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THE COMPARISON OF EFFICACY AND SIDE EFFECT BETWEEN ALBENDAZOLE AND METRONIDAZOLE IN THE MANAGEMENT OF GIARDIASIS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Indonesia and other developing countries have exposed to multiple types of neglected parasitic infections, including giardiasis. The reliability of metronidazole as first-line drugs is doubted for its side effects and compliance; albendazole could appear as another alternative. We established evidence of the efficacy and side effects between Metronidazole and Albendazole through systematic review and meta-analysis study. We performed online search followed by peer-reviewed literature in Pubmed, Cochrane, Clinical Key, Science Direct, and Google Scholar published before January 2018. Statistical analysis of size effects calculation was conducted using Review Manager 5.3 to provide an estimation of odds ratios (ORs) with 95% confidence interval (CIs). A total of 715 patients were enrolled in the pooled size analysis from six studies, which is suitable for further calculation. The efficacy of infection resolutions and adverse effects (abdominal pain, vomiting, anorexia, metallic taste, and dizziness) were contested against each other. Study analysis revealed that there were not any significant differences in the efficacy (OR 1.11 95% CI 0.66-1.87, p=0.22), as well as abdominal pain (p=0.14) and vomiting (p=0.22) between two agents. Nevertheless, metronidazole treated patients were more prone to anorexia (p<0.00), metallic taste (p<0.00), and dizziness (p=0.01) compared to Albendazole group. The meta-analysis results indicated that metronidazole was not superior to albendazole for giardiasis; however, there were fewer side effects that occurred among the albendazole treated patients. Therefore, it was suggested that the administration of albendazole should be considered among giardiasis patients in any situation.

1. Introduction

Diarrhea and gastroenteritis have been responsible for a high mortality rate, and it induces debilitating conditions throughout developing as well as developed countries.[1] Various types of agents, such as viral, bacterial and parasitic infections can cause diarrhea and can be prevented by vaccines. [2, 3] One of the leading intestinal protozoa infections producing diarrhea and gastroenteritis is *Giardia lamblia* (similarly, *G.duodenalis*, *G.intestinalis*) in addition to other parasitic species, such as *Blastocystis hominis*, *Dientamoeba fragilis*, *Entamoeba histolytica*, *Isospora belli*, and *Microsporidia*. *G.lamblia* was firstly introduced through Antonie van Leeuwenhoek's observation in 1681, and its pathogenesis had not yet been elucidated until several outbreaks occurred among newcomers in Uni Soviet who demonstrated similar symptomatology in the 1970s.[4]

G.lamblia is a ubiquitous organism which predominantly found in the tropical and subtropical region including Russia, South East Asia, South Asia, Africa, Mexico, and western part of South America.[5] WHO estimated that 200 million people suffer from giardiasis each year with a prevalence rate increases from 4% to 42%; specifically, the prevalence rate in developed countries is only 2-5% compared to 20-30% in developing countries. Bimodal peak incidence occurred in two main age groups; firstly, *G.lamblia* infects human during infancy thus children aged under five years old correlated significantly with the cause of giardiasis diarrhea with a prevalence of 15-20%.[6-8] and secondly prevalence rate tends to increase among adults aged 45-49 years.[9]

In 2012, there were 15,223 cases of giardiasis in the United States, with most cases occurred in the child population aged between 1 and 4 years, followed by children aged 5-9 years.[10,11]

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In 2014, 17,278 cases of giardiasis were reported in 23 European countries with the predominant age 0-4 years old, 16.2 cases in boys, and 8.6 cases in girls per 100,000 people.[12] In Indonesia, epidemiologic study has revealed a prevalence rate of giardiasis 2.9- 4.4% with no accurate data collected through the official governmental institution.[13]

