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Comparative Efficacy and Reinfection of Albendazole-mebendazole, Albendazole-pyrantel Pamoate, and Mebendazole on Soil-transmitted Helminths

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Abstract

BACKGROUND: Soil-transmitted helminths (STHs) infection (i.e., *Ascaris lumbricoides*, *Trichuris trichiura*, and hookworm) are commonly found as a single infection as well as a mixture of the three kinds of helminths that requires a broad anthelmintic spectrum. Some study revealed that combination of anthelmintic provides better efficacy.

AIM: The objective of the study was to compare the efficacy of combination treatment of albendazole-mebendazole, albendazole-pyrantel pamoate, and mebendazole alone in treating STHs infection as well as the rate of reinfection post-treatment.

METHODS: In 2018, a randomized controlled trial was conducted in Batubara district, North Sumatera. School-aged children diagnosed for STH were randomly allocated to (1) albendazole-mebendazole; (2) albendazole-pyrantel pamoate; or (3) mebendazole treatment groups. Here, we report the efficacy (cure rates [CRs] and egg-reduction rates [ERR]) and reinfection rates determined 12 weeks post-treatment. Chi-square test was used to compare the drug efficacy and reinfection rate between three groups.

RESULTS: A total of 309 children complete baseline and follow-up data. The efficacy was determined after 4 weeks post-treatment albendazole-pyrantel pamoate showed a significant higher efficacy against *A. lumbricoides* (CR: 93.5%; ERR: 100%) and *T. trichiura* (CR: 81.4%; ERR: 99%). For hookworm infection, results showed higher efficacy between the three groups after treatment. The reinfection rates 12 weeks after treatment for *A. lumbricoides* infection (Group 1: 3.1%; 2: 3%; 3: 1.3%) with $p > 0.05$ and for *T. trichiura* infection (Group 1: 19.2%; 2: 25%; 3: 1.5%) with $p < 0.05$.

CONCLUSION: This study showed the excellent efficacy of an albendazole-pyrantel pamoate combination against STHs infections. The highest reinfection rate was found in albendazole-pyrantel pamoate group for *T. trichiura* infection.

Introduction

Soil-transmitted helminths (STH) infections are one of the common chronic human infections in the world caused by a group of parasitic nematode worms. Infections occur through contact with parasite, eggs, or larvae that thrive in the warm and moist soil of the world's tropical and subtropical countries [1] The three main groups of STHs that infect humans are *Ascariasis lumbricoides*, *Trichuris trichiura*, and hookworm (*Ancylostoma duodenale* and *Necator americanus*) [2].

The prevalence of STHs infection in Indonesia in 2009 showed that 31.8% of children suffered from STH infections and survey in 2005 found that the prevalence was 30% [3], [4]. The prevalence of STH infection in Sumatera Utara in 2012 was 32.3% [5], and the prevalence in Medan in 2008 was 73% [6]. Study in Suka Village, North Sumatera, Indonesia, in 2004 found that the prevalence was 91.3% [7].

STHs infection is commonly found as a single or mixture of three groups of STH [8]. There are some anthelmintics such as albendazole, levamisole, mebendazole, and pyrantel pamoate that are effective against STH infections with their strength and weakness. In implementation, most of STH infection control programs only use benzimidazole such as albendazole and mebendazole [9]. Although one-dose treatment with both drugs shows high efficacy against *A. lumbricoides*, but only albendazole cures a satisfactory proportion of hookworm infections. Both drugs show low efficacy against *T. trichiura* [10]. The combination of albendazole-mebendazole and albendazole-oxantel pamoate has emerged as potential therapies against STH infections in a series of randomized controlled trials [11], [10]. These drug combinations were well tolerated and improved the proportions of patients cured of *T. trichiura*, *A. lumbricoides*, and hookworm infections. However, drug efficacy is affected by myriad factors (e.g., baseline infection intensity, parasite strain, host factors, and the diagnostic approach used), the findings were difficult to compare and interpret [10], [12], [13]. This study undertook a randomized controlled trial to compare the efficacy and safety of albendazole-mebendazole and

albendazole-pyrantel pamoate, with standard treatment (one-dose mebendazole), to identify the intervention with the greatest efficacy against STH in elementary school students.

Methods

This study conducted a randomized, controlled, OpenTrial from July to December 2018 in three primary schools, in Batubara district, North Sumatera.

