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Nitazoxanide-based therapeutic regimen as a novel treatment for *Helicobacter pylori* infection in children and adolescents: a randomized trial

D. SHAWKY[1], A.M. SALAMAH[2], S.M. ABD-ELSALAM[3], E. HABBA[3], M.H. ELNAGGAR[4], A.A. ELSAWY[4], N. BAIOMY[5], M.M. BAHAA[6], R.M. GAMAL[1]

[1]Department of Pediatrics, Faculty of Medicine, Tanta University, Tanta, Egypt
[2]Department of Pediatrics, Faculty of Medicine, Kafr El-Sheikh University, Kafr El-Sheikh, Egypt
[3]Department of Tropical Medicine and Infectious Diseases, [4]Department of Internal Medicine,
[5]Department of Clinical Pathology, Faculty of Medicine, Tanta University, Tanta, Egypt
[6]Pharmacy Practice Department, Faculty of Pharmacy, Horus University, New Damietta, Egypt

Abstract. – OBJECTIVE: Antibiotic resistance and poor patient compliance with treatment cause *Helicobacter pylori* to show increased resistance to typical first-line therapeutic regimens. This study aimed to evaluate the efficacy of the new nitazoxanide-based treatment regimens for *Helicobacter pylori* infection vs. the current metronidazole-based regimens to address the problem of increasing metronidazole resistance.

PATIENTS AND METHODS: This randomized clinical trial enrolled 100 patients with *Helicobacter pylori* infection. The patients were randomly assigned to one of two groups: group I received nitazoxanide-based triple therapy (nitazoxanide, proton pump inhibitor, and clarithromycin) for 14 days, whereas group II received standard treatment (metronidazole, omeprazole, and clarithromycin) for 14 days. On enrollment and after six weeks of treatment, all patients underwent careful history taking, full clinical examination, laboratory investigations (complete blood count, liver and renal function tests), and *Helicobacter pylori* stool antigen testing.

RESULTS: Of the patients, 92% in the nitazoxanide group and 84% in the metronidazole group recovered from infection, with no statistically significant difference between the two groups. Patients in the nitazoxanide group showed a 54% lower risk of resistant infection (odds ratio, 0.5; 95% confidence interval, 0.161-1.555) than those in the metronidazole group.

CONCLUSIONS: The nitazoxanide-based therapeutic regimen produced higher eradication rates than the standard treatment. However, the difference was not substantial in this particular group of patients.

Key Words:
Helicobacter pylori, Resistance, Nitazoxanide, Metronidazole, Eradication, Treatment.

Introduction

The gram-negative spirochete *Helicobacter pylori* (*H. pylori*) is the most prevalent cause of gastritis worldwide[1,2], with a prevalence of approximately 50%[3].

In developing countries, 50% of children are infected by age 10 years[4]. Only 10% of patients have an overt disease; the other 90% have subclinical disease[5]. In symptomatic Egyptian children, the prevalence of infection ranges from 64.6% to 72.4%[6-8].

If left untreated, *H. pylori* infection can damage the gastric mucosa, resulting in chronic gastritis, peptic ulcer, and gastric cancer[1]. Antibiotic resistance combined with poor patient compliance with treatment cause *H. pylori* to show increased resistance to typical first-line therapeutic regimens[9].

The treatment failure rate for *H. pylori* eradication is approximately 20% in the United States, whereas it can be as high as 60% in some countries[10]. The drug nitazoxanide (NTZ) has shown promise as an alternative therapy[11]. NTZ is a thiazolide antibiotic with similar microbiological properties to metronidazole (MTZ) but has fewer adverse effects[12-14]. The mechanism

Corresponding Author: Sherief M. Abd-Elsalam, MD; e-mail: sherif.abdelbaky@med.tanta.edu.eg

of action of NTZ is interfering with anaerobic metabolism[15,16]. NTZ also has substantial immunomodulation capabilities. Unlike MTZ, is nonmutagenic for *H. pylori* and exhibits antivacuolating toxin activity[17].

NTZ-based regimens have demonstrated promising results in *H. pylori* eradication in adults, avoiding the problem of drug resistance that MTZ causes at the same cost[11,14,18,19]. This study compared the current MTZ-based regimens and the new NTZ-based regimens for *H. pylori* eradication to solve the problem of resistance in Egyptian pediatric patients.

Patients and Methods

This randomized double-blinded (caregivers/participants and investigators) clinical trial enrolled 100 patients with *H. pylori* infection in the Gastroenterology, Hepatology, and Nutrition Unit, Department of Pediatrics, Tanta University Hospital, between September 2019 and June 2020.

The sample size was calculated using a prevalence rate of at least 65%, the precision of 5%, and a 95% confidence interval (CI) calculated from prior epidemiologic research[20]. This study was registered at ClinicalTrials.gov (NTC04415983) and was approved by the Faculty of Medicine of Tanta University (registration No. 33611/1/20).

The parents/caregivers signed a documented consent form. The study included patients with dyspepsia, hematemesis with or without melena, chronic epigastric pain, or vomiting and with *H. pylori* infection established using a stool antigen (Ag) test and a histopathologic study of gastric samples obtained through upper gastrointestinal tract endoscopy.

This study excluded patients aged >18 years; those with major illnesses, such as liver cirrhosis, renal impairment, and previous gastric or duodenal surgery or malignancy; those who had previously received *H. pylori* treatment; those with previous failed *H. pylori* treatment; those who were receiving medications (e.g., antacids [proton pump inhibitors (PPIs), H2 receptor antagonists], anticoagulants, or antibiotics) within 6 weeks before study enrollment; and those with an allergy to any of the drugs.