The infective stage of giardiasis initiates after ingestion of 10-25 mature cysts then followed by gastric acid and pancreatic exocrine secretion induced excystation leading to the production of trophozoites.[14] Trophozoites will migrate to jejunum and duodenum as well as attach to its microvilli using a 'sucker'; it outright marks the initiation of infection. Lectin on the surface of the organism will benefit for glucose uptake from the enterocyte surface.[15,16] However, all processes do not induce invasive transformation but progressively trigger enteric micro changes, such as villus atrophy, crypt hyperplasia, small intestine hyperosmolarity, and surface epithelial disruption that ultimately shed disaccharidase.[17] Based on recent investigations, there are cytopathic substances will accentuate the condition, such as glycoprotein, proteinase, and lectin directly inducing mucosal damage.[18,19] The amalgamation of that clinical pathology will turn the gut environment to be hostile for adequate nutritional absorption.

Giardiasis poses a threat to the global population and drawing attention relating to its progressive manifestation.[5] The primary clinical characteristic of infection is diarrhea; there are four putative reasons for diarrhea, it includes a structure in the surface glycoprotein of *G.lamblia* triggers fluid accumulation in the ileum, and secondly the organism also reduces electrolyte, water, and 3-O-methyl-D-glucose in jejunum causing malabsorption.[18,20] Giardiasis increases small intestine transit time and automatically boosts bowel contractility was demonstrated in literature as third putative reason, and lastly epithelial damage reduces disaccharidase activity, thus causing osmotic diarrhea.[21] In addition, fulminant diarrhea, abdominal cramp, bloating, fever, and rarely tenesmus can accompany the infection, but 35-70% of the infected population does not demonstrate symptoms or asymptomatic.[4] Diarrhea associated giardiasis is not inflammatory type gastroenteritis; accordingly, it does not contain blood, pus, or mucus as well as polymorphonuclear (PMN) on microscopic examination. Prolonged diarrhea (7-10 days) and lose weight (4.5kg) found among half of the infected population can also increase the likelihood of giardiasis as a diagnosis.[22]

A positive result of trophozoites or cysts in fecal microscopic examination should be treated as giardiasis. Standard anti-parasitic medication that widely used across the globe is a nitroimidazole derivate group, including metronidazole, tinidazole, and ornidazole.[23] In 1962, it firstly used for anaerobic infection since then metronidazole is frequently administered for giardiasis therapy or other parasitic manifestations.[24,25] Metronidazole (half-life 6.5 ± 2.9 hours) is metabolized by P-450 cytochrome to produce five primary metabolites, including 1-2 hydroxyethyl-2-hydroxy-methyl-5-nitroimidazole (*hydroxyl metabolite*) which controls anti-microbial activity. Furthermore, it will excrete through urine prior to first-pass metabolism for oxidation in liver tissue . There are several issues impeded the application of metronidazole in clinical settings, particularly its side effects and low compliance rate among patients. Recently, the use of albendazole has been applied for giardiasis as anti-parasitic medication.[26,27]

Albendazole has been used for a long time for anti-helminthic therapy.

Its first-pass metabolism in the liver will produce albendazole sulfoxide, which has a potent anti-parasitic effect with a half-life of 8-9 hours.[28]

According to one study, albendazole is considered as a plausible alternative drug for giardiasis. Nevertheless, its specific efficacy for giardiasis has not been known.[29]

Therefore, this meta-analysis aimed to investigate the effect of metronidazole and albendazole on the eradication rate among giardiasis patients and its side effects through statistical analysis.

2. Material and methods

Data Sources and Study Selection

A systematic literature search for articles published before 2018 was initially conducted using the following terms: "giardiasis," "albendazole," and "metronidazole" through PubMed, Google Scholar, Clinical Key, and Science Direct based on the methodology of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) without language restriction. The comprehensive evaluation enrolled two investigators to determine whether or not abstracts and its research materials were plausible to be included in the analysis. A meta-analysis study aimed to provide considerable evidence that ultimately establishes a firm conclusion. There are several reasons for exclusion criteria of studies, such as duplicate publications, studies using animal models, lacking comparison aspect between the efficacy of albendazole with metronidazole, review articles, and considered low quality according to Jadad criteria. The interpretation of the Jadad score ranging from 0 to 5 points with low-quality report earning ratings of 2 or less.[30] An RCT with Jadad score more or equal than three was included in the analysis. Jadad score examines whether or not there is randomization, double-blinding, and information on dropouts or withdrawals of samples.

