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### Review Article

## Evaluating Effect of Albendazole on *Trichuris trichiura* Infection: A Systematic Review Article

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<p>Received 11 Nov 2015 Accepted 14 Jun 2016</p>	<p><b>Abstract</b> <b>Background:</b> The aim of the study was assessment of defaults and conducted meta-analysis of the efficacy of single-dose oral albendazole against <i>T. trichiura</i> infection. <b>Methods:</b> We searched PubMed, ISI Web of Science, Science Direct, the Cochrane Central Register of Controlled Trials, and WHO library databases between 1983 and 2014. Data from 13 clinical trial articles were used. Each article was included the effect of single oral dose (400 mg) albendazole and placebo in treating two groups of patients with <i>T. trichiura</i> infection. For both groups in each article, sample size, the number of those with <i>T. trichiura</i> infection, and the number of those recovered following the intake of albendazole were identified and recorded. The relative risk and variance were computed. Funnel plot, Beggs and Eggers tests were used for assessment of publication bias. The random effect variance shift outlier model and likelihood ratio test were applied for detecting outliers. In order to detect influence, DFFITS values, Cook's distances and COVRATIO were used. Data were analyzed using STATA and R software. <b>Results:</b> The article number 13 and 9 were outlier and influence, respectively. Outlier is diagnosed by variance shift of target study in inferential method and by RR value in graphical method. Funnel plot and Beggs test did not show the publication bias (<math>P=0.272</math>). However, the Eggers test confirmed it (<math>P=0.034</math>). Meta-analysis after removal of article 13 showed that relative risk was 1.99 (CI 95% 1.71 - 2.31). <b>Conclusion:</b> The estimated RR and our meta-analyses show that treatment of <i>T. trichiura</i> with single oral doses of albendazole is unsatisfactory. New anthelmintics are urgently needed.</p>
<p><b>Keywords:</b> Meta-analysis, Albendazole, <i>Trichuris trichiura</i></p>	
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## Introduction

Meta-analysis is a systematic review of quantitative research based on mathematical and statistical principles (1). The most complete the Outlier detection techniques in the meta-analysis have been developed by Hedegs and Olkin (2).

Infections with soil-transmitted helminthes (STHs), namely *Ascaris lumbricoides*, *T. trichiura*, and the two hookworm species including *Ancylostoma duodenale* and *Necator americanus*, which are intestinal worms, are the most common infections worldwide. Globally, more than 1 billion people are infected with one or several species of STHs, mainly in areas with warm and moist climates where sanitation and hygiene are poor (3-5). The greatest numbers of STHs infections occur in sub-Saharan Africa, the Americas, China and East Asia (3). The majority of STHs infected individuals are children. An estimated 604 million to 795 million people are infected with *T. trichiura*, causing a global burden of 0.64 million disability-adjusted life years lost (3, 4, 6). *T. trichiura* lives in the large intestine, their eggs are passed in the feces of infected persons, and infection is caused by ingesting eggs.

Light infections of *T. trichiura* are often asymptomatic, heavy infections cause an array of morbidities, including dietary deficiencies and delayed physical and cognitive development. Additionally, this infection contributes to iron deficiency anemia (4, 7, 8).

The current strategy against *T. trichiura* and other STHs infections is administer to regularly anthelmintic drugs, mainly albendazole and mebendazole, to school-aged children and other at-risk populations (3, 9). Although both drugs show good therapeutic profiles against *A. lumbricoides*, mebendazole fails to effectively clear hookworm infections, and neither drug is satisfactory and/or present different therapeutic profiles against *T. trichiura*. However, there is considerable concern that large-scale administration of anthelmintics

might result in the development and spread of drug resistant nematodes (10).

The aim of the study was assessment of defaults and conducted meta-analysis of the efficacy of single-dose oral albendazole in treating patients with *T. trichiura* infection after survey this defaults.

## Materials and Methods

We searched PubMed, ISI Web of Science, Science Direct, the Cochrane Central Register of Controlled Trials, and the World Health Organization library database to identify clinical trials, and studies pertaining to the use of albendazole for treating infections with *T. trichiura*. We used the terms “albendazole” in combination with “trial” or “study” and “*Trichocephalus*”, “*Trichuris trichiura*”, “whipworm”, “trichuriasis”, and soil-transmitted helminths. Bibliographies of identified articles were screened for additional relevant studies. We identified 117 potentially relevant studies carried out in different countries using albendazole against *Trichuris trichiura*. According to inclusion and exclusion criteria, 104 excluded (97 non-randomized placebo-controlled trials; 7 drug dosage different than recommended). There were 13 randomized trials published between 1983 and 2014 that compared albendazole drug with a placebo (11-23).

The criteria such as sample size, age, diagnostic method, dosage, and cure rate (the percentage of individuals who became *T. trichiura* egg negative following treatment with albendazole) were checked in selected articles, and then were subjected to the relevant meta-analyses. Besides, all the studies had used a similar definition for recovery, the same amount and frequency of albendazole (a single dose of 400 mg of oral medication), and a similar binary response variable for recovery versus non-recovery.

