Efficacy of a Single Dose versus Triple Dose Regimen of Mebendazole against Hookworm Infection among School Children: A Randomized, Single blinded Trial.

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Abstract

**Background:** The current control efforts against soil transmitted helminthic infection focused on reducing morbidity and transmission potential through periodic anthelminthic chemotherapy of single dose of mebendazole and albendazole regimen. Single dose mebendazole is one of extensively applicable drug regimen as a preventive chemotherapy in hookworm endemic areas. However, nowadays, studies reveal single dose treatment regimen has poor and unsatisfactory efficacy status against hookworm infection. We evaluated the efficacy status of single dose (500mg) versus triple dose (100mg) of mebendazole against hookworm infection among school aged children.

**Methods:** This randomized, single-blinded clinical trial took place in a primary school on Burie and Debre Elias towns, Northwest Ethiopia among school-aged children (6-14). Using simple randomization, eligible hookworm positive children were randomly allocated (1:1) to either a single dose or triple dose of mebendazole arm. Stool samples were collected at baseline and follow-up period (14-21 days after treatment) for McMaster analysis. The primary and secondary outcome measures in this study were cure rate (CR) and egg reduction rate (ERR), respectively. Results were displayed using tables and figure. Independent t test was used to compare group means, logistic regression was used to calculate odds ratio (OR), and P-value < 0.05 at 95% CI was considered for statistical significance.

**Result:** 109 children were allocated for each treatment arm and 103 children were completed the drug efficacy follow up study. Cure rate against hookworm was significantly higher in triple dose (96.1%) than in single dose (30.8%) with (OR=55.125; 95% CI: 11.92-254.9; P < 0.001). Egg reduction rate against hookworm
infection in triple dose (99.5%) was also significantly higher than single dose (68.9%) with difference t (101) =5.38; 95% CI 230.95-505.36; P < 0.001.

**Conclusion:** Single dose regimen of mebendazole for the treatment of hookworm infection showed poor efficacy, while triple dose revealed satisfactory efficacy. Therefore, we recommend for giving special emphasis on current deworming program which implemented through single dose mebendazole for hookworm endemic area.

**Background**

Hookworms are nematodes belonging to the family Ancylostomatidae. It has two major genera that accounts almost all human infection, Necator (Necator americanus) and Ancylostoma (Ancylostoma duodenale)(1). They affect most impoverished people in the world(2). It is among the neglected tropical disease which poses a global disease burden by infecting over 576 million people around the world. The disease burden predominantly associated with anemia particularly in children and which causes physical and intellectual growth retardation (3). Moreover, it has considerable public health importance in low and middle income countries with an estimated 439 million people were infected and causing 3.2 million disability-adjusted life years (DALYs) (4–6). China and Sub Saharan Africa (SSA) are regions where highest prevalence of hookworm infection occur with nearly 200 million infections found in each country. It also occurs in almost half of SSA's poorest people, estimated with 117 million infected individuals, including 40-50 million school-aged children and 7 million pregnant women (5,7). Besides, it causes 1.6 million DALYs and US$139 billion annual productivity losses in this region (29,30). Because of its’ high transmission potential and regardless of
immune response produced by infected individual, the adult worm reside in the gut for many years\textsuperscript{(10)}.

In general, over 267 million preschool-age children and over 568 million school-age children live in areas where these parasites are intensively transmitted and are in need of treatment and preventive interventions \textsuperscript{(11)}.

Nowadays, control efforts for hookworm infection are implementing to reducing morbidity and infection intensity through periodic mass drug administration of affected populations with anthelminthic drugs in frame work of preventive chemotherapy\textsuperscript{(12,13)}.