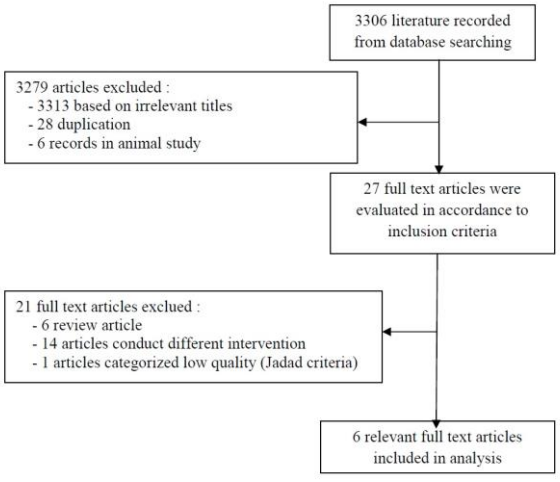

Figure 1. Flowchart of the study design process.

Data Extraction and Analysis

Research materials included in six randomized controlled trials were extracted by two reviewers; it contained the results of the primary outcome (eradication rate) as well as secondary outcome (side effects in few studies). The investigation was carried out independently while the finalization would compromise to the incompatibility of the data interpretation between two reviewers, such article characteristics, research method, samples (baseline characteristics of each treatment group, such as age, gender, comorbidities, clinical manifestations), results and the follow-up measurement.

Primary outcome was parasitic eradication rate defined as the period from the initiation of therapy until negative fecal examination for trophozoites and cysts and measured in days of treatment.

Meanwhile, the secondary outcome was then noted from several studies, RCTs must contain side effects reports, such as abdominal pain, vomiting, anorexia, metallic taste, and dizziness, during trial. Nevertheless, five randomized controlled trials (RCTs) must report the data on the comparison of the efficacy of albendazole with metronidazole for the treatment of giardiasis in humans. The calculation of inconsistency across trials was performed using the I2 statistic; the results range between 0% and 100%, where high values reflect increasing heterogeneity. Any individual RCTs were calculated independently for its Odds Ratio (OR) based on information demonstrated in the study (i.e., the percentage of people exhibiting parasitological cure in both groups) and 95% confidence intervals (CIs) was used in this method. A lower heterogeneity of p-value (<0.05) considered homogenous so that the fixed-effects model was used to analyze the data. Meanwhile, a p-value of ≥0.05 considered representing significant heterogeneity so that the randomized effect model was used. The statistical package Review Manager Software 5.3 (Cochrane Collaboration, Oxford, UK) was used to analyze the data.

3. Results

Study characteristics

Seven Randomized-controlled trials were defined fulfilled the inclusion criteria, but there was one study that did not achieve a minimum score of Jadad score, and it automatically excluded from the analysis. Therefore, there were 715 patients enrolled into six trials and several variables counted for pool effect size estimate including negative fecal trophozoite examination after drug administration (efficacy) as well as abdominal pain, vomiting, anorexia, metallic taste, and dizziness to represent the major incidence of side effects. All studies were designed randomized controlled trials (RCTs) and depicted in Table 1. In addition, most of the RCTs conducted a study in endemic regions for human giardiasis. Albendazole was opposed against metronidazole in identical mode; it means that the dosage similarity was observed in most studies, including 400 mg of albendazole for five days was administered among samples as well as metronidazole ranging from 125-500 mg thrice daily for 5-7 days.

Drug efficacy

The first outcome results of RCT analysis for clinical efficacy produced a p-value of 0.22, which means that the data were homogeneous; thus, the fixed-effects model was used.