Inclusion criteria

Children between 6 and 12 years of age whose stool samples were positive for single infection or co-infection with either *A. lumbricoides*, *T. trichiura*, or and hookworm were considered eligible.

Exclusion criteria

Children who have used anthemintics 1 month before the study were excluded from the study.

Ethical approval

Ethical approval was obtained from the Health Research Ethics Committee of the Faculty of Medicine, University of Sumatera Utara. Before the commencement of the study, permission was obtained from the school authority. The parents or guardians of the children were invited to the school and informed about the study procedure, including potential benefits and risks. Written informed consent was obtained from the parents or legal guardians and verbal assent from the participating children. Before treatment, the children were examined for clinical signs and symptoms of any existing disease and their weight and height were measured.

Study protocol

Children were randomly assigned, with the use of randomization table, to receive one of three treatments: Albendazole 400 mg plus mebendazole 500 mg, albendazole 400 mg plus pyrantel pamoate 10 mg/kg, or 500 mg of mebendazole. Children, study-site investigators, and laboratory scientists were aware of the randomized study groups. After 4 and 12 weeks of treatment, stool samples were collected from the children for the diagnosis of STH infections. Stool samples were transferred to the laboratory and Kato-Katz thick smears were examined by skilled laboratory scientists for eggs of *A. lumbricoides*, *T. trichiura*, and hookworm. At the end of the study, all children remaining infected received treatment.

Treatment efficacy was assessed 4 weeks after treatment. The efficacy was assessed using cure rates (CRs) and egg reduction rates (ERR). CR was defined as the percentage of individuals who became helminth egg negative after treatment with anthelminthic drugs [10], [14]. Reinfection rates were defined as children positive at baseline, negative 12 weeks, and positive 12 weeks post-treatment [15].

Statistical analysis

The Chi-square test was used to compare the variable between the treatment group and CRs, ERR, and reinfections. Data processing was performed using Statistical Package for the Social Sciences for Windows (SPSS) version 24.0, 2016 with $p < 0.05$ was significance and 95% confidence interval.

Results

Study participants

In total, 840 children who were invited to participate, 676 had complete baseline data. The prevalence of STHs infection was 45.7% (309/676). We randomly assigned 309 eligible children infected with STHs between, to one of the three treatment groups (Figure 1). Demographic and baseline laboratory characteristics of the 309 children included in the analysis are summarized in Table 1. Treatment groups were well balanced at baseline in terms of age, sex, and nutritional status.

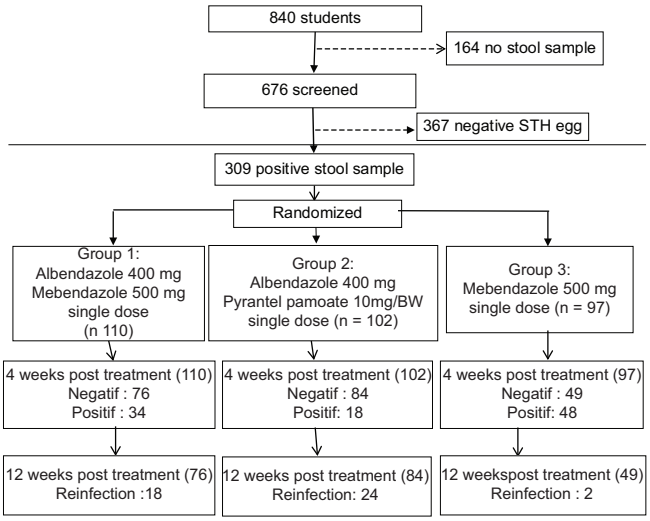

Figure 1: Study flow chart

CRs and ERR among 309 children with STHs infection are shown in Table 2. Treatment with albendazole-pyrantel pamoate resulted in a significantly higher CR among children with *A. lumbricoides* and *T. trichiura* infection than did albendazole-mebendazole

