



Efficacy of Albendazole and Albendazole-Mebendazole against *Trichuris trichiura* Infections

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Abstract

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BACKGROUND: *Trichuris trichiura* infections treatment using albendazole or mebendazole as a single dose is rated unsatisfactory. The combination of albendazole-mebendazole is viewed to have better efficacy against *T. trichiura* infections due to the nature of each drug.

AIM: This study compared the efficacy of albendazole and albendazole-mebendazole for *T. trichiura* infection treatment in Talawi, Batu Bara, North Sumatra, among primary school children.

METHODS: An open randomized clinical trial was carried out in Talawi, Batu Bara. The efficacy of albendazole as a single dose and albendazole-mebendazole as a single dose was compared. Research subjects were school children aged 6–12 years old with *T. trichiura* infections. Chi-square test was performed to compare the cure rate and unpaired t-test was done to compare the number of eggs per gram (epg) in both groups.

RESULTS: From a total of 463 children, 235 of them suffered from *T. trichiura* infections. The cure rate of the group with 400 mg albendazole as a single dose was 52.5%, while the other group with albendazole 400 mg – mebendazole 500 mg as a single dose was at 71.1% cure rate. The cure rate of the two groups showed a significant difference with $p = 0.011$. Both groups were observed to have a significant reduction in the number worm eggs with $p = 0.04$.

CONCLUSION: Albendazole 400 mg – mebendazole 500 mg combination as a single dose treatment has better efficacy than albendazole 400 mg alone, where the drug combination gave a higher cure rate and greater reduction in the number of *T. trichiura* eggs.

Introduction

Soil-transmitted helminths (STHs) are groups of worms (nematodes) that cause infections in humans through contact with soils that contain infective worm eggs or larvae. The most common species in STH are roundworms (*Ascaris lumbricoides*), whipworms (*Trichuris trichiura*), hookworms (*Ancylostoma duodenale* and *Necator americanus*), and threadworms (*Strongyloides stercoralis*) [1], [2], [3], [4].

Trichuris trichiura infections are distributed widely in tropical and subtropical area. The highest STH infections were found in Sub-Saharan Africa, one of the areas with poor hygiene, including East Asia, China, India, and South America [4]. Indonesia, with its geographical location at tropical climate, is suitable for the growth of *Trichuris trichiura*. Therefore, helminthiasis is still a major health concern [5].

The prevalence of *T. trichiura* infection in Indonesia is still classified as high, especially within low-income groups with poor sanitation and no sufficient access to toilets and clean water. Based on the survey done by The Ministry of Health of the Republic of

Indonesia in 2015, the prevalence of helminthiasis for all ages in Indonesia was around 40–60%. Whereas the prevalence of children aged 1–6 years old was 30% and 7–12 years was reaching almost 90% [6]. Another survey done by Lee and Ryu (2019) showed a 34% prevalence of *T. trichiura* infections in Indonesia [7]. A study by Barus and Hanie (2017) in Kabanjahe, North Sumatera, reported 81.5% prevalence of STH infection with 20% of *T. trichiura* species distribution [6].

The management strategy for *T. Trichiura* and other STH infections is the administration of anthelmintic drugs such as albendazole or mebendazole. Both albendazole and mebendazole are chosen as the anthelmintics for the treatment of *T. Trichiura* because they have better effectivity than levamisole and pyrantel pamoate. In *T. Trichiura* infections cases, the cure rate with albendazole can reach 10–70%, while mebendazole can reach 45–100%, pyrantel pamoate can reach 0–56%, and levamisole can reach 16–18% [7]. However, this management strategy is viewed to have an unsatisfactory cure rate for *T. Trichiura* infections.

The World Health Organization (WHO) aims to reduce the prevalence of soil-transmitted helminths in children to 1% in the year 2020. However, all the

medication has got low efficacy towards *T. trichiura* infections. Mebendazole, however, shows the highest cure rate compared to other types of anthelmintics [8]. A study done by Olsen *et al.* (2009) about *T. Trichiura* infections in school children in Uganda showed only 7.5% cure rate with the administration of albendazole 400 mg as a single dose, whereas in mebendazole 100 mg administration twice a day for 3 days showed 11.7% cure rate [9]. In Ethiopia, a study done by Mekonnen *et al.*, (2013) reported 102 children with albendazole 400 mg as a single dose showed 29.3% worm eggs reduction. Meanwhile, 103 children who were given mebendazole 500 mg as a single dose had an average of 60% reduction in worm eggs. In the same study, 90 children were given albendazole 400 mg as a single dose, while the other 90 children were given mebendazole as a single dose for 2 consecutive days. The number of eggs was reduced after albendazole and mebendazole administration by 73.5% and 87.1%, respectively [10]. The report from past researches has shown the importance of seeking alternative treatments to get a higher cure rate of *T. trichiura* infections. This has triggered the author to combine albendazole-mebendazole.