The overall effect size model acquired p-value >0.05 with OR 1.11 95% CI 0.66-1.87, then statistically, there was no significant difference of efficacy between two agents. The fine black line represents the effect size across mid-diamond shape diagonally, and it also demonstrated varying results of efficacy with moderate heterogeneity (I^2 = 30%) based on Cochrane's Q calculation. Cannete et al. has the most significant weight sign represented by a bolder square with OR 0.82 95% CI 0.34-1.97, while the remaining studies have a wide confidence interval, which indicated precision in a meta-analysis study. One study has similar findings of cure among two groups but Hall et al. demonstrated that metronidazole was more favorable in treating giardiasis (OR 0.11 95% CI 0.01-2.14).

Research articles	Year	Study design	Jadad Score	Number of Patients	Age (Years)
Hall et al.[33]					
Albendazole	1993	RCT	4	68	5-10
Metronidazole				63	5-10
Dutta et al.[32]					
Albendazole	1994	RCT	3	75	2-10
Metronidazole				75	2-10
Karabay et al.[47]					
Albendazole	2004	RCT	3	28	41±12
Metronidazole				29	38±14
Yereli et al.[31]					
Albendazole	2004	RCT	3	52	8,3±3,4
Metronidazole				55	8,2±3,3
Alizadeh et al.[40]					
Albendazole	2006	RCT	4	60	21,3±8,9
Metronidazole				60	22,9±12,1
Cañete et al.[41]					
Albendazole	2011	RCT	5	75	29(18-36)
Metronidazole				75	30(19-38)

Table 1. Characteristic of RCT included in the meta-analysis study.

Adverse effects

The secondary outcome measured in the study was abdominal pain as side effects, which proves insignificant statistically among albendazole and metronidazole treated-group (p-value 0.14 OR 2.11 95% CI 0.88-5.05); yet, the mid part of diamond located in albendazole group with a wider confidence interval. In the presence of vomiting, the result of overall effect size analysis produced a p-value of 0.22, which means that the data are homogeneous so that the fixed effects model was applied to analyze the data. Finally, three studies included in the analysis demonstrated metronidazole more prone to the incidence of vomiting with the most substantial weight found in the study conducted by Canete et al. (OR 0.30 95% CI 0.09-0.96); it was concluded that vomiting predominantly occurred in the metronidazole group. There were three outcomes, such as anorexia, metallic taste, and dizziness statistically proven that the findings have predominant incidence found among the metronidazole group.

Anorexia was evaluated in three RCTs stated that two RCTs were consistent with a larger confidence interval (p-value 0.00 OR 0.22 95% CI 0.11-0.42) while Dutta et al. demonstrated more positive patients with anorexia in albendazole group (OR 1.57 95% CI 0.53-4.65). Lastly, the metallic taste was also assessed in three RCTs, which statistically calculated through its total size effect (p-value 0.00 OR 0.02 95% CI 0.01-0.09).

The incidence of metallic taste was higher among metronidazole treated patients (n=59) in comparison with albendazole (n=1). In addition, the effect size for dizziness was evaluated from two eligible RCTs demonstrated that metronidazole treated group was more susceptible to the event (p-value 0.01 OR 0.35 95% CI 0.15-0.78); the statistical analysis proved significant as well as the narrative reviews of two studies consistently observed a high incidence of dizziness among metronidazole group.

