

Efficacy of Albendazole and Mebendazole With or Without Levamisole for Ascariasis and Trichuriasis

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Abstract

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BACKGROUND: Helminthiasis in school-aged children potentially causing physical growth and intellectual development retardation. Trichuriasis was the most common type of helminthiasis in children.

AIM: To investigate the efficacy and side effects of albendazole, albendazole combined with levamisole and mebendazole combined with levamisole for trichuriasis and ascariasis.

METHODS: This study was conducted as a double-blind, randomised clinical trial by comparing the efficacy and side effects of albendazole, albendazole combined with levamisole and mebendazole combined with levamisole for trichuriasis. The sample of this study were 180 elementary school students at Deli Serdang Regency State Elementary School, Medan, Indonesia. The study was conducted from April to June 2015.

RESULT: The cure rate of helminthiasis on the 7th day was 81.7% after albendazole therapy, 88.3% after albendazole levamisole therapy, and 83.3% after mebendazole combined with levamisole therapy ($p = 0.577$). Cure rate on the 14th day was 88.3%, 95%, and 91.7% for albendazole, albendazole combined with levamisole, and mebendazole combined with levamisole therapy, respectively ($p = 0.418$). On the 21th day, the cure rate was 88.3%, 96.7%, and 91.7% ($p = 0.230$). Combination of albendazole and levamisole showed the highest cure rate, despite the statistically insignificant difference for all groups ($p > 0.05$). Combination of albendazole combined with levamisole showed better cure rate for mild trichuriasis (95.8%) than albendazole therapy (46.2%) and mebendazole combined with levamisole (83.3%), ($p < 0.05$).

CONCLUSION: Single-dose albendazole, a combination of albendazole and levamisole, and a combination of mebendazole and levamisole had similar efficacy in reducing egg count in helminthiasis. Combination of albendazole and levamisole showed better cure rate for mild trichuriasis and mixed infections. Side effects were similar in all treatment groups.

Introduction

Intestinal worm infection is still a major public health problem in Indonesia, especially in rural areas. In Indonesia and other developing countries, *Ascaris lumbricoides*, *Trichuris trichiura*, and hookworm are the most common intestinal parasites [1], [2]. World Health Organization (WHO) estimated that at least two billion people or nearly one-third of the world's population had been infected with soil-transmitted helminths (STH) or helminthiasis [3]. About 300 million infected people suffered from severe illness, and about 400 million school-aged children worldwide had been infected [4], [5].

Many species of worms had been reported to cause infection in Indonesia. *Trichuris trichiura*, was resided in the human caecum, was the most common cause of helminthiasis and one of the most important intestinal nematodes in human [6], [7]. School-age children were frequently infected with helminthiasis, which potentially causing diarrhoea, nutritional deficiency, anaemia, growth disorders, and intellectual disturbance [8], [9].

Public health program to control helminthiasis was largely dependent on the administration of anti-helminthic drugs for elementary-school children [10]. Theoretically, there were several broad-spectrum anti-helminthic drugs such as albendazole, levamisole,

mebendazole, and pyrantel pamoate with variable advantages and disadvantages [11], [12], [13], [14]. Benzimidazole group was the most common anti-helminthic used in a public health setting [15], [16], [17].

We conducted a clinical trial to compare the efficacy and side effects of albendazole, albendazole with levamisole and mebendazole with levamisole therapy against trichuriasis and ascariasis in elementary-school children to determine the most effective regimen.

Material and Methods

This study was a double-blind, randomised clinical trial comparing the efficacy and side effects of albendazole, albendazole combined with levamisole and mebendazole combined with levamisole for trichuriasis. The sample of this study were 180 elementary-school students at Deli Serdang Regency State Elementary School, Medan, Indonesia. The study was conducted from April to June 2015. Study steps consisted of preparation, data collection, processing, data analysis, and data improvement.