Single dose mebendazole (500 mg) is one of extensively used and recommended benzimidazole (BZ) class of drugs under the list of world health organization (WHO) essential medicine for treating and controlling helminthic infection in the endemic areas \textsuperscript{(14)}. This controlling effort implement without prior information on the diagnosis status of individual and efficacy status of the drug. As a result, current literatures showed complete cure of hookworm in not achieved with any drug used as a single dose and variable efficacy profiles were observed in terms of cure rate (CR) and faecal egg reduction rate (ERR) against hookworm infection \textsuperscript{(15)}.

For instance, based on a recent randomized clinical trial conducted in Tanzania, triple dose (100 mg per day over three consecutive days) of mebendazole treatment shows satisfactory efficacy status against hookworm infection (CR = 98%), while single dose of mebendazole failed to achieve complete cure of this infection with (CR = 13%)\textsuperscript{(16)}. Moreover, a study conducted on the efficacy status of single dose mebendazole in terms of faecal egg count reduction rate from six soil transmitted helminthes endemic countries among school children revealed ranged from 65.4\% – 95\% and with pooled result 80.6\% \textsuperscript{(17)}. And also, other studies revealed
inconsistent and unacceptable efficacy status of single dose mebendazole in terms of CR ranged from 17.6% – 58.5% for treating hookworm infection (14,18–20). Generally, this predominantly used drug as a preventive chemotherapy gave unsatisfactory results for clearing hookworm infections in different region throughout the world, despite its relatively cheap cost and wide availability (21). Furthermore, A triple dose (100 mg per day over three consecutive days) mebendazole is among the recommended and widely used anthelminthic drug for treating hookworm and other soil transmitted helminthic infection throughout the world (22,23). However, this regimen is widely applicable, only few studies were conducted to evaluate its efficacy status against hookworm infection. The reported result showed varied efficacy status in terms of CR ranging from 26–97.9% and ERR from 85–100% (16,20,24). This inconsistent efficacy status of the drug did not allow concluding on its treatment effect. Therefore, this varied and unsatisfactory efficacy status of mebendazole, especially the single dose which currently underway as a public health intervention mechanism against STH are enforced us for evaluating mebendazole for treating hookworm infection.

Furthermore, based on electronic data search, this is the first randomized, clinical trial for evaluating the efficacy status of single dose versus triple dose regimen of mebendazole for treating hookworm infection in the study site and another endemic area in Ethiopia.

Methods

This randomized, single-blinded clinical trial was conducted at Burie and Debre Elias towns’ primary schools, Northwest Ethiopia among school-aged children (6-14). Before the initiation of the study, ethical clearance was obtained from Ethical and
Review Committee of School of Biomedical and Laboratory Sciences, College of Medicine and Health Sciences, University of Gondar, Ethiopia. This trial is retrospectively registered with www.pactr.org, number PACTR201911466695052 on November 26, 2019.

Prior to participant enrolment, all parents/legal guardians’ of children whose aged 6 – 14 years attending the primary school of Debre Elias and Burie town were invited to inform about the objective, the purpose, the procedure of the study, and the potential risk and benefit which that happened in the participant by the research team at school. Parents/legal guardian of the participant had the chance to ask any questions which need clarification or create any confusion related to the study before they were asked whether they wanted their child to be part of the study or not willing. After all, parents/legal guardians who permit their child to include in the study were asked to give a written informed consent and verbal assent from each participant.

Moreover, for those parents/legal guardians who unable to read and write were asked to give thumbprint after reading all information which available in the informed consent form by the data collector.

The desired sample size for this study was calculated based on WHO recommended guideline for anthelminthic efficacy assessment study(25). It recommend a sample of 50 positive participants were desired for each parasite tested, therefore based on the guideline a minimum of 100 eligible hookworm positive individual were needed for this study. Based on the guideline to achieve the minimum required sample size, we screened 300 school aged children based on the following assumption: we assume that the prevalence of hookworm infection in the target population is 50% due to lack of recent publication at the study site and with 80% compliance rate at
a two-sided 5% statistical significance level. Moreover, 20% as a non-response rate was added by consider the potential loss to follow up.

