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Efficacy of Nitazoxanide Compared to Ornidazole or Metronidazole as a Treatment for Intestinal Amebiasis among Egyptian Patients

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ABSTRACT

Background: Entamoeba histolytica is considered the third leading cause of death from parasitic infections**.**

Objective: This study aimed to compare the efficacy of Metronidazole, Ornidazole, and Nitazoxanide in the treatment of intestinal amoebiasis.

Methods: 265 patients diagnosed with intestinal amebiasis by stool analysis were randomly assigned to one of three groups: Group 1 included 89 patients who received metronidazole 500 mg three times daily for 14 days, group 2 included 88 patients who received ornidazole 500 mg twice daily for 5 days, and group 3 included 88 patients who received nitazoxanide 500 mg once daily for 3 days. A total of 225 patients attended post-treatment follow-up visit and had stool analysis, and accordingly, have been included in the study. Extraintestinal amebiasis was ruled out before enrollment. Two stool samples were collected from each patient: One day pre-treatment: to confirm the diagnosis of intestinal amebiasis through the identification of E. histolytica trophozoites or cysts and one day post-treatment: to assess treatment efficacy. Eradication of E. histolytica infection after completion of treatment was the primary endpoint.

Results: Baseline characteristics were comparable between the three treatment groups. After treatment majority of all groups became negative after being positive with significant change (88% for group 1, 76% for group 2 and 84% for group 3) but without significant difference among groups (p = 0.19).

Conclusions: All three regimens demonstrated significant parasitological response rates; however, no significant difference in treatment efficacy was observed. Further large-scale, multicenter studies are warranted to confirm these findings.

Keywords: E. histolytica, Intestinal amebiasis, Stool analysis.

INTRODUCTION

As the third most common cause of parasite infection-related deaths, Entamoeba histolytica (E. histolytica) is regarded as a significant worldwide health concern [(1)]. According to some estimates, up to 50% of people in impoverished nations are infected with E. histolytica [(2)]. Infection is frequently found in tropical and subtropical regions, although it is also observed in developed nations among immigrants and tourists [(3)].

Intestinal amebiasis and extraintestinal symptoms are caused by the protozoan E. histolytica. About 50 million people develop symptoms from E. histolytica infections, and approximately 100,000 people die each year, despite the fact that 90% of infections are asymptomatic [(4)]. The genus Entamoeba includes at least seven species that can live in the human gut (E. histolytica, E. coli, E. hartmanni, E. polecki, E. dispar, E. moshkovskii and E. bangladeshi) and one that can live in the oral cavity (E. gingivalis). With the large intestine as the primary target organ, E. histolytica is currently the only species identified as an etiologic agent of amoebic invasive illness [(5)].

With a subacute onset, amoebic colitis can cause a variety of symptoms, such as cramping stomach pain, watery or bloody diarrhea, anemia, fever, and weight loss [(6)]. Ameboma formation is thought to be a rare symptom of amebic colitis. It may manifest as symptoms of intestinal blockage or as pain and edema in the right iliac fossa [(7)]. The most frequent extraintestinal sign of amebiasis is an amebic liver abscess, which can occur in people of any age [(8)]. With a 40% fatality rate, fistulizing perianal ulcerations, toxic megacolon and fulminant necrotizing colitis are uncommon but dangerous side effects that might happen, particularly if diagnosis and treatment are delayed [(9)].

The following diagnostic methods can be used to identify amebic infections: Colonoscopy with histological analysis, molecular approaches, antigen detection, serology, and microscopy. Because it is morphologically identical to E. dispar and E. moshkovskii, which are regarded as non-pathological species, the sickness produced by E. histolytica cannot be identified by the presence of cysts or trophozoites in stool [(10)]. Even asymptomatic carriers should receive treatment for all E. histolytica infections in order to stop the spread of the illness and stop invasive disease from developing [(1)].

The first line of treatment for intestinal amebiasis and amoebic liver abscess is metronidazole, which is followed by a luminal drug. Adults usually take 500–750 mg of metronidazole three times a day for seven–ten days. Diiodohydroxyquinoline, diloxanide furoate, and paromomycin are examples of luminal agents. Tinidazole, ornidazole, and nitazoxanide are substitutes for metronidazole [(3)]. Compared to metronidazole, other nitroimidazole medications with longer half-lives, like ornidazole, allow for shorter treatment durations and are

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better tolerated. These medications have been suggested as substitutes for metronidazole as anti-amoebic medications because of their successful use in shorter terms [12]. When compared to metronidazole, nitazoxanide, a thiazolide anti-infective with a similar structure, exhibits stronger antiparasitic action against a range of intestinal protozoal and parasitic illnesses [13].