Written informed consent was conducted by all subjects' parents or guardian two weeks before the scheduled intervention date. A container was given to each subject to keep their stool sample at home. The collected stool samples were qualitatively and quantitatively examined by the Kato-Katz method at Parasitology Laboratory of Medical Faculty, University of Sumatera Utara, Medan. Stool sample with a positive finding of trichuriasis was randomised as the study subjects into the three treatment groups. Stool sample examination for evaluation was done on day 7, day 14 and 21 after treatment.

Each subject in the first group was given one tablet of 400 mg albendazole. Second group was given one tablet of 400 mg albendazole and 2 tablets of 25 mg levamisole (for children weighed 10 – 20 kg), or one tablet of 400 mg albendazole and 4 tablets of 25 mg levamisole (for children weighed 21 – 40 kg), or one tablet of 400 mg albendazole and 6 tablets of 25 mg levamisole (for children weighed > 40 kg). The third group was given one tablet of 500 mg mebendazole and levamisole dose is the same as the second group. For the following 14 days, parents were instructed to record any side effect after treatment. Comparison of recovery rate between the intervention groups was analysed using Chi-square test or Wilcoxon test as suitable. The p-value of less than 0.05 was considered significant.

Results

There were 807 Deli Serdang elementary students; after the exclusion, we found 185 students with helminthiasis based on stool examination. Five of them had started therapy before the study. Therefore, they were excluded. The remaining 180 students were study subjects who undergone randomisation into three intervention groups (60 students in each group). The characteristics of the subjects can be seen in Table 1.

Table 1: Characteristics of Subjects

Characteristics	First Group Albendazole (N = 60)	Second Group Albendazole + Levamisole (N = 60)	Third Group Mebendazole + Levamisole (N = 60)
Age, years (mean ± SD)	9.2 ± 1.734	8.9 ± 1.540	9.1 ± 1.567
Sex, n (%)			
Male, n (%)	35 (58.3)	28 (46.7)	31 (51.7)
Female, n (%)	25 (41.7)	32 (53.3)	29 (48.3)
Weight, kg	27.2 ± 7.957	27.1 ± 6.374	27.9 ± 7.363
Height, cm (mean ± SD)	129.5 ± 13.944	132.0 ± 18.516	128.4 ± 12.785
Wight/height (mean ± SD)	97.1 ± 6.574	95.7 ± 13.014	94.1 ± 17.757
Parental occupation			
Entrepreneur	38 (16.7)	14 (23.3)	16 (26.6)
Farmer	11 (18.3)	45 (75)	38 (63.3)
Civil servant	1 (1.6)	-	1 (1.6)
Others	10 (16.6)	1 (1.6)	5 (8.3)
Parental education, n (%)			
Uneducated	1 (0.83)	7 (5.83)	13 (10.83)
Elementary school	22 (18.33)	36 (30)	25 (20.83)
Junior high school	46 (38.33)	38 (31.67)	42 (35)
Senior high school	3 (35.83)	39 (32.5)	38 (31.67)
University	8 (6.67)	-	2 (1.67)
Helminthiasis (%)			
A. lumbricoides	47 (78.3)	34 (56.7)	11 (18.3)
T. Trichur	6 (10)	19 (31.0)	12 (20)
A. lumbricoides + T. trichiura	7 (11.7)	7 (11.7)	36 (60)
A. lumbricoides + T. trichiura + Enterobiuss	-	-	1 (1.7)

The most common helminthiasis was infection by *Ascaris lumbricoides*, followed by mixed infection by *Ascaris lumbricoides* with *Trichuris trichiura*, *Trichuris trichiura* only, and mixed infection by *Ascaris lumbricoides* with *Trichuris trichiura* and *Enterobius vermicularis* as seen in Table 2.

Table 2: Prevalence of helminthiasis

Helminthiasis Etiology	Numbers (%)
<i>Ascaris lumbricoides</i>	92 (51.11)
<i>Trichuris trichiura</i>	37 (20.55)
A. lumbricoides + T. trichiura	50 (27.78)
A. lumbricoides + T. trichiura + E. vermicularis	1 (0.56)

Subjects with mild *A. lumbricoides* infection were 50 children (83.3%) in the first group, 39 students (65%) in the second group, and 46 students (76.7%) in the third group. Subjects with mild *T. trichiura* infection were 13 children (21.7%) in the first group, 24 children (40%) in the second group, and 24 children (40%) in the third group.

