

Comparison between Nitazoxanide and Metronidazole in the Treatment of Protozoal Diarrhea in Children

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Abstract

Diarrheal disease is a leading cause of illness and death in children worldwide. Diarrhea is caused by a blend of bacterial, viral and parasitic pathogens. Enteric protozoal infections such as giardiasis, amebiasis and cryptosporidiosis are among the most common and most prevalent forms of gastrointestinal parasitic infections worldwide. Both nitazoxanide and metronidazole are used in treatment of protozoal diarrhea. Nitazoxanide was found to have a very broad spectrum of activity against many forms of parasites. Metronidazole also produces good results when it is used for treatment of parasitic infections. The aim in this study was to evaluate and compare the effect of nitazoxanide and metronidazole in treatment of protozoal diarrhea in children. This study was carried out on 160 diarrheic patients (83 males and 77 females), aged from 1-11 years old collected from the-clinics of pediatric department at Beni suef University Hospital. Patients were divided into two groups. Group A received Nitazoxanide 100 mg in 1-4 years aged patients and 200 mg in 4-11 years aged patients twice daily for 3 days respectively, Group B received Metronidazole 50 mg/Kg/body weight daily for 7 days. Patients were represented to full history taking, physical examination, laboratory investigations in the form of stool analysis, culture and complete blood count (CBC). There was a significant increase in the number of cases resolved by Nitazoxanide compared to Metronidazole group in both amebiasis and giardiasis (p -value < 0.05) with similar clinical improvement when using Nitazoxanide for 3 days and Metronidazole for 7 days. This study confirms the efficacy and safety of nitazoxanide as a 3-day treatment of diarrhea due to giardiasis & amebiasis in children. A 3-day course of nitazoxanide could replace much longer regimens of metronidazole.

Key Words: Gastroenteritis, diarrhea, metronidazole, nitazoxanide

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Introduction

Diarrhea is defined as increased volume, fluidity or frequency of fecal discharges compared with the patient's normal stools. Clinical features vary greatly depending on the cause, duration and severity of the diarrhea, on the area of bowel affected and on the patient's general health [1]. Diarrheal diseases can be classified into acute, chronic and persistent diarrhea [2]. Acute diarrhea implies a sudden onset, generally over hours rather than days and duration of less than one week. Chronic diarrhea is more gradual in onset and lasts more than one to two weeks [3]. Whereas, persistent diarrhea refers to diarrheal episodes of infectious etiology that begins acutely but have an unusual long duration, often more than 14 days [4].

Most cases of diarrheal disease are due to the action of pathogenic organisms in the small or large bowel [5]. Diarrhea is caused by a blend of bacterial, viral and parasitic pathogens [6]. Diarrhea is produced by a variety of different mechanism such as malabsorption, osmotic particle accumulation within the GI lumen, hyper secretion, intestinal motility abnormalities and finally exudation [7]. Nitazoxanide, (2-acetylloxy-N (5-nitro-2thiazolyl) benzamide), is the only agent that has broad coverage against both common intestinal parasitic protozoa and helminthes [8]. Nitazoxanide interferes with pyruvate ferredoxin-oxidoreductase (PFOR) enzyme dependent electron transfer reaction which is important for anaerobic glucose energy metabolism [9]. Metronidazole, (1-(2-hydroxyethyl)-2-methyl-5- nitroimidazole), is a drug used to treat infections caused by parasites and anaerobe bacteria [10]. It works by stopping the growth of bacteria and protozoa. This anti-infective agent only treats bacterial and protozoal infections. It will not work for viral infections [11].

The aim of the present study was to evaluate and compare the effect of nitazoxanide and metronidazole in treatment of diarrhea in children.

Patients and Methods

A local hospital research ethics committee approval was obtained for the patients study (approved number: IORG0006240). Patients were collected in this study from pediatric department at Beni suef University hospital with diarrhea. An informed consent was obtained from their parents.

Inclusion criteria:

Patients diagnosed as diarrhea

Exclusion criteria:

- 1- Patient with severe dehydration.
- 2- Patient with any serious concomitant illness that needs antibiotic treatment.
- 3- If severe adverse events occur at any time.
- 4-Cytotoxic drugs, food & chemical poisoning

All Patients in the study were evaluated by detailed history and thorough examination, which include name, age, sex and present history and laboratory investigations in the form of CBC, stool analysis and stool culture.