For each of the 13 articles, the total number of participants, the number of those infected with *T. trichiura* as well as those recovered following the intake of albendazole (for each of the two groups), the effect size, and variance of the intervention were computed. Each study was composed of both albendazole and placebo groups, the responses produced would follow a dichotomous variable. To compare the effect of albendazole on *T. trichiura*, the cure rates were used to compare two groups under study. The priority index of the effect of albendazole as cure ratio in intervention group to the placebo group was considered the relative risk (RR) and 95% confidence interval (CI). The effect size or RR is shown by  $\theta$ ; then test statistic has to be defined for the significance of the effect size. Test statistics is defined by  $Q = \sum w_i (y_i - \hat{\theta})^2$  in which  $w_i = \frac{1}{v_i}$  and  $\hat{\theta} = \frac{\sum w_i y_i}{\sum w_i}$ . Under the null hypothesis,

for all the effect sizes, which were similar or symmetrical, the distribution of Q statistics was distribution  $\chi^2$  with K-1 degree of freedom (24).

In the present study, assessment the defaults of meta-analysis included publication bias and the presence of outliers and influence. Funnel plot, Beggs and Eggers tests were used for investigate of publication bias. In addition, the

random effect variance shift outlier model (RV SOM) and likelihood ratio test were applied for detecting outliers. In order to detect influence, DFFITS values, Cook's distances and COVRATIO were used (24, 25). Then meta-analysis was carried out after removal of outlying study. In this study for meta-analysis, the STATA software was used and the R software was employed to administer this method (26).

### Results

According to Funnel plot and the Beggs test, there were no indication of publication bias ( $P=0.272$ ). However, based on the Eggers test, there was a publication bias ( $P=0.034$ ). RV SOM and likelihood ratio showed that article 13 is outlier, and it was withdrawal for our meta-analysis. In addition, DFFITS values, Cook's distances and COVRATIO showed that article 9 is influence. For the treatment of *T. trichiura* infection, 12 randomized placebo-controlled trials met our inclusion criteria (Table 1).

Meta-analysis conducted on these studies showed that the estimated relative risk is 1.99 (95% CI, 1.71 - 2.31). Forest plot its related is shown in Fig. 1.

**Table 1:** Results from 12 clinical trial studies that investigated the effect of albendazole on patients with *T. trichiura* (T.t) infection (11-22)

Reference	Control group		Treatment group	
	T.t-	T.t+	T.t-	T.t+
1	24	3	18	11
2	17	8	5	26
3	24	2	9	20
4	40	1	39	2
5	159	16	97	49
6	15	0	17	0
7	10	0	30	22
8	60	26	44	49
9	233	75	198	99
10	43	11	39	20
11	123	12	112	19
12	219	39	160	77