Albendazole and mebendazole are classified in the same group of benzimidazole. However, they have different chemical structures, hence the differences in the pharmacokinetics of the two drugs. Albendazole sulfoxide is metabolized first in albendazole and after that it is being used as a strong anthelmintic to fight worms, whereas mebendazole has got active components that can directly fight worms. This means that the worms can be in contact with the active ingredients in mebendazole for a period of time and followed by contact with albendazole sulfoxide [11]. Therefore, the combination of several drug regimens needs to be considered in treating *T. Trichiura* infections [10].

This research was conducted to compare the efficacy between albendazole 400 mg as a single dose and albendazole 400 mg – mebendazole 500 mg as a single dose in primary school children suffering from *T. trichiura* infections in Talawi, Batu Bara regency, North Sumatra.

Methods

The research was an open randomized clinical trial, where research subjects were selected using a simple random sampling method comparing the cure rate of *T. trichiura* infections after single albendazole and albendazole-mebendazole treatments in primary school children located in Talawi, Batu Bara regency, North Sumatra. This research was conducted from January – February 2020. Research samples were school children with helminthiasis who met the inclusion and exclusion criteria. Inclusion criteria were

school children in primary level I – VI, tested positive for single or double *T. trichiura* STH infections based on Kato-Katz analysis and lived within the same area of research location. Exclusion criteria were children who did not follow the research procedure such as sampling procedure or refused to drink anthelmintic drugs, allergic to anthelmintic drugs, consumed other types of anthelmintic ≤ 1 month before the research, and the children suffered from chronic disease.

Parental consent from all research subjects was obtained upon explanation on the research. This research was ethically reviewed and approved by Health Research Ethical Committee, Medical Faculty, Universitas Sumatera Utara registered under No. 15/TGL/KEPK FK USU-RSUP HAM/2020.

First, the research team conducted a nutritional status examination using CDC curve. Next, feces were collected in feces pots and examined using Kato-Katz analysis. The results showed samples with *T. trichiura* positive and they were divided into two groups using simple randomization method. The first group of school children received albendazole 400 mg as a single dose therapy, while the second group received albendazole 400 mg – mebendazole 500 mg as a single dose therapy. After 1 month, all the research subjects went through another feces examination using Kato-Katz analysis.

Data analysis was done using Statistical Package for the Social Sciences for Windows (SPSS) software version 19, 2010, with 95% confidence interval (CI) and significance level of $p < 0.05$. Chi-square test was done to know the difference in cure rate of *T. trichiura* infections based on intention-to-treat analysis. Moreover, unpaired t-test was done to know the comparison on worm eggs intensity of the two groups in the determined period of time. Finally, paired t-test was used to identify the comparison of eggs intensity in each group before and after treatment.

Results

Characteristic data of research samples

The research was done using data from analytical research that compared the cure rate of *T. trichiura* infections after single albendazole treatment with the cure rate after albendazole-mebendazole treatment. From 463 children examined, 32 children did not return the pot, 235 children were negative *T. trichiura* infection and 196 children were positive *T. trichiura* infection. Next, 196 children tested positive were randomly divided into two groups. The first group consisted of 99 children who received albendazole 400 mg as a single dose and the second group received the combination of albendazole 400 mg – mebendazole 500 mg as a single dose. The research profile can be seen in Figure 1.

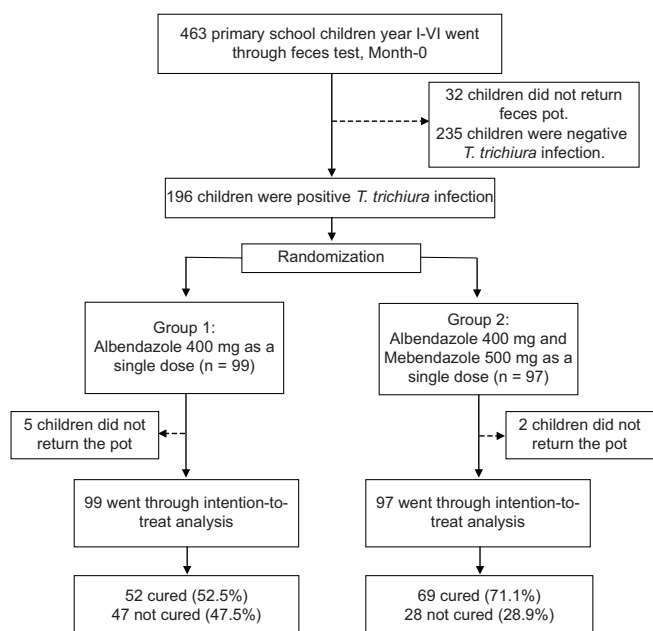


Figure 1: Consort flow diagram

The prevalence of *Trichuris trichiura* helminthiasis in Talawi, Batu Bara regency was at 45.4% (196/431), where the intensity of *T. trichiura* infection in both groups was mostly mild. The basic characteristic data of research samples is presented in Table 1. The median age of the albendazole group was higher at 9.3 years old than albendazole-mebendazole group (8.5 years old). Infection cases were higher in boys than girls for both groups. There were more subjects with good nutritional status in the albendazole group, while in albendazole-mebendazole group, more samples were at poor nutritional status.