Patients were divided into two equal groups A, B. Group A represents patients who received nitazoxanide 100 mg in 1-3 years aged patients and 200 mg in 4-11 years aged patients twice daily for 3 days respectively. Group B represents patients who received metronidazole 50 mg/Kg/body weight daily for 7 days.

All these patients were subjected to; Detailed history taking including frequency of stool passage, with blood, mucus or watery diarrhea. Thorough examination at the start and after receiving each drug. Laboratory investigation in the form of stool analysis, culture, and CBC before the start and after receiving the drug by 7-10 days.

Because of the infrequent passage of the cysts in the stool, the method of stool analysis was achieved by two (the operator and the assistant) experienced persons and the patients with a negative result, stool re-examined in 2- 3 weeks.

Statistical analysis

The Chi-square test (χ^2) was used to compare between the effect of Nitazoxanide and Metronidazole.

Results

The study was conducted on 160 (83 male & 77 female) diarrheic patients, collected from pediatric department at Beni suef University hospital. Their ages ranged from 1 to 11 years old. The study was designed to compare between Nitazoxanide and Metronidazole in treatment of protozoal diarrhea in children. This study was done on 80 (49 males, 31 females) cases taking Nitazoxanide and another 80 (34 males, 46 males) cases taking Metronidazole ranging from 1 to 11 years old. After the stool culture it was found that 16 patients (7 male & 9 female); 10% of each group had no parasites in their stool. Hence the rest of the patients were as followed; 72 (46 males, 26 females) cases taking Nitazoxanide and another 72 (30 males, 42 males) cases taking Metronidazole ranging from 1 to 11 years old.

110 patients (54 male & 56 female); 68.75% were infected with *Entamoeba histolytica* while 34 patients (22 male & 12 female); 21.25% were infected with *Giardia lamblia*. All children were given information on the study and consent was obtained from the parents after explaining the aim and procedures of the study. Demographic and disease-related characteristics of the study population by treatment group in amebiasis and giardiasis are shown in table (1, 2)

There was no significant difference in the examination of the patient with giardiasis and amebiasis regarding stool culture and CBC.

Proportions of children resolving diarrhea in amebiasis by stool analysis was 90.9 % in case of Nitazoxanide and 83.6 % in Metronidazole group ($p\text{-value} < 0.05$); While in giardiasis diarrhea had resolved in 14 out of 17 (82.3%) in the Nitazoxanide treatment group compared to 13 out of 17 (76.47%) for Metronidazole ($p\text{-value} < 0.05$). After treatment, there was no significant difference between male and female in case of Giardiasis and amebiasis ($p\text{-value} < 0.05$).

The clinical improvement with the use of nitazoxanide for 3 days was similar to improvement after 7days with metronidazole.

In severe cases, the patient was admitted to the hospital and fluids, electrolytes imbalance were corrected either by intravenous fluids or oral fluids.

Table 1. Demographic and disease-related characteristics of the study population by treatment group in amebiasis

	Nitazoxanide	Metronidazole	Total
Gender (male: female)	32: 23	22: 33	54: 56
Stool frequency:			
3-10/ day	53	55	108
>10/day	2	0	2
Stool consistency			
Liquid	23	15	38
Liquid and semi-solid	2	2	4
Semi-solid	30	38	68

Table 2. Demographic and disease-related characteristics of the study population by treatment group in Giardiasis

	Nitazoxanide	Metronidazole	Total
Gender (male: female)	14: 3	8: 9	22: 12
Stool frequency			
3-4/ day	10	12	22
≥5/day	7	5	12
Stool consistency			
liquid	13	12	25
soft	4	5	9

Discussion

Diarrheal diseases are among the leading causes of morbidity and mortality among children in developing and even developed countries [12]. Diarrhea is caused by a blend of bacterial, viral and parasitic pathogens [6]. Diarrheal diseases can be classified in various ways. The first major subdivision is acute, chronic and persistent diarrhea [2]. Diarrhea can be also classified according to stool consistency into dysentery and watery diarrhea [13]. Nitazoxanide offers a new ray of hope. It is the only agent that has broad coverage against both common intestinal parasitic protozoa and helminthes [8]. Nitazoxanide acts by interference with pyruvate ferredoxin-oxidoreductase (PFOR) enzyme dependent electron transfer reaction which is important for anaerobic glucose energy metabolism. This results in cell swelling, membrane damage and vacuole injury of the trophozoites, resulting in dysfunction of the parasite [9].