**Participant data and stool sample collection procedure**

After obtaining written informed consent from participants’ parent/legal guardian and verbal assent from each participant age, sex grade level and other relevant participant data were recorded using WHO prepared protocol for the evaluation of anthelminthic drug efficacy form. Then specific identification number was given to each participant who had permission to participate in the study. Afterward, each participant received a sterile stool containers labeled with their unique identification number and were asked to provide approximately 10gm of fresh fecal specimen. Children were reminded to avoid any contamination of specimen and specimen were transferred to the nearby health center laboratory in Debre Elias and hospital laboratory in Burie within an hour after the sample collected. McMaster concentration technique, which is the standard reference method for evaluating drug efficacy in Veterinary Parasitology and has recently been evaluated for human helminthes was used for this study(25,26).

Upon completion of all the baseline parasitological and participant information survey, all children who found positive for hookworm infection were subjected to physical and clinical examination by senior health officer. Then height was measured with a standard meter (to the nearest 0.1 cm), and weight with an electronic balance (to the nearest 0.1 kg). Haemoglobin levels were measured in capillary blood using the finger-prick method (HemoCue®301).

Hookworm positive children, who were healthy; based on medical history, physical examination, vital signs, hemoglobin level, participants who had signed informed consent by parents/ legal guardians and verbal assent from each participant age
<18 years) according to Ethiopian regulation, participants did not took any anthelminthic with in past 4 weeks, females with negative pregnancy test age >12 years, participant who had hemoglobin level >8g/dl, and children who were able to chew the drug were subjected for randomization in the allocated treatment arm. But those individual who has taken any form of medication containing mebendazole or any other treatment for STH infection within 30 days of entry into the study, who had diarrhea at the time of the first sampling, who experience a severe concurrent medical condition, participant with haemoglobin level below 8g/dl, with known history of allergic reaction to mebendazole, and participants infected with other parasitic infection were excluded from the allocated treatment.

**Randomization and drug administration**

Finally, eligible hookworm positive children were randomly assigned with (1:1) ration either to the single dose (500mg) or triple dose regimen of mebendazole (100 mg twice a day for three consecutive days) arm of the study. Randomized children were neither stratified by age nor sex or by any means of personal parameter before randomization. Using simple randomization lottery techniques, 55 eligible children were categorized into single dose arm, whereas 54 eligible children in triple dose mebendazole arm. The drug which administered for the study were found in the local market triple dose (100 mg twice a day for three consecutive days) (WORMIN tab) and single dose (500mg) (Vermox®) of mebendazole. A slice of biscuit was given to each eligible child before time of drug administration. Eligible children who were randomized in single dose mebendazole ordered to take the drug in front of their parents and public health officer at school. While children who were randomized in triple dose arm; parents/guardians were asked to took the sealed drug with envelops and instructed to give the drug for their child with proper
time to avoid interruption of time for the second dose of administration. Moreover parents/guardians were instructed to follow their child up to the end of treatment and reminded not to drink alcohol.

Moreover, participants/parents/guardians were reminded to notify about any medical discomfort happen following treatment to the investigators or the nearby health extension worker. Children were revisited after 14 -21 days of drug administration and asked to provide approximately 10gm of fresh fecal specimen for the second time using sterile stool container labeled with their identification number.

At the time of second visit, children were asked about the occurrence of vomiting and diarrhea following drug administration. A participant who vomited within 4 hours after drug administration and participant with diarrhea were excluded for the final analysis. Similarly, to the baseline parasitological investigation McMaster diagnostic technique was utilized at follow up time. Laboratory quality control was performed through re-reading 10% of the slides of each laboratory technician by an expert microscopist.