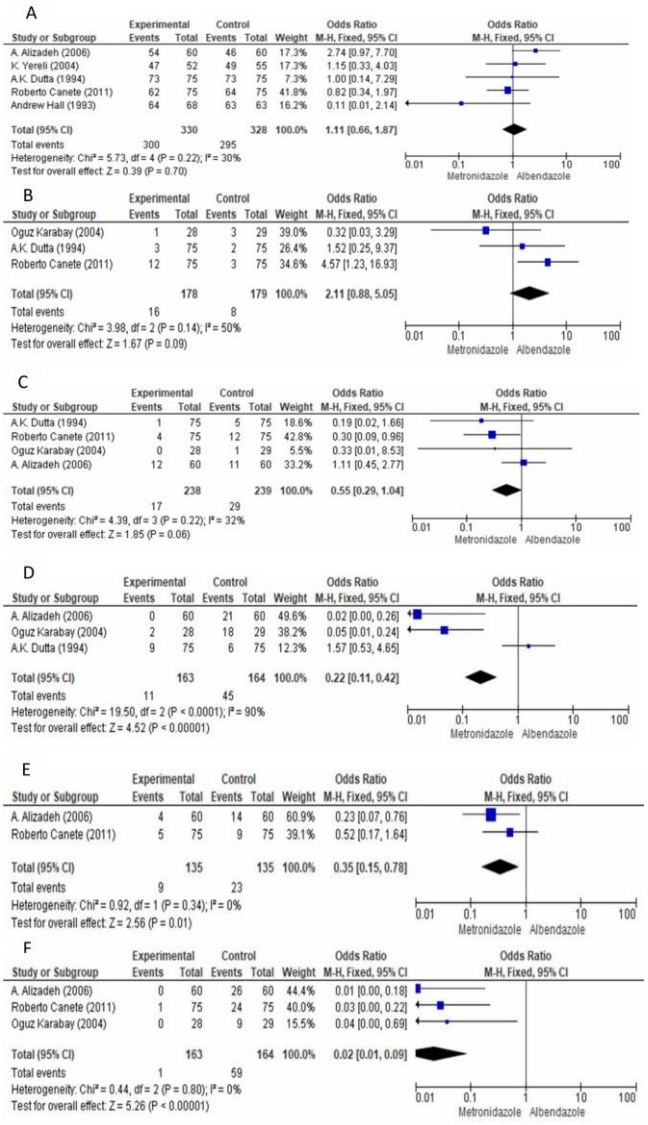

Figure 2. Forest plot deciphering several variables included in the meta-analysis (A) efficacy, (B) Abdominal pain, (C) Vomiting, (D) Anorexia, (E) Metallic taste and (F) Diziness.

4. Discussion

The significant findings of this meta-analysis are the non-superior efficacy among the use of albendazole and metronidazole, in fact adverse events of two agents, are predominantly demonstrated in the metronidazole group. The dosage similarity was fulfilled in five RCTs since the study utilized albendazole 400 mg for five days, whereas only two studies administered albendazole using the dosage based on body weight (10 mg/kg of body weight).[31]

Metronidazole was delivered in the equal duration of therapy (five days), but varying dosage for each population differs from one RCT to the remaining. RCTs involved child population aged between 2-10 years old mainly used the dosage based on body weight (kg).[31-33]

Metronidazole has been used and clinically proven in several investigations could eradicate *G.lamblia* as well as anaerobic infection but persistence administration could reverberate poor compliance and side effects in some reports.[34-37] Albendazole has also been widely recognized as the first-line drug of anti-helminthic medication with scarce evidence of its application among giardiasis patients.[38,39]

Firstly, this study compared clinical efficacy in terms of patients' recovery based on the absence of stool parasites since the initiation of therapy as the major outcome. It was concluded that the ability of albendazole to cure patients with giardiasis had no superiority to metronidazole (OR 1.11, 95% CI: 0.66; 1.87, p=0.22). A study conducted in Iran[40] has demonstrated a superior outcome of albendazole compared to metronidazole. Similarly, Yereli et al. also reported that the number of parasite-free patients was achievable in a shorter time among the albendazole group (57.7% vs.25.5% on day 7); yet the completion of drug administration resulted in similar eradication period on 14th day of treatment course.[31] Hall et al. presented RCTs with two-phase design; nevertheless, only phase two that been admitted in the current meta-analysis and the study result was contrary that the percentage of recovered patients given metronidazole was higher compared to the patients treated with albendazole.[33] The remaining studies have shown that there was no superior result between two modalities of treatment. However, Canete et al.[41] concluded that albendazole was as effective as metronidazole used among giardiasis patients (eradication rate for albendazole and metronidazole were 82.6% and 85.3% respectively).