It has been shown that nitazoxanide and its main metabolite are effective against both luminal and invasive forms [14]. Therefore, this study aimed to assess the effectiveness and tolerability of metronidazole, ornidazole, and nitazoxanide in treating intestinal amebiasis in Egyptian patients due to the paucity of comparison data among these therapeutic drugs.

PATIENTS AND METHODS

This study employed a prospective, open-label, randomized controlled trial design, conducted at Badr University Hospital in Cairo, Egypt, between June 2023 and December 2023. Participants were recruited from patients presenting with any of the following symptoms: Abdominal pain, abdominal distension, constipation, dysentery and/or diarrhea with undergoing stool analysis that clearly confirm the diagnosis of E. histolytica infection based on the accurate identification of E. histolytica/dispar trophozoites or cysts in stool samples. Following a comprehensive evaluation, which consists of laboratory tests and imaging studies to rule out extraintestinal amebiasis. Eligible patients were randomized to receive either metronidazole, ornidasole or nitazoxanide.

Exclusion criteria: Past medical history of E. histolytica treatment, allergies to study medications, concurrent use of interfering drugs, presence of any significant comorbidities, significantly compromised immune systems, pregnancy, lactation, and refusal to provide written informed consent.

Two hundred sixty-five patients diagnosed with E. 89 patients in group 1 received 500 mg of metronidazole three times a day for 14 days, 88 patients received 500 mg of ornidazole twice a day for 5 days, and 88 patients received 500 mg of nitazoxanide once a day for 3 days. Histolytica patients were randomly assigned to one of the three treatment groups using a straightforward randomization method (closed envelops). After treatment, only 225 patients (75 in each group), attended the post-treatment follow-up visit, and had stool analysis and accordingly, have been included in the study. The remaining 40 patients (14 patients from group 1, 13 patients from group 2, and 13 patients from group 3), were excluded due to lost follow-up.

Each patient had two stool samples taken: Before therapy (to identify E. histolytica trophozoites or cysts and confirm the diagnosis of intestinal amebiasis) and one day after treatment ended (to evaluate the effectiveness of the treatment). Microscopic methods used in stool examination included permanent stained smears, Lugol's/Dobell's/D'Antoni iodine wet mounts, concentration techniques, and saline wet mounts. [15]. All stool samples were examined within one hour of collection to ensure accurate results.

Data Collection included: a) Demographic and clinical data (age, gender, residency, occupation and a detailed record of clinical presentation such as: Diarrhea, dysentery, abdominal pain, abdominal distension, constipation, general weakness, vomiting, anorexia, urge to defecate after meals, as well as relevant physical examination findings: General and abdominal examination findings), b) Laboratory tests, such as serum creatinine, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), liver function tests (SGPT, SGOT), and complete blood count (CBC). c) Adverse events: (keeping an eye out for any potential drug-related side effects, such as headache, dizziness, skin rashes, nausea, vomiting, diarrhea, lack of appetite, and metallic taste).

The primary outcome was parasitological cure, defined as the absence of E. histolytica trophozoites or cysts in stool samples collected one day after completion of the respective treatment regimen.

The secondary outcomes were clinical cure **(**defined as the resolution or significant improvement of our patients` clinical symptoms within one day after the completion of treatment. This was assessed by evaluating changes in the severity of diarrhea, abdominal pain, fever, and other clinical manifestations), adverse events (this included any adverse event that led to the discontinuation of the study medication). Other adverse events were also monitored, including gastrointestinal symptoms such as diarrhea, abdominal pain, nausea, vomiting, and constipation. Systemic symptoms such as weakness and fatigue. Neurological symptoms such as headache and dizziness, and dermatological manifestations such as skin rashes**.** Treatment failure in our study was defined as persistence of E histolytica cysts or trophozoites in stool analysis after treatment completion.