Table 1: Baseline subject characteristics

Characteristics	Albendazole-mebendazole (n = 110)	Albendazole-pyrantel pamoate (n = 102)	Mebendazole (n = 97)
Age (year), mean (SD)	8.3 (1.58)	8.9 (1.8)	8.8 (1.63)
Nutritional status, n (%)			
Severe malnutrition	6 (5.5)	3 (2.9)	1 (1.03)
Mild malnutrition	52 (47.3)	45 (44.1)	35 (36.0)
Well nourish	47 (42.7)	45 (44.1)	51 (52.5)
Overweight	2 (1.8)	5 (4.9)	5 (5.1)
Obesity	3 (2.7)	4 (3.9)	5 (5.1)
Sex, no (%)			
Male	56 (35.7)	54 (34.4)	47 (29.9)
Female	54 (35.5)	48 (31.6)	50 (32.9)
Infection, no (%)			
A. lumbricoides	28 (25.5)	31 (30.4)	29 (29.9)
T. trichiura	103 (94.5)	97 (95.1)	93 (95.9)
Hookworm	12 (10.9)	15 (14.7)	8 (8.2)
EPG feces, median (range)			
A. lumbricoides	831 (132–62424)	1512 (192–11592)	1342 (97–38808)
T. trichiura	763 (48–19103)	726 (48–9786)	772 (72–9657)
Hookworm	21 (9–97)	18 (8–89)	16 (6–39)
Multiple infection, no (%)			
Double infection	32 (29.1)	41 (40.2)	33 (34.0)
Triple infection	1 (0.9)	0 (0.0)	0 (0.0)

A. lumbricoides: Ascaris lumbricoides, T. trichiura: Trichuris trichiura.

and mebendazole (*A. lumbricoides* 93.5% vs. 57.1% vs. 27.6%, $p < 0.05$; *T. trichiura* 81.4% vs. 69.2% vs. 65.6%, $p < 0.05$). We observed no significant differences between the three-drug combinations with respect to CRs in hookworm infection. Mebendazole monotherapy resulted in a significant lower CR than combination drug, especially in *A. lumbricoides* and *T. trichiura* infection.

Table 2: Comparison of efficacy between the three groups after treatment

Efficacy (%)	Albendazole-mebendazole (n = 110)	Albendazole-pyrantel pamoate (n = 102)	Mebendazole (n = 97)	P*
Efficacy of STH	69	82	50	0.001
CRs				
A. lumbricoides	57.1	93.5	27.6	0.001
T. trichiura	69.2	81.4	65.6	0.037
Hookworm	91.7	100.0	87.5	0.605
ERRs				
A. lumbricoides	100.0	100.0	96.6	0.357
T. trichiura	99.0	99.0	100.0	0.625
Hookworm	100.0	100.0	87.5	0.187

*The Chi-square test. *A. lumbricoides: Ascaris lumbricoides, T. trichiura: Trichuris trichiura*, STH: Soil-transmitted helminth, CRs: Cure rates, ERR: Egg-reduction rates.

After 12 weeks post-treatment, 44 out of 201 (21.9%) children were reinfected with *A. lumbricoides* and *T. trichiura*. For *A. lumbricoides*, the prevalence at baseline was 28.5% by design. This study observed that 7 of the 88 children (8%) were reinfected with *A. lumbricoides* 12 weeks after treatment. For *T. trichiura* infection, 37 of the 293 (12.7%) cured children were found to be reinfected 12 weeks after being treated. All reinfections were of mild intensity. There was a significant difference in the reinfection level of *T. trichiura* infection between three treatment groups, but there was no significant difference in *A. lumbricoides* reinfections (Table 3).

Table 3: The incidence of reinfection after drug administration

Reinfection (%)	Albendazole-mebendazole (n = 110)	Albendazole-pyrantel pamoate (n = 102)	Mebendazole (n = 97)	p*
Reinfection, n (%)				
A. lumbricoides	3 (3.1)	3 (3.1)	1 (1.3)	0.786
T. trichiura	15 (19.2)	21 (25)	1 (1.5)	0.001

*The Chi-square test. *A. lumbricoides: Ascaris lumbricoides, T. trichiura: Trichuris trichiura.*

Discussion

The prevalence of STHs infection in this study was 45.7%, consisting of *A. lumbricoides* 28.5%, *T. trichiura* 95.1%, and hookworm 11.3%. However, the prevalence was lower than the reports from the previous study in Medan (2008) was 73% [6], in Kabupaten Karo (2002) was 95.4% [14], and 91.3% (2004) [7]. The prevalence of STHs infection observed in this study was lower than the previous study which may be as a result of the helminthiasis control program by government targeted at preschoolers (1–4-year-old) and elementary school-aged children (5–12-year-old) [3]. *T. trichiura* infection in our study was higher than the other helminth infections. It may result from the use of albendazole in the helminthiasis control program, which is *T. trichiura* is less sensitive to single-dose albendazole [3], [8], [16].