Albendazole belongs to the group of benzimidazoles together with benzimidazole, thiabendazole, and mebendazole which target their effect on beta-tubulin of helminth, there were several observations of structural similarity of beta-tubulin between helminth and *G.lamblia* that surge possibility that albendazole could affect *G.lamblia* structural integrity.

In in-vitro studies, albendazole has 30 to 50 times of its anti-giardiasis activity than metronidazole; albendazole affects microtubule integrity then causing trophozoite detachment and distortion of cell membrane grossly.[42-44]

In addition, albendazole also triggers oxidative stress via reactive oxygen species (ROS) generation against susceptible clones of *G.lamblia* as well as DNA oxidative disruption followed by cell apoptosis.[45] In an in-vivo study, the anti-giardia effect was also observed by administration of albendazole 100mg/kg twice daily to mice; it eliminated trophozoite in small intestine and inhibited cyst excretion while maintaining drug concentration with higher dose but it was plausible that the faster gastrointestinal transit time in giardia-infected animals affects drug pharmacokinetics.[46]

Overall, side effects in the form of abdominal pain, vomiting, anorexia, metallic taste, and dizziness were frequently reported in patients undergoing albendazole and metronidazole treatment. The results of this meta-analysis showed a comparison of abdominal pain incidences between albendazole and metronidazole and it did not demonstrate significant results (OR 2.11, 95% CI: 0.88; 5.05, p = 0.9). Through descriptive analysis, one case has been reported for abdominal pain after initiating albendazole compared to three cases in the metronidazole treated groups in a study.[47] In contrast, two other studies demonstrated albendazole poses vulnerability for abdominal pain.[32]

The results of the meta-analysis did not show significant difference for the existence of vomiting in both groups, but it was noticeable that the incidence of vomiting was slightly higher in patients receiving metronidazole compared to albendazole treatment (OR 0.55, 95% CI: 0.29; 1.04, p 0.22).

Dutta et al.[32] reported that there was only one case experienced vomiting among the albendazole treated patients, whereas in the metronidazole group there were five cases. Meanwhile, Alizadeh et al.[40] showed that the incidences of vomiting are more common in patients given albendazole therapy, this can be seen in the percentage of vomiting incidences which was more significant in the albendazole compared to metronidazole group. The other three side effects, such as anorexia, metallic taste, and dizziness earned significant results based on statistical analysis. This meta-analysis found that the incidences of anorexia were higher in the metronidazole compared to albendazole group (OR 0.22, 95% CI: 0.11; 0.42, p <0.00001). Alizadeh et al.[40] discovered there was no findings of anorexia among albendazole compared to 18.3% of participants admitted having loss of appetite in metronidazole treated patients. In addition, Karabay et al.[47] also showed that anorexia predominantly occurred in the metronidazole compared to albendazole group. Nevertheless, Dutta et al.[32] demonstrated a contrast findings that anorexia had similar susceptibility among both of treatment groups. Meanwhile, metallic taste incidences were also investigated by Alizadeh et al.[40] and Karabay et al.[47] in which both studies demonstrated higher incidence of metallic taste among metronidazole treated patients. This analysis only included two studies to unfold dizziness incidence among both treatment groups and it concluded that dizziness prominently appeared in patients treated with metronidazole compared to albendazole (OR 0.23, 95% CI: 0.07; 0.76, p = 0.01).

5. Conclusions

This meta-analysis study has demonstrated similar efficacy between albendazole and metronidazole among giardiasis patients making metronidazole has no superiority than the long last used anti-parasitic drugs, albendazole. Additionally, there were several side effects that emerged during the course of treatment among both groups while unprecedently predominant among metronidazole treated patients. Therefore, considering two aspects (efficacy and side effects) in choosing an antiparasitic agent for the general population, it must not neglect the use of albendazole for giardiasis patients, particularly for patients with poor compliance when using metronidazole.

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