Metronidazole is a drug used to treat infections caused by parasites (amoeba) and anaerobe bacteria. It can be given to treat diarrhea caused by *Entamoeba histolytica*, *Giardia lamblia*, or *Clostridium difficile*. It can also be used to treat vaginal infections or various types of bacterial infections [10].

Metronidazole is active against a variety of protozoa and bacteria. It enters the cell as a prodrug by passive diffusion and is activated in either the cytoplasm of the bacteria or specific organelles in the protozoa. The metronidazole molecule is converted to a short-lived nitroso free radical by intracellular reduction, which includes the transfer of an electron to the nitro group of the drug. This form of the drug is cytotoxic and can interact with the DNA molecule. The activated reduced metronidazole molecule binds nonspecifically to bacterial DNA, inactivating the organism's DNA and enzymes leading to a high level of DNA breakage, with immediate action of the drug but no cell lysis [14,15].

From the results, it was found that number of patient infected with *Entamoeba histolytica* was higher than those infected with *Giardia*. Proportions of children resolving diarrhea (by stool analysis) in amebiasis is higher than those in giardiasis in case of nitazoxanide and metronidazole. Also, there was no significant difference between male and female in case of

giardiasis and amebiasis. There was no significant difference in the examination of the patient with giardiasis and amebiasis by stool culture and CBC.

The study confirms the efficacy and safety of nitazoxanide as a 3-day treatment of giardiasis in children. The 3-day treatment was equivalent to a 7-day course of metronidazole. Also, this study indicates an important role for nitazoxanide in resolving symptoms associated with intestinal amebiasis. A 3-day course of nitazoxanide could replace much longer regimens of metronidazole, providing an advantage with respect to convenience.

Previous study described Prevalence of intestinal protozoa infection among school-aged children on Pemba Island, Tanzania. Cure rate was 60%, 57.1%, 42.1%, 52% for albendazole, nitazoxanide, nitazoxanide-albendazole combination, placebo respectively for giardiasis while cure rate for amebiasis was 56.5%, 60.9%, 67.7%, 54.5% respectively [16].

Concerning studies for Giardiasis to compare the efficacy and safety of nitazoxanide and tinidazole in children infected with *Giardia lamblia*. the frequency of parasitological cure following a single dose of tinidazole was significantly higher than that following six doses of nitazoxanide (90.5% v. 78.4%; $P, 0.05$). Both treatment schedules were well accepted and well tolerated, with only mild, transient and self-limited side-effects reported [17].

Pointing to a study conducted in outpatients with amebiasis from the Nile Delta of Egypt. Four days after completion of therapy, 32 (94%) of 34 nitazoxanide treated patients resolved symptoms compared with 15 (50%) of 30 patients who received placebo ($P < 0.001$). Thirty-two (94%) of 34 nitazoxanide treated patients were free of *Entamoeba histolytica* in two post-treatment stool specimens compared with only 13 (43%) of 30 patients receiving placebo ($P < 0.0001$) [18].

Another study was carried out to evaluate the effectiveness of nitazoxanide compared with that of quinifamide, mebendazole, or both in the treatment of intestinal protozoa and helminthic infections. Nitazoxanide had a higher eradication rate in amebiasis treatment: 85.1 and 93.3% for single and associated parasitoses respectively.

In *Giardia lamblia* infections, the eradication rates for single parasitosis and associated parasitosis were 56.2 and 63.6% with nitazoxanide versus 61.0 with mebendazole and 57.4% with mebendazole and quinifamide [19]. The study between metronidazole and co-trimoxazole

(septrin) on eradication of *entamoeba histolytica* in both children and adults showing that Metronidazole with septrin produced a response rate of 95% after a 10 day course of Metronidazole [20].