Ethical considerations: All participating patients gave their informed consents and the study protocol was approved by Helwan University Faculty of Medicine's Ethical Committee (series number: 68-2023). The study included 225 patients who had been diagnosed with intestinal amebiasis. To protect participant privacy and data confidentiality, each patient was assigned a code number. The study followed The Declaration of Helsinki through its execution.

Statistical Analysis

The statistical package for the social sciences (SPSS version 20.0) was used to do the statistical analysis. In accordance with the data type, qualitative variables were represented by numbers and percentages, while quantitative variables were represented by means ± standard deviations. The Chi square test (X^2) was utilized to determine whether the differences were significant. ANOVA-based differences between quantitative multiples. For significant results, the P value was set ≤ 0.05, and for very significant results, it was ≤ 0.001.

RESULTS

Age was distributed as 34.68 ± 12.1, 32.52±13.3 and 33.16 ±12.9 respectively with no significant difference (P = 0.556) among groups. Also, there was no significant difference among groups regarding weight or sex (p = 0.685 and 0.065 respectively) but urban was significantly associated with 3rd group regarding residence distribution. Regarding food source among the studied groups the majority of meals were based on homemade food in ornidazole and nitazoxanide groups (Table 1).

Table (1): Demographic data among the studied groups

Variables			Metronidazole Group N = 75	Ornidazole Group N = 75	Nitazoxanide Group N = 75	F/ X^2	P
Age (years)			34.68±12.1	32.52±13.3	33.16±12.9	0.574	0.556
Weight			74.32±11.32	73.20±10.2	74.60±10.13	0.374	0.685
Sex	Female	N	51	51	45	5.95	0.065
		%	68.0%	68.0%	60.0%		
	Male	N	24	24	30		
		%	32.0%	32.0%	40.0%		
Residence	Rural	N	51	45	33	9.152	0.012*
		%	68.0%	60.0%	44.0%		
	Urban	N	24	30	42		
		%	32.0%	40.0%	56.0%		
Food	Home made	N	36	45	69	32.43	0.00**
		%	48.0%	60.0%	92.0%		
	Non	N	39	30	6		
		%	52.0%	40.0%	8.0%		

Regarding clinical presentation of the studied groups before treatment: There was no significant difference or association between groups and complaints distribution, with major complaint was abdominal pain affecting about 60% in the 1st group, 64% in the 2nd group and 56.0% in the 3rd group. Abdominal distention in about 60% in the 1st group, 56% in the 2nd group and 56.0% in the 3rd group. Constipation affected about 44% in the 1st and 3rd groups, and 48% in the 2nd group. Diarrhea affected about 44% in the 1st group, 48% in the 2nd group and 36.0% in the 3rd group (Table 2).

Table (2): Clinical presentation of the studied groups before treatment

Variables			Group			X^2	P
			Metronidazole Group N = 75	Ornidazole Group N = 75	Nitazoxanide Group N = 75		
Dysentery	-VE	N	66	69	72	3.26	0.19
		%	88.0%	92.0%	96.0%		
	+VE	N	9	6	3		
		%	12.0%	8.0%	4.0%		
Abdominal pain	-VE	N	30	27	33	0.84	0.36
		%	40.0%	36.0%	44.0%		
	+VE	N	45	48	42		
		%	60.0%	64.0%	56.0%		
Abdominal Distension	-VE	N	30	33	33	3.31	0.19
		%	40.0%	44.0%	44.0%		
	+VE	N	45	42	42		
		%	60.0%	56.0%	56.0%		
Constipation	-VE	N	42	39	42	0.321	0.851
		%	56.0%	52.0%	56.0%		
	+VE	N	33	36	33		
		%	44.0%	48.0%	44.0%		
Diarrhea	-VE	N	42	39	48	2.85	0.23
		%	56.0%	52.0%	64.0%		
	+VE	N	33	36	27		
		%	44.0%	48.0%	36.0%		

As regards laboratory results of the studied groups: First group was significantly lower regarding TLC & PLT (6.93 ± 1.62 and 299.04 ± 66.86 respectively) but significantly higher regarding ESR 2 (19.92±6.54). Third group was significantly higher regarding Eosinophil (1.54±0.354) but significantly lower regarding CRP, ESR1 & 2 (6.99±2.17 and 13.12±4.58 respectively).

Regarding ultrasonography data of the studied groups: There was no significant difference among groups regarding US findings (p value for liver and spleen size equal 0.102 and 0.085 respectively).