Data entry and analysis

Data was entered to Epi-data software to check data completeness and clearance then transferred to SPSS version-23 for statistical analysis. The baseline characteristics of the study population were summarized using frequencies, mean and standard deviation. Only participants who complete baseline and follow up data were included to determine the treatment efficacy. Infection intensity with hookworm were grouped in to light, moderate and heavy infections, according to WHO guideline for soil transmitted helminthes(27).
CR and ERR were used to assess the efficacy of the drug based on the following mathematical calculation. CR means the proportion of individual hosts positive for parasites who become parasitologically negative after treatment (28). Whereas ERR is the arithmetic mean egg count at baseline of the treatment group minus mean egg count at the end of treatment period divided by the mean egg count at the baseline and express it in percent (29).

$$\text{ERR} = 100\% \times \frac{1 - \text{arithmetic mean (post-intervention FEC)}}{\text{Arithmetic mean (pre-intervention FEC)}}$$

Confidence interval for ERR was calculated using bootstrap re-sampling method with 5000 iterations.

Independent t-test was used to compare group means, whereas CRs were compared by calculated Odds Ratio (OR) using logistic regression. For all statistical analyses a P-value of 0.05 was considered as the limit for statistical significance.

Result

A total of 300 school aged children were enrolled in the baseline screening. Of these, 120 (40%) children; (64 females and 56 males) had parasitological confirmed hookworm infection. The remaining 180 children were excluded because they were microscopically negative for hookworm infection. Moreover, eleven hookworm infected children were excluded because they were absent from school on the clinical and physical examination day. Furthermore, from the remaining 109 randomized infected children, one child from the single dose of mebendazole arm was not willing to receive the allocated treatment. Afterward, 108 eligible children, 54 in each treatment arm had completed baseline data and received allocated treatment. At the end, 103 children with complete data records, 52 in single dose
and 51 in triple dose mebendazole arm were included for the final efficacy analysis (Figure 1).

**Baseline survey**

At baseline, the eligible children allocated in the two treatment groups were comparable in terms of several characteristics. Participant’s characteristics expressed in the form of mean ± standard deviation (SD), age in single dose group was 10.78 ± 2.1 years; while in the triple dose it was 10.48 ± 1.34 years. The mean weights of the participants for single and triple dose were 31.45 ± 7.96 and 29.69 ± 6.2 kg, respectively. Moreover, most of the participant diagnosed with light infection intensity for hookworm and other participant characteristics (see table 1).

**Efficacy of triple and single dose regimen of mebendazole for treating hookworm infection**

In this analysis, the follow up fecal egg intensity of hookworm infection in terms of arithmetic mean were 378.04 EPG and 5.88 EPG in single and triple doses regimen of mebendazole, respectively. Cure rates of single and triple dose regimen of mebendazole for treating hookworm infection were 30.8% (19.2 – 44.2%) and 96.1% (90.2-100%), respectively.

In addition the ERRs were 68.9% in single and 99.5% in triple dose. Overall, 36 (69.2%) school aged children treated with single dose and two (3.9%) treated with triple dose mebendazole were remained hookworm-egg positive microscopically (see table 2).

**Comparative efficacy status of triple versus single dose regimen of mebendazole for treating hookworm infection**

A statistical significance difference was observed when comparing the CR and ERR of triple dose versus single dose regimen of mebendazole for treating hookworm
infection among school aged children. The CR of triple versus single dose regimen of mebendazole using binary logistic regression revealed with (CR: 96.1% vs. 30.8%; OR=55.125; 95% CI: 11.92-254.9; p < 0.001).

In terms of ERR the triple dose with arithmetic mean (ERR= 99.5%) was also significantly more effective than single dose (ERR = 68.9%) with difference t (101) =5.38; 95% CI 230.95-505.36; p <0.001.

Discussion

The current STH control strategy in Ethiopia, relies on periodic administration of single dose albendazole and mebendazole among WHO recommended anthelminthic drugs (30). Moreover, triple dose mebendazole was used for treatment hookworm infection and other STH infection (23)

The effectiveness of both doses of mebendazole assessed through either CR or ERR following drug administration (31). But studies which conducted before revealed varied efficacy status and its inconsistency make a challenge on treatment recommendation. In this study, head to head comparison of triple versus single doses of mebendazole for the treatment of hookworm infection may provide clear and applicable results, since single and triple doses of mebendazole are widely used drugs for treating STHs with variable efficacy status in endemic countries.