Table 3: Basic Characteristics of Research Based on Intensity of Infection

Characteristics	First Group Albendazole (N = 60)	Second Group Albendazole + Levamisole (N = 60)	Third Group Mebendazole + Levamisole (N = 60)
The intensity of infection, n (%)			
<i>Ascaris lumbricoides</i>			
Mild	50 (83.3)	39 (65)	46 (76.7)
Moderate	4 (6.7)	2 (65)	1 (1.7)
<i>Trichuris trichiura</i>			
Mild	13 (21.7)	24 (40)	24 (40)
Moderate	-	2 (3.3)	1 (1.7)

The Statistical analysis did not show a significant reduction in egg count on the 7th day after therapy in all groups, whereas there was a significant reduction in the 14th and 21st day in all groups. Determination of egg reduction rate can be seen in Table 4.

Table 4: Egg Reduction Rate on Day 7th, 14th, 21th

Parasites	Anthelmintics regimen	Total eggs per gram			P value
		Mean (SD) 7 th day	Mean (SD) 14 th day	Mean (SD) 21 st day	
A. lumbricoides	Albendazole	34.00 ± 165.64	-	-	0.651
	Albendazole + Levamisole	14.40 ± 111.54	-	-	
	Mebendazole + Levamisole	34.80 ± 126.25	-	-	
T. trichiura	Albendazole	33.60 ± 95.91	24.80 ± 81.23	20.40 ± 74.96	0.247
	Albendazole + Levamisole	20.00 ± 89.38	12.40 ± 73.47	7.60 ± 47.89	
	Mebendazole + Levamisole	40.00 ± 122.66	18.80 ± 68.03	8.80 ± 29.63	

The cure rate of helminthiasis on the 7th day was 81.7% after albendazole therapy, 88.3% after albendazole + levamisole therapy, and 83.3% after mebendazole + levamisole therapy ($p = 0.577$). Cure rate on the 14th day was 88.3%, 95%, and 91.7% for albendazole, albendazole + levamisole, and mebendazole + levamisole therapy, respectively ($p = 0.418$). On the 21st day, the cure rate was 88.3%, 96.7%, and 91.7% ($p = 0.230$). Combination of albendazole and levamisole showed the highest cure rate, despite the statistically insignificant difference for all groups ($p > 0.05$). Determination of cure rates analysis can be seen in Table 5.

Table 5: The Cure Rates Analysis On Day 7th, 14th, 21th

Recovery Therapy	Recovered		Not Recovered		P
	n	%	n	%	
Albendazole (Day-7)	49	81.7	11	18.3	0.577
Albendazol + Levamisole (Day-7)	53	88.3	7	11.7	
Mebendazol + Levamisole (Day-7)	50	83.3	10	16.7	
Albendazole (Day-14)	53	88.3	7	11.7	0.418
Albendazole + Levamisole (Day-14)	57	95.0	3	5.0	
Mebendazole + Levamisole (Day-14)	55	91.7	5	8.3	
Albendazole (Day-21)	53	88.3	7	11.7	0.230
Albendazol + Levamisole (Day-21)	58	96.7	2	3.3	
Mebendazol + Levamisole (Day-21)	55	91.7	5	8.3	

Combination of albendazole combined with levamisole showed better cure rate for mild trichuriasis (95.8%) than albendazole therapy (46.2%) and mebendazole + levamisole (83.3%), $p = 0.00$. Determination of cure rate mild helminthiasis analysis can be seen in Table 6 and Table 7.