As regards results of stool analysis in the studied groups after treatment: After treatment majority of all groups turned to negative after being positive with significant change between metronidazole, ornidazole and nitazoxanide groups (88%, 76% and 84% respectively) but with no significant difference among groups (P = 0.19) (Table 3 & figure 1).

Table (3): Results of stool analysis in the studied groups after treatment

Variables			Group			X^2	P
			Metronidazole Group N = 75	Ornidazole Group N = 75	Nitazoxanide Group N = 75		
Stool analysis after TTT	**Negative**	**N**	66	57	63	3.92	0.19
		%	88.0%	76.0%	84.0%		
	Positive	**N**	9	18	12		
		%	12.0%	24.0%	16.0%		

Regarding clinical presentation of the studied groups after treatment: All complaints significantly improved among all groups without significant difference among them except for diarrhea post as nitazoxanide group was significantly lower than both other groups.

As regards drugs adverse events in the studied groups: Metallic taste & nausea were significantly associated with metronidazole group (80% and 44% respectively) but diarrhea & chromaturia were significantly associated with nitazoxanide group (12% and 32% respectively) (Table 4 & figure 2).

Table (4): Drugs adverse events in the studied groups

Variables			Group			X^2	P
			Metronidazole Group N = 75	Ornidazole Group N = 75	Nitazoxanide Group N = 75		
Metallic taste	**-VE**	N	15	75	69	140.3	0.00**
		%	20.0%	100.0%	92.0%		
	+VE	N	60	0	6		
		%	80.0%	0.0%	8.0%		
Skin rash	**-VE**	N	75	75	75	0.0	1.0
		%	100.0%	100.0%	100.0%		
	+VE	N	0	0	0		
		%	0.0%	0.0%	0.0%		
Nausea	**-VE**	N	42	63	57	15.47	0.00**
		%	56.0%	84.0%	76.0%		
	+VE	N	33*	12	18		
		%	44.0%	16.0%	24.0%		
Vomiting	**-VE**	N	75	75	75	0.0	1.0
		%	100.0%	100.0%	100.0%		
	+VE	N	0	0	0		
		%	0.0%	0.0%	0.0%		
Abdominal Pain	**-VE**	N	66	66	69	0.84	0.65
		%	88.0%	88.0%	92.0%		
	+VE	N	9	9	6		
		%	12.0%	12.0%	8.0%		
Diarrhea	**-VE**	N	75	75	66	18.74	0.00**
		%	100.0%	100.0%	88.0%		
	+VE	N	0	0	9		
		%	0.0%	0.0%	12.0%		
Chromaturia	**-VE**	N	75	75	51	53.74	0.00**
		%	100.0%	100.0%	68.0%		
	+VE	N	0	0	24		
		%	0.0%	0.0%	32.0%		