Table 1: Basic characteristic of research samples

Characteristic	Albendazole 400 mg (n = 99)	Albendazole 400 mg + Mebendazole 500 mg (n = 97)
Median age, years old (min-max)	9.3 (5.0–12.0)	8.5 (6.0–12.0)
Gender, n (%)		
Male	61 (61.6)	52 (53.6)
Female	36 (38.4)	45 (46.4)
Nutritional status, n (%)		
Malnutrition	0 (0)	6 (6.2)
Poor nutrition	36 (36.4)	47 (48.5)
Good nutrition	55 (55.6)	39 (40.2)
Overweight	4 (4)	3 (3.1)
Obese	4 (4)	2 (2.1)
Total eggs/gram feces, geometric mean epg. (SD)		
<i>T. trichiura</i>	537.03 (5.14)	630.95 (4.17)
Level intensity of Eggs <i>Trichuris trichiura</i> , n (%)		
Mild	60 (60.6)	64 (65.9)
Moderate	39 (39.4)	32 (32.9)
Severe	0 (0.0)	1 (0.1)

Comparison of cure rates

The cure rate of *Trichuris trichiura* infection was dependant on the treatment given. The two-drug regimens resulted in a meaningful difference toward *Trichuris trichiura* infections with $p < 0.05$. There was a correlation between the type of therapy and the cure rate. Based on the cure rate of each group shown in Table 2, control event rate (CER) calculation

and experimental event rate (EER) were at 0.47 and 0.28, respectively. Therefore, absolute risk reduction (AAR) could be obtained at 0.19. Number needed to treat (NNT) was obtained by dividing AAR value, 0.19, with 1, which was equal to 5. NNT was used to see the number of patients required to be treated to get 1 good result or to avoid 1 treatment failure.

Table 2: The cure rate comparison of both groups after 1-month treatment

Efficacy	Albendazole 400 mg (n = 99)	Albendazole 400 mg + Mebendazole 500 mg (n = 97)	p*
Cured	52 (52.5)	69 (71.1)	0.011
Not cured	47 (47.5)	28 (28.9)	

*Chi-square test

Comparison of eggs reduction

There was a reduction in *Trichuris trichiura* worm eggs observed from the re-examination after the therapy. The statistical analysis result showed a significant reduction in worm eggs from both groups with $p = 0.040$. The data are shown in Table 3.

Table 3: The reduction in the number of eggs in both groups after 1-month treatment

Efficacy	Albendazole 400 mg (n = 99)	Albendazole 400 mg + mebendazole 500 mg (n = 97)	p*
Total eggs/gram feces, geometric mean epg. (SD) <i>T. trichiura</i>			
Month-0	537.03 (5.14)	630.95 (4.17)	0.438
Month-1	223.87 (2.82)	131.82 (2.87)	0.040

*Unpaired t-test

The statistical analysis for eggs reduction showed a significant result in each group after 1 month of therapy. The result is shown in Table 4.

Table 4: The comparison of eggs reduction in each group after 1-month treatment (pre-post)

Efficacy	Before treatment	After treatment	p*
Total eggs/gram feces, geometric mean epg. (SD) Albendazole 400 mg group			
<i>T. trichiura</i>	912.01 (3.60)	223.87 (2.82)	0.001
Albendazole 400 mg + mebendazole 500 mg group			
<i>T. trichiura</i>	2.041 (2.75)	131.82 (2.87)	0.001

*Paired t-test

Discussion

This research was conducted in four primary schools in Talawi, Batu Bara Regency, North Sumatera, from January to February 2020. The prevalence of *T. trichiura* infections in primary school children was 45.4% (196/431). The result was categorized as a moderate prevalence (≥ 20 – $< 50\%$). There were several factors affecting this condition. A systematic review and meta-analysis study done by Strunz *et al.* (2014), as well as a study by Manz *et al.* (2017), reported an important correlation among water, sanitation, hygiene, environment, and exposure to the soil to the prevalence of STHs [12], [13]. The prevalence in this study was lower than the other study done to school children in

Singkuang and Sikapas, North Sumatra, by Nasution *et al.* (2019), with a prevalence of 57.1% and 78.1%, respectively [14]. This difference may be caused by the administration of anthelmintic to children in Talawi through a program held by the government in 2019.