Table 6: The Cure Rate of Mild Helminthiasis

Parasite(s)	Treatment	Recovery				P
		Cured		Not Cured		
		n	%	n	%	
A. lumbricoides	Albendazole	46	92	4	8	0.176
	Albendazole + Levamisole	39	100	-	-	
	Mebendazole + Levamisole	42	91.3	4	8.7	
T. trichiura	Albendazole	6	46.2	7	53.8	0.01
	Albendazole + Levamisole	23	95.8	1	4.2	
	Mebendazole + Levamisole	20	83.3	4	16.7	

The side effects during the treatment process in each group had been observed. Side effect observed in the albendazole group were 13.3%, Albendazole combined with Levamisole was 26.7%,

and Mebendazole combined with Levamisole were 20 %.

Table 7: Cure Rate of Each Intervention Group

Parasite(s)	Intervention	Cure Rate (%)	P Value
A. lumbricoides	Albendazole	100	-
	Albendazole + Levamisole	100	
	Mebendazole + Levamisole	100	
T. trichiura	Albendazole	66.7	0.136
	Albendazole + Levamisole	94.7	
	Mebendazole + Levamisole	92.3	
A. lumbricoides + T. trichiura	Albendazole	28.6	0.079
	Albendazole + Levamisole	85.7	
	Mebendazole-Levamisole	66.7	

Observation data of side effect can be seen in Table 8

Table 8: Side Effects analysis

Side Effect	Albendazole n (%)	Albendazole + Levamisole n (%)	Mebendazole + Levamisole n (%)
None	52 (86.7)	44 (73.3)	48 (80.0)
Yes	8 (13.3)	16 (26.7)	12 (20.0)

Discussion

Helminthiasis has still been a major health problem in Indonesia. A. lumbricoides, T. trichiura and hookworm (N. americanus and A. duodenale) were the most common aetiology. WHO data on 2012 reported a high prevalence of helminthiasis in North Sumatera, i.e. 80% of school-aged children [18], [19].

Statistical analysis did not show a significant reduction in egg count on the 7th day after therapy in all groups, whereas there was a significant reduction in the 14th and 21st day in all groups. Even after the reduction in egg number at 14th and 21st day, we still found several T. trichuria eggs in subjects' stool, indicating the difficulty in eradicating trichuriasis as mentioned in the literature [20]. A study by Saputri in 2010 found significant egg reduction rate in single-dose mebendazole and mebendazole with levamisole therapy for A. lumbricoides and T. trichuria infections [21]. The contradictive result was found by Sihite et al., (2014) and Knopp et al., (2010) study, which found no significant difference in the treatment with mebendazole, albendazole, and mebendazole with levamisole [22], [23].

Based on Table 5, the combination of albendazole and levamisole showed the highest cure rate, despite the statistically insignificant difference for all groups ($p > 0.05$). Therefore, this finding indicated the similar efficacy of albendazole, albendazole + levamisole, and mebendazole + levamisole therapy.

Based on Table 6, the combination of albendazole with levamisole showed better cure rate for mild trichuriasis (95.8%) than albendazole therapy (46.2%) and mebendazole combined with levamisole (83.3%), $p = 0.01$. We hypothesised that levamisole had enhanced efficacy than albendazole and mebendazole for mild trichuriasis. Previous studies

showed that a single dose of albendazole or mebendazole had 28% and 36% recovery rate, respectively [16], [23]. For mixed infection, albendazole combined with levamisole was more effective (cure rate 85.7%) than single albendazole (28.65%) or mebendazole combined with levamisole (66.7%), $p = 0.079$ that showed on Table 7. A study by Sihite et al., (2014) found no significant difference in the recovery of helminthiasis with mebendazole + levamisole or single mebendazole therapy [22]. Another study found no significant differences in the recovery rate of helminthiasis between mebendazole with or without levamisole therapy [21]. The most common side effects in all groups were nausea and diarrhoea. No serious side effects were observed in this study, and mild side effects had recovered by their own. Table 8 shows that there was no difference in side effects between intervention groups.

It can be concluded that single-dose albendazole, a combination of albendazole and levamisole, and the combination of mebendazole and levamisole had similar efficacy in reducing egg count in helminthiasis. Combination of albendazole and levamisole showed better cure rate for mild trichuriasis and mixed infections. Side effects were similar in all treatment groups.

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