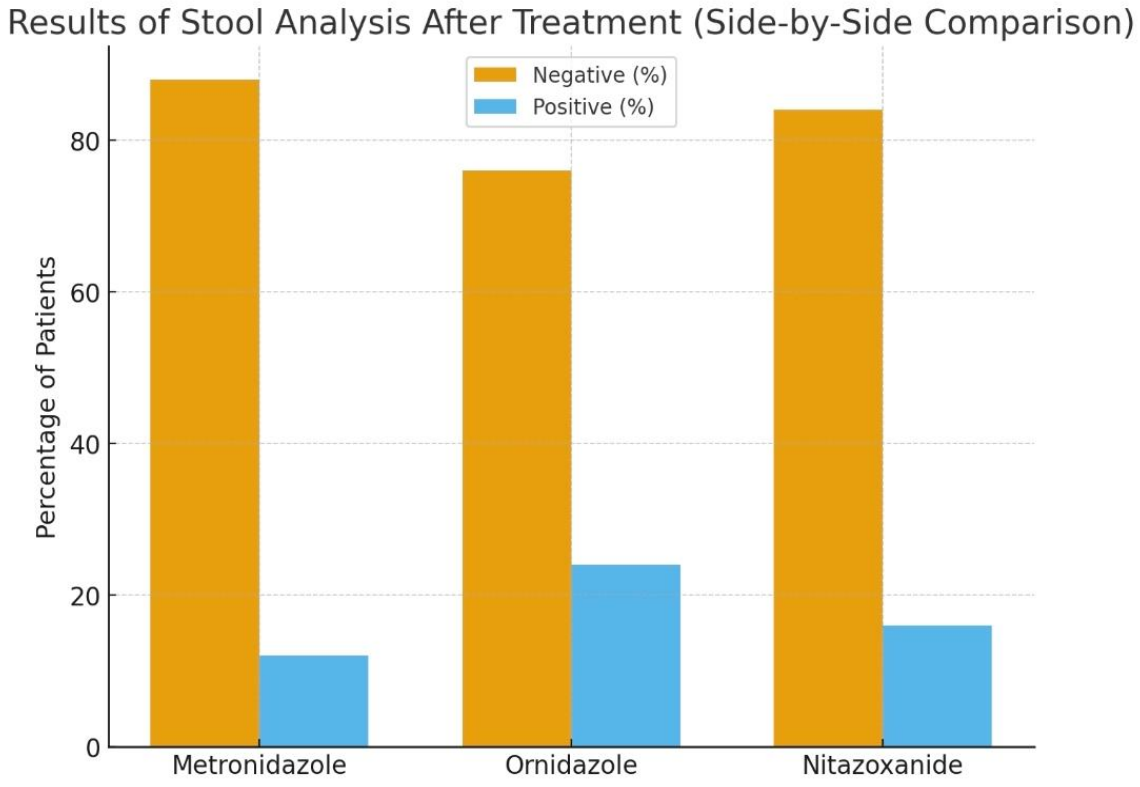

Figure (1): Results of stool analysis in the studied groups after treatment.

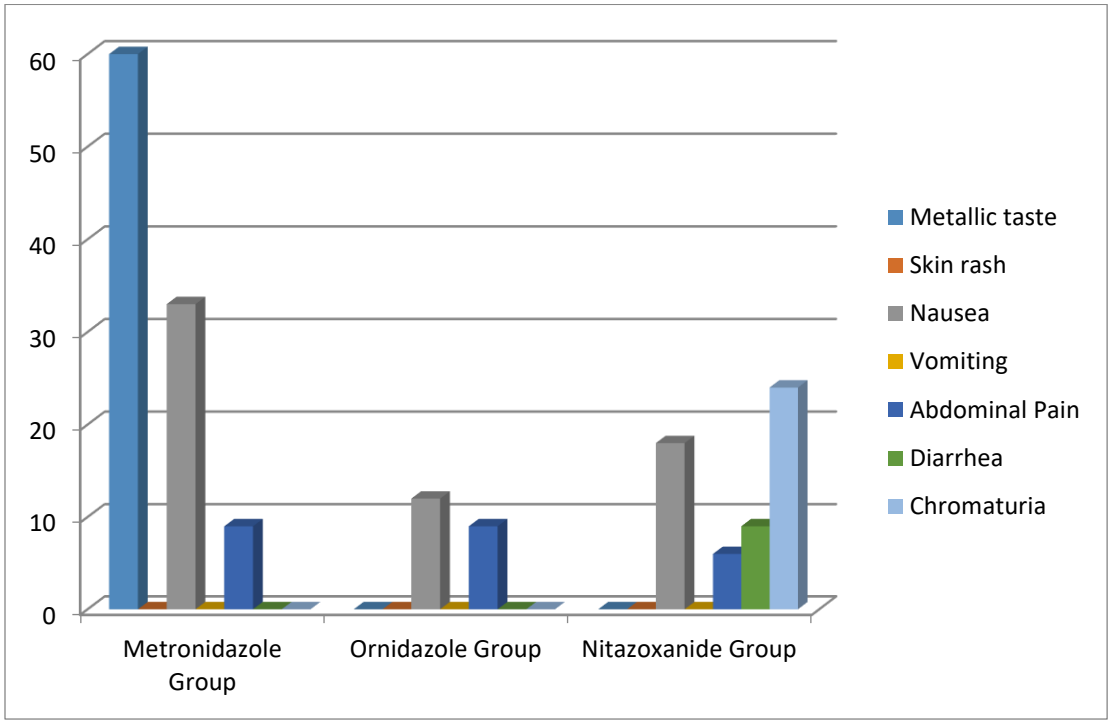

Figure (2): Side effect distribution among studied groups.