This study clearly showed that triple dose is significantly more effective at clearing of hookworm infection than single dose of mebendazole (96.1% vs. 30.8) with (OR = 55.125; 95% CI: 11.92-254.9; P < 0.001). It indicated that participants who treated with triple dose mebendazole had 55 times more likely to cured from hookworm infection than single dose of mebendazole. This significant efficacy variation between the two mebendazole doses might be due to extensive and frequent uses
of single dose regimen of mebendazole for deworming program unlike triple dose mebendazole. As a result of this frequent and wide-range use of single dose may raise concern on drug resistance or tolerance. Our finding strongly agreed with another head to head comparative RCT study, which revealed superiority efficacy status of triple dose over single dose mebendazole (CR = 13%, OR 389.1, 95% CI 95.2 to 2885.7%, p = 0.001)(16).

In this study almost all children who were infected by hookworm were cured (CR = 96.1%) with the ERR 99.5% following administering triple dose of mebendazole. This is strongly in agreement with other RCT studies conducted in Tanzania with CR = 98% and ERR = 100% (16). But it is considerably higher than study reported in China (CR = 58.5) (20) and Brazil (CR = 58.5%)(32). This result variability between our result and summary estimate of other randomized control trial could be due to several factors such as the diagnostic technique, the sample size variation, the age of study participants, the parasite strain, the location of study where it was conducted. For instance, both of the two studies which compared with our finding applied Kato-Katz diagnostic techniques and the one which is conducted in Brazil used Hoffmann’s spontaneous sedimentation techniques in addition to Kato-Katz techniques. Besides, both studies were carried out in all age group and with a sample size of 41 and 83 participants in the treatment arm(20,32).

The present study also showed that the efficacy status of single dose mebendazole for the treatment of hookworm infection in terms of CR and ERR were30.8% and 68.9%, respectively. This ERR status indicates that single dose of mebendazole had unsatisfactory efficacy profile for treating hookworm infection as per WHO guideline(25). The efficacy status of 500 mg mebendazole showed doubtful efficacy profile (< 70 &>60%).
The observed CR for single dose mebendazole in this study was in line with results from RCTs conducted in terms of CR in China (31%) in Vietnam (38%) (20, 24), and ERR in line from RCTs conducted in Tanzania (ERR = 68%) (16). However, it is considerably lower than from other RCT studies conducted in terms of CR in Tanzania (95.4%), and in Cameroon (70.4%) (33, 34), whereas in terms of ERR in collaboration of six endemic countries (79.6%), Cameroon (77%), and PDR (76.3%) (18, 26, 33). On the other hand it is higher than a RCT study reported in terms CR in Tanzania (13%), Zanzibar (7.6%), Tanzania (24.4), and PDR (17.6%) (16, 18, 19, 35). This discrepancy between our finding and other studies could be due to several influencing factors such as the diagnostic techniques applied, the study population, location of the study, allocated sample size, follow up period, and the strain of the parasite (16, 18–20, 34, 35). For instance, majority of the study utilized the Kato-Katz diagnostic techniques for the assessment of drug efficacy. As a result of the sensitivity and specificity variation of the diagnostic technique utilized might be the possible source for discrepancy of findings.

Conclusion

In this study, triple dose regimen of mebendazole showed satisfactory efficacy and has significantly higher CR and ERR than single dose regimen against hookworm infection. As a result, there is an imminent need to revise the treatment guideline and give special emphasis on the current deworming programs. Moreover, we recommend conducting further study on the efficacy of single and triple dose regimen of mebendazole against hookworm using molecular diagnostic techniques to explore and investigate the parasitic infection other than larval/oval stage of the parasite. And also better to undergo further investigation on species identification
with respect to efficacy status of the drug.