T.t+ :Improved after treatment /T.t- : Not improved after treatment

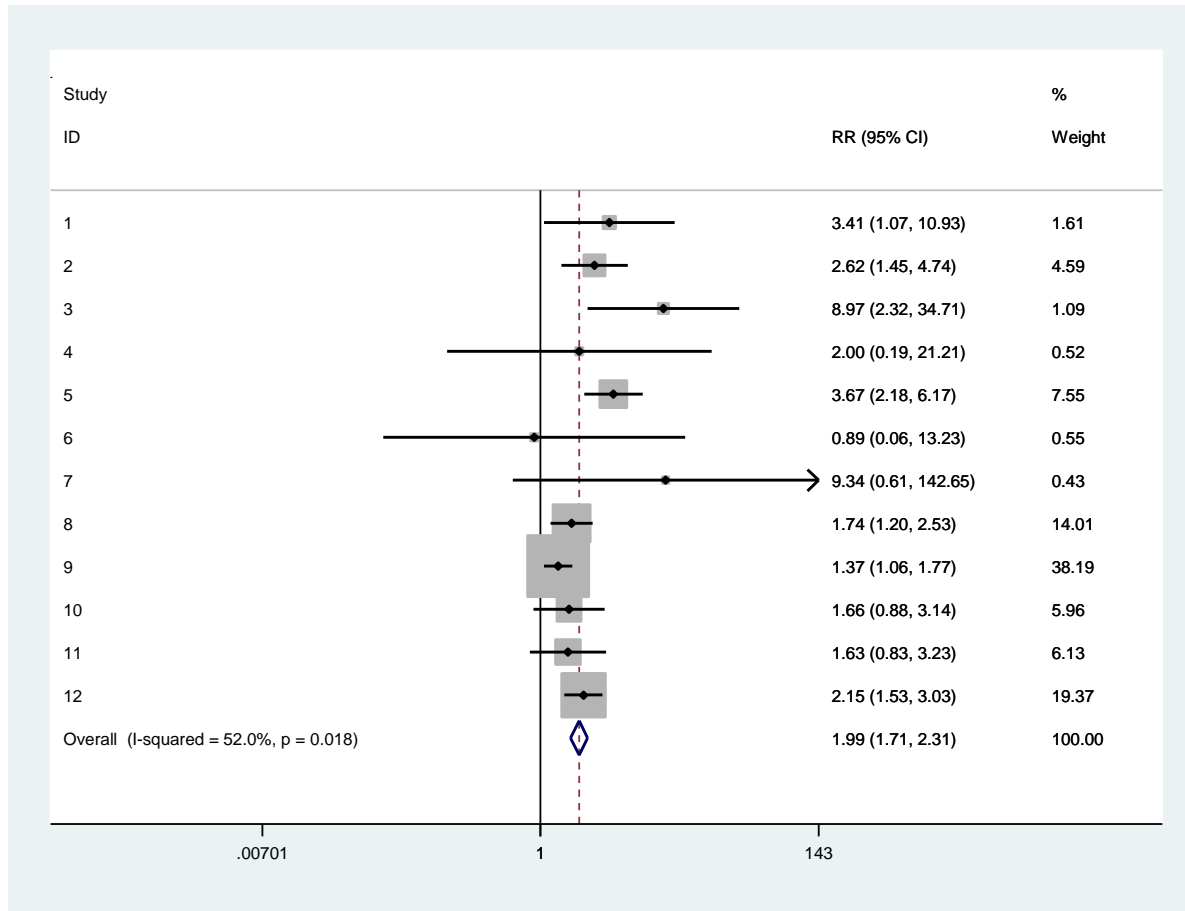


Fig. 1: Forest plot to study the effect of albendazole on *T. trichiura*

## Discussion

The articles under study had already been published in internationally indexed journals from 1983 to 2014. Albendazole drug is currently on the World Health Organization model list of essential medicines. In this study, funnel plot and Beggs test did not show the publication bias. However, the Eggers test confirmed it.

The results obtained from our meta-analytic evaluation of 13 placebo- controlled trials investigating the effect of albendazole on patients with *T. trichiura*, detected articles 9 and 13 as influence and outliers, respectively. For detect outliers in data was used diagram of Studentized deleted residuals and RVSOM. In addition, DFFITS values, Cook's distances

and COVRATIO values were used for detect influence. In current study, by using inferential method or RVSOM was diagnosed that trial 13 is outlier and that the finding was largely reliable. The results obtained from the graphical methods including plot of the Studentized deleted residuals, DFFITS values, Cook's distances and COVRATIO values indicated that the trial in row 9 served as influence in our meta-analyses. Since with the removal of trial of row 9, significant of these variables coefficient is changed, so this study is influence.. It is worth mentioning that outlier is diagnosed by variance shift of target study in inferential method and by relative risk (RR) value in graphical method. Recently, the anthelmintic efficacy of albendazole in the treatment of patients with hookworm has been reviewed,

and by using four methods of plot of the studentized deleted residuals, DFFITS values, Cook's distances and COVRATIO values, only two out of 15 trials were identified as outlier. Mentioned study showed that the results of meta-analytic studies largely reliable, and RR estimate for albendazole against hookworm infection was calculated 2.94 with 95% confidence interval of 2.59 to 3.33, showed that the cure ratio of individuals infected with hookworm using albendazole were nearly three times more than those who did not take drug (27).

Alavi -Majd et al. in meta-analytic evaluation of 14 studies investigating the effect of albendazole on patients with *Ascaris lumbricoides*, detected 3 trials (trials 4, 7, and 12) as outliers by RVSOM. They reported RR estimate of 2.91 (95% CI, 2.6 - 3.25), indicated that improve ratio of individuals infected with *Ascaris Lumbricoides* used albendazole were nearly three times more than those who did not take drug (28).

In the present study, the estimated RR was 1.99 with 95% confidence intervals of 1.71 to 2.31, indicating that the cure ratio of individuals infected with *Trichuris trichiura* using albendazole was almost two times more than those who did not use the drug. The results obtained from the tests and the relevant figures in our meta-analyses showed that efficacy of the anthelmintic albendazole in treating *Trichuris trichiura* has been lower than curing *Ascaris lumbricoides* (28) and hookworm infection (27).

In another meta-analysis study, the RR estimate for the effect of albendazole on two groups of case and control patients affected with *T. trichiura* was 2.06 with 95% confidence intervals of 1.76 to 2.4. Therefore, with such results in mind, it can be claimed that the cure ratio of individuals infected with *T. trichiura* using single-dose oral albendazole two times more than those who did not use the drug (10-19).

Results of this study showed that by using graphical and inferential methods can detect

outlier and influence studies, although these two methods show different points. So, is recommended that both methods be used simultaneously to detect these points.

With regard to the results obtained from estimated RR and our meta-analyses for evaluating effect of albendazole on *T. trichiura* infection, treatment of *T. trichiura* with single oral doses of current anthelmintic is unsatisfactory. Therefore, our findings stress the pressing need for discovery and development of novel anthelmintic drugs, ideally with different mechanisms of action to complement the current therapeutic arsenal (29).

## Conclusion

The estimated RR and our meta-analyses for evaluating effect of single-dose oral albendazole in treating patients with *T. trichiura* infection showed that cure rates against *T. trichiura* infection when used in a single oral dose is disappointment. Therefore, the discovery and development of novel anthelmintic drugs against infections with *T. trichiura* has a high priority.

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