T. trichiura infection often occurs in children aged 5–15 years old. The infection cases in children are also related to age. With the increasing of age, children go through the higher intensity of playing and activity patterns which may lead to lower personal hygiene [15]. In this research, *Trichuris trichiura* infections were found in primary school children with an average of 9.3 and 8.5 years old in the two groups. Moreover, this study recorded higher cases in boys than girls. They are more affected as they tend to play outside and eat dirt [16].

The nutritional status of children with *T. trichiura* infection in this research was between poor to good nutrition. This is because the majority of infections found had light intensity. Nutritional disorders are usually observed at moderate to severe infection intensity [17]. Another study done by Simarmata *et al.* (2015) in Kabanjahe, Karo regency, also showed a close relationship between poor nutritional status and light-moderate infection intensity [18].

In this research, 99 children with albendazole 400 mg as a single dose treatment showed 52.5% (52/99) cure rate, whereas the other group of children with albendazole 400 mg–mebendazole 500 mg as a single dose was at 71.1% (69/97) cure rate. This result is higher than the study done by Steinmann *et al.* (2011) in China in which the cure rate of *T. trichiura* infection with albendazole 400 mg as a single dose was 34% while mebendazole 500 mg as a single dose resulted in 40% cure rate. In the same study, albendazole 400 mg treatment for 3 consecutive days showed a 56.2% cure rate, while treatment with mebendazole 500 mg showed a 70.7% rate [19].

A study done by Knopp *et al.* (2010) in Tanzania to school children reported a less satisfactory result. The treatment with albendazole 400 mg as a single dose only led to a 9.8% cure rate, while mebendazole 500 mg had an 18.8% rate. In the same study, the combination of albendazole-ivermectin gave 37.9% rate and mebendazole-ivermectin showed 55.1% rate [20]. Another study done in Ivory Coast by Patel *et al.* (2020) showed only a 16.3% cure rate post albendazole 400 mg as a single dose treatment and 17.1% cure rate post albendazole 800 mg as a double dose treatment [21].

Given the poor treatment efficacy in *T. trichiura* infection, a systematic review and meta-analysis study was done by Moser *et al.* (2017) to reveal the resistance of drugs that caused the reduction in efficacy over time. The result showed that albendazole therapy led to 30.7% cure rate, while mebendazole treatment gave a 42.1% rate. The average *Trichuris trichiura* eggs reduction after albendazole and mebendazole treatment was 44.9% and 66%, respectively. This study also presented data

of stratification by publication year – before and after 2000, where there was a significant reduction in the cure rate for albendazole treatment from 38.6% to 16.4% and egg reduction rates from 72.6% to 43.4%, while with mebendazole, the rate decline from 91.4% to 54.7% [8].

In 2015, more than 1 billion of people were infected by parasitic filariasis and soil-transmitted helminths. Therefore, the use of albendazole might trigger drug resistance [22]. However, the resistance in human is yet proven, while other factors related to the interaction of drugs, diagnostics, or hosts may contribute in the reduction in cure rate, as well as the number of eggs. Therefore, further research on this matter should be conducted [23].

In this research, NNT value was also calculated for albendazole 400 mg – mebendazole 500 mg as a single dose in comparison to albendazole 400 mg as a single dose treatment. NNT value obtained was 5, which means that 5 patients were required to go through the treatment to obtain a good result or to prevent a failure.

The reduction in the number of eggs in this study was found to be good in both groups with different treatment. This is because either albendazole or mebendazole is larvicidal and virucidal, as well as ovicidal [24].

Despite some side effects reported in the consumption of albendazole and mebendazole, there were no side effects reported upon the administration of albendazole as a single dose or the combination of albendazole-mebendazole. Anthelmintic drugs have low absorption in the digestive tract; therefore, only little absorption took place and most of them work in intraluminal [25].

This study was the first to be done in Indonesia. The results can provide insight to the local Public Health Service about the importance of combined anthelmintic drugs to improve the cure rate of helminthiasis, especially in *T. trichiura* infection cases. Regular and continuous administration of albendazole 400 mg – mebendazole 500 mg as a single dose twice a year in areas with a prevalence of ≥ 20 – $< 50\%$ is based on the helminthiasis control guidelines by the Ministry of Health of the Republic of Indonesia year 2012, as well as promoting deworming program from WHO. However, this research was lacking of weekly efficacy measurement for cure rate and eggs reduction.

Conclusion

The combination of albendazole 400 mg – mebendazole 500 mg as a single dose has a better efficacy of cure rate and reduction in the number of eggs in *Trichuris trichiura* infections compared to albendazole 400 mg as a single dose.

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