of body weight based on height for all groups within normal limits. There were no statistically significant differences in the average number of eggs between the groups before treatment **(Table 1).**

Drug effectiveness based on egg reduction rate **(Table 2)** was significantly different between group III (combination treatment) from group II (levamisole alone) each of the 1st to 4th week after treatment. There was no significant difference in egg reduction

Table 1. Baseline characteristics of subjects

Characteristics	Group I Mebendazole (n = 64)	Group II Levamisole (n = 65)	Group III Mebendazole + Levamisole (n = 63)
Gender, n (%)			
Males	34 (53.1)	34 (52.3)	31 (49.2)
Females	30 (46.9)	31 (47.7)	32 (50.8)
Mean age (SD), years	9.0 (1.84)	9.2 (2.06)	9.7 (1.62)
Mean weight/height, % (SD)	94.1 (8.02)	97.7 (8.03)	95.8 (7.89)
Mean egg count, n (SD)	416.8 (203.81)	397.4 (192.97)	397.8 (190.16)
Type of worm eggs, n (%)			
A. lumbricoides	31 (48.4)	33 (50.7)	30 (47.6)
T. trichiura	18 (28.1)	20 (30.8)	20 (31.7)
A. lumbricoides + T. trichiura	15 (23.4)	12 (18.5)	13 (20.7)

Table 2. Drug effectiveness based on egg reduction rate (1st to 4th weeks after treatment)

Variables	Group I Mebendazole (n = 64)	Group II Levamisole (n = 65)	Group III Mebendazole + Levamisole (n = 63)	95% CI of differences	P
Mean egg count, n (SD)					
1st week					
	34.1 (62.14)[a]	48.1 (69.91)[b]	17.8 (52.81)	10.40 - 51.66	0.016
2nd week	14.3 (36.53)[c]	48.1 (69.91)[d]	17.8 (52.81)	10.40 - 51.66	0.001
3rd week	7.5 (20.92)[e]	24.1 (44.43)[f]	3.2 (13.61)	10.38 - 32.69	0.006
4th week	2.9 (10.52)[g]	13.8 (29.54)[h]	0.4 (2.89)	6.26 - 21.48	0.0001

a: mebendazole-levamisole vs mebendazole; P=0.085
b: mebendazole-levamisole vs levamisole; P=0.009
c: mebendazole-levamisole vs mebendazole; P=0.806
d: mebendazole-levamisole vs levamisole; P=0.009
e: mebendazole-levamisole vs mebendazole; P=0.249
f: mebendazole-levamisole vs levamisole; P=0.0001
g: mebendazole-levamisole vs mebendazole; P=0.068
h: mebendazole-levamisole vs levamisole; P=0.001

Table 3. Drug effectiveness based on cure rate (1st to 4th weeks after treatment)

Variables	Group I Mebendazole (*n* = 64)	Group II Levamisole (*n* = 65)	Group III Mebendazole + Levamisole (*n* = 63)	95% CI of differences	P
Cure rate, n (%)					
1st week	43 (67.2)[a]	29 (44.6)[b]	49 (77.8)	0.15 - 0.49	0.001
2nd week	50 (78.1)[c]	39 (60.0)[d]	53 (84.1)	0.08 - 0.39	0.006
3rd week	55 (85.9)[e]	47 (72.3)[f]	58 (92.1)	0.08 - 0.34	0.005
4th week	59 (92.2)[g]	49 (75.4)[h]	62 (98.4)	0.12 - 0.36	0.0001

a: mebendazole-levamisole vs mebendazole; P=0.257
b: mebendazole-levamisole vs levamisole; P=0.001
c: mebendazole-levamisole vs mebendazole; P=0.491
d: mebendazole-levamisole vs levamisole; P=0.004
e: mebendazole-levamisole vs mebendazole; P=0.366
f: mebendazole-levamisole vs levamisole; P=0.003
g: mebendazole-levamisole vs mebendazole; P=0.102
h: mebendazole-levamisole vs levamisole; P=0.0001

rate between group III and group I (mebendazole alone) each of the 1st to 4th weeks after treatment.

We found significant differences in cure rates between group III (combination treatment) and group II (levamisole alone) each of the 1st to 4th weeks after treatment. No significant differences were found between group I (mebendazole alone) and group III (**Table 3**).