Concerning a study describe Comparison between metronidazole and furazolidone against *giardia lamblia* in children. Four weeks after the therapy, the efficacy of metronidazole and furazolidone were 87 % and 81.6%, respectively [21].

A study done by Alizadeh was conducted to compare between albendazole and metronidazole in giardiasis in both children and adult. Cure rate was 90% for albendazole and 77% for metronidazole [22]. In the study by Yereli who compared albendazole and metronidazole effects on giardiasis of children. Cure rate was 90% for albendazole and 89% for metronidazole [23]. Another study for ornidazole and metronidazole on giardiasis of children in turkey. Cure rate was 96%-100% for ornidazole while 89% for metronidazole [24].

Pointing to a study showing comparative clinical trial of mebendazole and metronidazole in giardiasis of children. Cure rate was 86% for mebendazole and 90% for metronidazole [25].

This study is similar to the results of Ortiz et al., study in the year of 2001. They made a randomized clinical study of nitazoxanide compared to metronidazole in the treatment of symptomatic giardiasis in children from Northern Peru. Diarrhea had resolved in 47 children out of 55 (85%) in the nitazoxanide treatment group before the day 7 follow-up visit, compared to 44 out of 55 (80%) for metronidazole ($p= 0.6148$) [26].

Also is comparable to the results of Rossignol et al., study in the year of 2007. They made a randomized clinical study of nitazoxanide compared to placebo in the treatment of amebiasis in children. Diarrhea had resolved in 16 children out of 17 (94%) in the nitazoxanide treatment group compared with 15 (50%) of 30 patients who received placebo ($p<0.001$) [18].

And is similar to the results of Pehr and Elias, study in the year of 1984. They made a long-term follow up study of amoebiasis treated with Metronidazole. Diarrhea had resolved in 15 children out of 17 (88.23%) for metronidazole [27].

Although metronidazole has been a common and effective treatment for giardiasis, it has some disadvantages, such as long duration of treatment, a multiple-dose regimen and frequent

side-effects, such as a metallic taste, nausea, vomiting, abdominal cramps, headache, anorexia and neurological side effects. All of these features may result in poor compliance in a significant number of patients, especially if those patients are children [28].

Metronidazole failures have been reported in immunodeficient patients, including patients with AIDS. Some experts suggest repeating the course of treatment with a higher dose of metronidazole [29].

Nitazoxanide is another nitro heterocyclic compound that exhibited limited side effects [30] promising results for the treatment of giardiasis in both children and in adults [31]. At the ultrastructure level, Giardia trophozoites exposed to nitazoxanide show swelling and various changes in their cellular morphology with the formation of large empty areas in the cytoplasm and the disruption of the plasma membrane [32].

Nitazoxanide has an important role in resolving symptoms associated with intestinal amoebiasis and in clearing organisms from the intestinal tract.

A 3-day course of nitazoxanide could replace much longer regimens of metronidazole followed by a luminal amoebicide, providing an advantage with respect to convenience and potential advantages with respect to cost and availability (versus luminal agents) [18].

Conclusions

This study confirms the efficacy and safety of Nitazoxanide as a 3-day treatment of giardiasis & amebiasis in children. The 3-day regimen was equivalent to a 7-day course of Metronidazole. A 3-day course of Nitazoxanide could replace much longer regimens of Metronidazole, providing an advantage with respect to convenience. The clinical improvement with the use of Nitazoxanide for 3 days was similar to improvement after 7 days with Metronidazole. Proportions of children resolving diarrhea (had no parasites in their stool) in the Nitazoxanide group was higher than Metronidazole group in giardiasis and amebiasis. Also Nitazoxanide appears to be well tolerated, has a relatively low incidence of adverse effects and displays no significant drug drug interactions. However, Metronidazole has some disadvantages, such as long duration of treatment, a multiple-dose regimen and frequent side-effects. All of these features may result in poor compliance in a significant number of patients, especially if those patients are children.

Hence, it is recommend the use of nitazoxanide in treatment of diarrhea due to *Giardia lamblia* and *Entamoeba histolytica*

Competing interests

No competing interests

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