Declarations

Authors’ contributions

TE conceptualized the study, contributed to the format of the data collection instruments, analysis, and write up of the first draft manuscript. MA contributed to the study protocol, development of the data collection tools field data collection and analysis. AJ was participated in the proposal development and analysis; revise the draft and final manuscript. All authors read and approved the final manuscript before submission.

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Competing interests

The authors declare that they have no competing interests.

Availability of Data and Materials

The data generated or analyzed during this study is included in this manuscript. Other data will be available from the corresponding author upon request.

Consent for publication

Not applicable

Ethics approval and consent to participate

Before starting the data collection process, Ethical clearance was obtained from
Ethical and Review Committee of School of Biomedical and Laboratory Sciences, College of Medicine and Health Sciences University of Gondar, Ethiopia. Then, permission and support letters were obtained from Zonal Health bureau and District Health Office. Finally, after obtaining written informed consent from each participant parent/guardian, data were collected anonymously.

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**Abbreviations**

AM: Arithmetic Mean; BZ: Benzimidazole; CI: Confidence Interval; CR : Cure Rate; DALYs: Disable Adjusted Life Years; EPG: Egg per Gram; ERR: Egg Reduction Rate; MDA: Mass Drug Administration; OR: Odds Ratio; SSA: Sub Saharan Africa; STH: Soil Transmitted Helminthes; WHO: World Health Organization

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Tables

Table 1. Baseline characteristics of hookworm infected eligible school aged children, at Burie and Debre Elias towns, North West Ethiopia, January - June 2019.
### Table 2

**Cure and Egg Reduction Rate of single and triple dose of mebendazole against hookworm infection among school aged children from Burie and Debre Elias towns, January – June 2019**

|                                                                 | Single dose (N=52)          | Triple dose (N=51)          |
|----------------------------------------------------------------|-----------------------------|-----------------------------|
| **Sex**                                                        | Male                        | Female                      |
| **No. of hookworm-infected children before treatment (%)**    | 17 (32.7%)                  | 28 (54.9%)                  |
| **Mean (SD) age, year**                                       | 10.78 (2.1)                 | 10.48 (1.34)                |
| **Mean (SD) weigh, KG**                                       | 31.45 (7.96)                | 29.69 (6.2)                 |
| **Mean (SD) height, m**                                       | 1.35 (0.13)                 | 1.34 (0.08)                 |
| **Mean (SD) haemoglobin, g/dl**                               | 13.8 (1.09)                 | 14.02 (0.93)                |
| **Baseline EPG**                                               |                             |                             |
| **Arithmetic mean (95% CI)**                                  | 1216.35 (845.84-1586.86)    | 1134.3 (864.4-1404.2)       |
| **Infection intensity**                                       |                             |                             |
| **Light (1-1999 EPG)**                                        | 43 (82.7%)                  | 45 (88.2%)                  |
| **Moderate (2000-3999)**                                      | 7 (13.5%)                   | 5 (9.8%)                    |
| **Heavy (>=4000)**                                            | 2 (3.8%)                    | 1 (2%)                      |

SD = standard deviation

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**Figures**
Figure 1

The trial profile. This diagrammatical representation showed the allocation and selection procedure of eligible children for this study.

- Microscopically hookworm positive (n=120)
  - Eligible
- Microscopically hookworm negative (n=180)
  - Not eligible

- Excluded (n=11)
  - Absent during treatment time
- Randomized (n=109)

- Allocated to single dose mebendazole (n=55)
  - 54 received allocated intervention
  - Lost to follow-up (n=2)
  - Included in the final analysis (n=52)

- Allocated to triple dose mebendazole (n=54)
  - 54 received allocated intervention
  - Lost to follow-up (n=3)
  - Included in the final analysis (n=51)