The treatment for STH single infection has good results, but the treatment for mixed infections shows unsatisfactory results [9]. The meta-analysis comparing CRs of single dosed drugs have various results [11].

Four weeks after treatment, CRs of *A. lumbricoides* achieved with the combination of albendazole-pyrantel pamoate were 93.5%, albendazole-mebendazole was 57.1%, and mebendazole was 27.6%. In earlier studies, CR of albendazole-oxantel pamoate, albendazole-mebendazole, and mebendazole was 97.7%, 100%, and 95.4%, respectively [15]. Another study comparing the CRs after albendazole-oxantel pamoate and mebendazole treatments also demonstrates high CRs, that is, 94.4% and 91.2%, respectively [10].

Albendazole-pyrantel pamoate had greater efficacy against *T trichiura* compared with the established standard treatment of one-dose mebendazole. This study shows that the CRs of *T. trichiura* after treated with albendazole-pyrantel pamoate were 81.4%. Previous studies of combinations albendazole-oxantel pamoate documented high efficacy against *T. trichiura* [10], [12], [15]. The CRs resulted in the previous study are lower than this study, but that result was the highest CRs among the treatment groups in that study.

Albendazole-pyrantel pamoate treatment shows high CRs from *A. lumbricoides* and *T. trichiura* because these drugs have different pharmacokinetics and pharmacodynamics, meaning that pyrantel pamoate will disable helminth, and active metabolism of albendazole will kill the worms, eggs, and larva [13], [17], [18], [19]. The CRs of albendazole-mebendazole against *A. lumbricoides* and *T. trichiura* were good in this study. It is resulted by the mechanism of drugs, mebendazole is an active component that will contact with the worm, followed with the metabolism of albendazole, so the worm will have long contact with drugs [14].

The CRs of Hookworm showed the greatest efficacy in our study. The CRs achieved with the combination of albendazole-mebendazole were 91.7%, albendazole-pyrantel pamoate was 100%, and mebendazole was 87.5%. This result was different with the previous study. In an earlier study, CRs of albendazole-mebendazole were 48.8%, albendazole-oxantel pamoate was 48%, and mebendazole was 24.4% [12]. The different can cause of large of sample and parasite strains at the two study sites might account for this contradictory finding.

A study at Tanzania in 2015 that assessed egg reduction in STHs infections reported that reduction of *T. trichiura* and hookworm eggs after treated with mebendazole was unsatisfactory [12]. Egg reduction in our study was good for all treatment groups. Although mebendazole had very poor CRs in this study, it still has great efficacy to reduce the eggs.

In our study, reinfection was found in *A. lumbricoides* and *T. trichiura*, but not in hookworms. It can be caused by the life cycle of hookworm that can survive for a few weeks on the soil under suitable conditions [20]. *A. lumbricoides* and *T. trichiura* are very durable in the right environmental condition and infective for several months, so individuals can be reinfected from the eggs that survive in the environment [21]. There are significant differences in reinfection of *T. trichiura* between the three treatment groups. In our study, the reinfection rate of *T. trichiura* 12 weeks post-treatment for albendazole-pyrantel pamoate was 25%, albendazole-mebendazole was 19.2%, and mebendazole was 19.2%. In another study, the reinfection rate in mebendazole group was 50%, albendazole-oxantel pamoate was 30.9%, and albendazole-mebendazole was 22.2% [15].

The reinfection rate in our study was not as high as in the previous study, probably due to various factors that influence the incidence of STH reinfection. STH infection is closely related to poverty, poor hygiene, lack of clean water access, and poor sanitation [22]. These factors also influence reinfection. However, the factors that influence STH reinfection are not report in our study.

Conclusion

We identified two combination therapies against STHs that have significantly higher efficacy than the standard treatment of mebendazole alone: Albendazole plus pyrantel pamoate and albendazole plus mebendazole. On the one hand, the combination including pyrantel pamoate cured a larger proportion of patients than the combination with mebendazole. This combination could become a key element in controlling STH infections, especially in highly endemic settings. Further, trials should evaluate reinfection rates with pyrantel pamoate 6 and 12 months after treatment and ideally after several rounds of treatment.

The reinfection rate observed for *A. lumbricoides* and *T. trichiura* is worrying. This finding supports the necessity of integrated control approaches, including regular treatment, improved sanitation and health education, to reduce the burden of STH infections.

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