DISCUSSION

This randomized controlled study included 225 patients in final analysis, with 75 patients divided into three treatment groups at random: Group 1 was given 500 mg of oral metronidazole, group 2 was given 500 mg of oral ornidazole and group 3 was given 500 mg of oral nitazoxanide. Stool examinations were performed twice for all patients: At the time of diagnosis to confirm the presence of E. histolytica trophozoites or cysts, and one day after the completion of the respective treatment regimen to assess treatment efficacy.

Demographic data analysis revealed no significant differences in age: Group 1: 34.68 ± 12.1 years, group 2: 32.52 ± 13.3 years and group 3: 33.16 ± 12.9 years), weight, or sex distribution among the three study groups. This finding contrasts with the observation by **Shirley *et al.*** [16] that invasive amoebiasis, particularly liver abscess and colitis, is more prevalent in males than in females in the adult population, with a male-to-female ratio ranging from 3:1 to 10:1. Moreover, our findings align with **Kantor *et al.*** [17] who reported similar rates of amebic colitis between males and females, emphasizing the global burden of amoebiasis, especially in developing countries with poor sanitation and socioeconomic conditions.

In line with earlier findings, the majority of amoebiasis patients selected for our study lived in rural areas as opposed to urban ones. **Flaih *et al.*** [18] reported a significantly higher prevalence of intestinal amoebiasis in rural areas (69.4%) compared to urban areas (30.6%) ($p < 0.01$). Similarly, **Al-Damerchi and Nimnim** [19] found a higher prevalence of infection in rural populations (97 patients) compared to urban populations (89 patients) ($p<0.05$). These findings underscored the association between limited access to adequate sanitation and hygiene, often prevalent in rural settings, and the increased risk of E. histolytica infection.

In terms of food sources, there was a noteworthy correlation found between the consumption of non-homemade food and the metronidazole and ornidazole groups. This result is consistent with the research by **Hasan *et al.*** [20] who reported a higher rate of amoebiasis among individuals consuming non-homemade food (86.12%) compared to those consuming homemade food (13.87%; $p = 0.000$). Concerning the distribution of presenting complaints, no significant differences were observed between the study groups. Abdominal pain and distension were the most common presenting complaints, followed by constipation and diarrhea. This aligns with the established understanding that a significant proportion of E. histolytica infections are asymptomatic as reported by **Li *et al.*** [21].

Several studies have highlighted the high prevalence of asymptomatic E. histolytica infections. **Tharmaratnam *et al.*** [22] reported that approximately 90% of infected individuals remain asymptomatic, while only 10-20% develop symptomatic disease. Similarly, **Shirley *et al.*** [14] observed that 90% of E. histolytica infections are asymptomatic, attributing this to factors such as variations in the gut microbiome, proinflammatory cytokine responses and the host's antibody response to the parasite's Gal/GalNAc attachment lectin. Additionally, **Uribe-Querol *et al.*** [23] discovered that only a small percentage (10–20%) of E. histolytica infections proceed to clinical disease with the rest being asymptomatic. Although the precise reasons are still unknown, a number of risk factors such as young age, malnutrition, pregnancy, cancer, alcoholism, corticosteroid usage and limited access to essential urban services have been linked to an increased severity of the condition. Abdominal pain and diarrhea, which can be either watery or bloody due to trophozoites rupturing the intestinal barrier and blood vessels, are the most typical signs of symptomatic amebiasis.

Regarding treatment, our study demonstrated a significant improvement in parasitological outcomes in all groups, with a majority of patients testing negative for E. histolytica after treatment. Nevertheless, there were no statistically significant variations in the effectiveness of treatment between the groups receiving metronidazole, ornidazole and nitazoxanide. The effectiveness of nitroimidazole drugs, such as metronidazole and tinidazole, in getting rid of invasive trophozoites has been demonstrated in earlier research. For the treatment of amebic liver disease and amebic colitis, these medications are still advised. In a modest single-center experiment conducted in Egypt, nitazoxanide, a thiazolide with broad-spectrum antibacterial characteristics, showed encouraging results. Patients with intestinal and hepatic amebiasis experienced high rates of clinical and microbiological response. However, the unexpectedly high response rates observed in the placebo group (40-50%) in that study raised concerns about potential methodological limitations. Furthermore, **Marie *et al.*** [24] reported comparable efficacy between metronidazole and ornidazole in treating both clinical and parasitological manifestations of amebiasis, with similar adverse effect profiles. While nitazoxanide may be more effective than placebo in reducing clinical failure, its efficacy in preventing parasitological failure may be limited.