Discussion

We found the prevalence of STH in our study to be 47.5%, comprised of 48.7% ascariasis, 29.4% trichuriasis, and 21.8% mixed infection. Human intestinal helminths and malaria are among the most common infections in the developing world.[10] One-third of the world's population is infected with one or more species of intestinal helminths,[11] and children are reported to have a prevalence rate ranging between 50-80%.[12] Infection with *T. trichiura* and *A. lumbricoides* typically reaches the highest incidence at 5 to 10 years of age.[3]

We hoped that our study results would help guide the WHO program, so schoolaged children were selected as the study sample since they are at high risk of STH infection. The mean age of subjects was 9.3 years, with similar incidence between males and females. The World Health Assembly urged the international community to take firm action against STH infections in 2001. Since then, the Partners for Parasite Control (PPC) set out to regularly deworm 650 million school-aged children at risk of STH and schistosomiasis by 2010.[13] The WHO recommends mass treatment of children in school, where the prevalence of infection with schistosomes or intestinal nematodes is 50% or greater.[14]

Antihelminthics used in this study were single-dose mebendazole and levamisole, alone or in combination. Both the selection of drugs and doses were based on WHO recommendations. Effective, broad-spectrum, single-dose, safe, and relatively inexpensive drugs are now available for the treatment of helminth infections.[15] The four drugs recommended by WHO for treatment are albendazole (400 mg), levamisole (2.5 mg/kg), mebendazole (500 mg), and pyrantel pamoate (10 mg/kg).[16] All four anthelminthics are given as a single dose and are not recommended in children <12 months of age.[17] The goal of treatment for STH infections is to remove adult worms from the gastrointestinal tract. The drugs most commonly used for the eradication of STH infections are mebendazole and albendazole. Both agents are effective against ascaris in a single dose. However, in hookworm infections, a single dose of mebendazole has a low cure rate, and albendazole is more effective. Conversely, a single dose of albendazole is not effective in many cases of trichuriasis. Both pyrantel pamoate and levamisole are regarded as alternative drugs for the treatment of hookworm and ascaris infections, although the former is not effective for the treatment of trichuriasis and their doses are based on body weight.[1]

Two indicators used to determine the efficacy of an antihelminthic in human medicine are the cure rate (CR) and the egg reduction rate (ERR).[18] A study in Zanzibar showed very high efficacy of mebendazole and levamisole alone or in combination against *A. lumbricoides* (ERR 98.5%, 99.0%, 99.1%; CR 96.5%, 91.2%, 98.5%, for levamisole, mebendazole, and mebendazole-levamisole combination, respectively). Mebendazole alone and in combination with levamisole had better efficacy than levamisole alone for *T. trichiura* infection (ERR 81% and 85% vs 41.5%), respectively. Using a combination treatment, the egg reduction rate for hookworm infection was 88.7% with CR 26.1%, with significantly lower ERR and CR for either drug alone (ERR 61.3%, CR 11.9% for levamisole and ERR 52.1%, CR 7.6% for mebendazole).[8]

More than 60 clinical trials showed a high efficacy of levamisole against *A. lumbricoides* and hookworm infections. Cure rate of 86-100% and ERR of 96-98% with a single dose have been reported for *A. lumbricoides* infection. For hookworm infection, CR in the range of 66-100% and ERR 86-99% have been reported. Levamisole had a varied effect against *T. trichiura*, with CR of 16-18% and ERR of 73%.[19] In an Iranian study, treatment of STH with a single-dose of levamisole (2.5 mg/kg) showed of high efficacy, with CR of 100% for hookworm infections, 96% for ascariasis, and 98% for trichuriasis.[20]

In our study at the end of the 4th week of stool examination, the egg reduction rates were 99.3%, 96.5%, and 99.9% for mebendazole alone, levamisole alone, and the combination, respectively. Cure rates

were 92.2%, 75.4%, and 98.4% for mebendazole alone, levamisole alone, and the combination, respectively. Mebendazole alone and in combination with levamisole were more effective than levamisole alone for ascariasis and trichuriasis STH infections. The efficacy of mebendazole did not differ significantly from that of its combination with levamisole.

Overall, side effects of antihelminthic drugs were negligible and important adverse events were virtually nonexistent. However, the safety of anthelminthic drugs is of utmost importance because large portions of the population are normally treated.[15] No adverse events were noted in our study.

A limitation of this study was that no blinding was done, so we cannot exclude the possibility of bias. Also, we did not assess the effectiveness of anthelminthics based on worm type. We only assessed the effect of worm infection on the occurrence of malnutrition. The malnutrition status was assessed by the percentage of body weight according to height. We found good nutritional status for all three groups of subjects studied. Further research will be needed to assess the effectiveness of anthelminthics by worm type and the effect of worm infections on children.

In conclusion, a single dose of mebendazole and its combination with levamisole have a better efficacy than a single dose of levamisole alone for STH treatment. The highest efficacy of these treatments is noted at the 4th week after drug administration.

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