Furthermore, supporting the efficacy of nitazoxanide, **Ali *et al.*** [25] showed that a 3-day treatment of nitazoxanide was just as safe and effective as a 7-day course of metronidazole in treating pediatric giardiasis. This shorter treatment duration offers a significant advantage in terms of patient convenience. Ornidazole, another nitroimidazole agent, shares a similar mechanism of action with metronidazole but exhibits a longer half-

life, remaining in the bloodstream for approximately 1.7 times longer (half-life: 11-14 hours) compared to metronidazole [12]. There is currently not enough data to conclusively prove that ornidazole is better than metronidazole for treating amebic colitis, despite the possibility that it has some pharmacokinetic benefits. As treating intestinal amebiasis, larger, higher-quality studies are necessary to ascertain whether ornidazole or other nitroimidazole drugs significantly enhance clinical outcomes, such as lower rates of clinical failure and parasitological persistence, as compared to metronidazole. **Samar *et al.*** [26] revealed that the control and study groups' post-treatment cure rates were: Wet mount and ironhematoxylin-stained fecal samples collected three days after therapy were examined under a stool microscope to determine the cure rate and the removal of cysts and trophozoites. Although the metronidazole-control group had a greater cure rate for Entamoeba infections (91.2%) than the N. sativa-intervention group (78.8%), the difference was not statistically significant [26].

Nagaraja *et al.* [27] revealed that taking metronidazole can cause a number of dangerous side effects, such as headaches, nausea, vomiting, and a metallic or bitter taste in the mouth. More severe side effects include anorexia, ataxia, and skin rashes or itching. Although nitazoxanide has demonstrated potential, there are still worries about possible adverse consequences. **Hashan *et al.*** [28] revealed that nitazoxanide had a considerably greater effect than a placebo in two Egyptian studies looking into the drug's ability to cure diarrhea caused by E. histolytica (RR value of 1.80 [95% CI 1.35-2.40], P-value < 0.001). However, these studies also documented some nitazoxanide side effects, such as vomiting, abdominal pain, minor sclera discoloration (26.83%), and yellow urine (24.82%). Furthermore, **Samar *et al.*** [26] found that the most common adverse effects of metronidazole-controls were metallic taste in 11/34 (32.35%) and anorexia in 6/34 (17.6%). Despite being asymptomatic before to therapy, five patients experienced diarrhea and stomach pain as side effects of metronidazole.

Goel *et al.* [13] reported significantly higher frequencies of adverse effects with metronidazole compared to nitazoxanide. Nausea occurred in approximately 40% of patients receiving metronidazole compared to only 3% of those receiving nitazoxanide. Metronidazole was also associated with a higher incidence of metallic taste (8%) and chromaturia (16.7%) compared to nitazoxanide (0% and 33.3% respectively). Further research is needed to comprehensively evaluate the efficacy, safety, and tolerability of different anti-amebic agents, including nitazoxanide and ornidazole, compared to metronidazole in larger, well-designed clinical trials.

LIMITATIONS

There are several restrictions on this study. First, the results may not be as broadly applicable to different populations due to the single-center methodology and rather small sample size. Secondly, the brief follow-up period of 10 days may not adequately reflect long-term treatment efficacy and safety. Despite these limitations, the study provided valuable comparative efficacy data between metronidazole, ornidazole, and nitazoxanide, contributing to the limited existing literature on this subject.

CONCLUSION

This study confirmed that metronidazole, ornidazole and nitazoxanide were all effective therapeutic options for the treatment of intestinal E. histolytica infection, achieving high rates of both parasitological and clinical cure. Metronidazole demonstrated a slightly higher rate of parasitological clearance, whereas nitazoxanide showed superior improvement in diarrhea and was generally associated with fewer adverse effects compared to metronidazole. Ornidazole proved to be highly effective as well, particularly in relieving abdominal pain and distension, which represented major complaints in affected patients. Overall, the three regimens were well tolerated, and most reported side effects were mild, transient, and did not require treatment discontinuation. These findings emphasized the importance of tailoring therapy to individual patient needs, with careful consideration of efficacy, safety, tolerability, patient preference and overall treatment accessibility, in order to optimize clinical outcomes in the effective and reliable management of intestinal amebiasis.

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