The patients were randomly assigned to one of two groups: group I received NTZ-based triple therapy (NTZ, PPI, and clarithromycin) for 14 days, whereas group II received standard treatment (MTZ, omeprazole, and clarithromycin) for 14 days[21-24].

Detailed history taking and full clinical examination were performed. All patients also underwent abdominal ultrasonography and upper gastroenterology endoscopy (Pentax EG-2990i, 9.8 mm; Pentax, Tokyo, Japan), during which tissue samples were obtained for evaluations, including histologic determination of *H. pylori* infection. Empiric therapy was recommended while awaiting histopathologic confirmation of the hallmark *H. pylori* findings of nodularity and erosive or ulcer disease. Complete blood count, liver function tests, and renal function tests were performed as laboratory tests. *H. pylori* stool Ag testing was performed at the start of the study and after 6 weeks of treatment.

Stool samples were collected in sterile, clearly labeled containers and immediately sent to the laboratory for *H. pylori* stool Ag testing using an immune-card test (Epitope Diagnostics Inc)[25]. Fresh (within 1 day) stool samples were used for the test. A vortex mixer homogenized the fecal sample (100 mg) in 1 mL dilution buffer. Stool analysis was performed at least 4 weeks after the end of *H. pylori* therapy to avoid false-negative *H. pylori* stool diagnostic tests caused by the inhibitory effect of PPI on *H. pylori*.

The patients were considered clinically cured if they had a negative *H. pylori* stool Ag test and were free of symptoms at 6 weeks after starting treatment. Failure of treatment was defined as failure to meet any of these endpoints. The caregivers were interviewed, and empty prescription containers were recovered to determine patient compliance.

Statistical Analysis

The Statistical Package for the Social Sciences (version 21; SPSS Inc., IBM, Armonk, NY, USA) was used to collect, code, modify, and statistically analyze the data. Qualitative data are presented as numbers and percentages, and quantitative data with a parametric distribution are expressed as means, standard deviations, and ranges. The chi-square test was used to compare qualitative data between two groups, and Fisher's exact test was used instead of the chi-square test when the expected count in any cell was <5. An independent *t*-test compared quantitative data with a parametric distribution between two groups. The CI was set at 95%, whereas the acceptable margin of error was set at 5%. A *p*-value of <0.05 indicated statistical significance.

Results

This study recruited 100 children. In terms of demographics, clinical presentations, and endoscopic features, no statistically significant differences were observed between the study groups (children who received MTZ triple therapy [group I] *vs.* children who received NTZ triple therapy [group II]), as indicated in Table I .

H. pylori stool Ag testing was used to assess the response of both groups to the treatment regimen. Cure was achieved in 92% of patients who received NTZ (group I) and in 84% of patients who received MTZ (group II). The difference between the two groups was statistically insignificant. However, the failure rate was greater in children treated with MTZ triple therapy (16%) than in children treated with NTZ triple therapy (8%) (Table II).

Patients with clinical failure reported mild gastrointestinal symptoms (abdominal discomfort, nausea, or vomiting). Patients in the NTZ group had a 54% lower risk of resistant infection (odds ratio, 0.5; 95% CI, 0.161-1.555) than those in the MTZ group. A case of resistant *H. pylori* infection was avoided for every 13 patients treated with NTZ for 6 weeks. NTZ-containing therapeutic regimens seemed well tolerated, with none of the patients experiencing any adverse effects.

Discussion

For *H. pylori* eradication, PPIs combined with clarithromycin, amoxicillin, and MTZ for 7-14 days have been proven effective[26,27]. However, due to antibiotic resistance's emergence, the efficacy

Table I. Characteristics of the studied patients.

Variables	Group I (n = 50)		Group II (n = 50)		*t*	*p*-value
Age, years						
Range	5-17		2-17		0.612	0.543
Mean ± SD	10.16 ± 3.59		9.52 ± 3.80			
	N	%	N	%	χ^2	*p*-value
Sex						
Female	38	76.0	30	60.0	1.471	0.225
Male	12	24.0	20	40.0		
Family history						
Negative	36	72.0	40	80.0	0.110	0.740
Positive	14	28.0	10	20.0		
Clinical presentation						
Generalized abdominal pain	12	24.0	20	40.0	1.471	0.225
Epigastric pain	34	68.0	26	52.0	1.333	0.248
Persistent vomiting	20	40.0	10	20.0	2.381	0.123
Dyspepsia	12	24.0	8	16.0	0.500	0.480
Hematemesis/melena	14	28.0	16	32.0	0.095	0.758
Occult blood in stool	0	0	4	8.0	2.083	0.149
Generalized abdominal pain	12	24.0	20	40.0	1.471	0.225
Histopathologic and endoscopic findings						
Gastritis					3.391	0.183
Mild	26	52.0	20	40.0		
Moderate	12	24.0	24	48.0		
Severe	12	24.0	6	12.0		
Duodenitis					0.439	0.508
Negative	36	72.0	40	80.0		
Positive	14	28.0	10	20.0		
Others					FE	0.495
Fundal ulcer	0	0	2	4.0	0.080	0.773
Hiatus hernia	8	16.0	6	12.0		

SD, standard deviation; FE, Fisher's exact test.

Table II. *H. pylori* eradication rates among the studied patients.

H. pylori stool Ag test after treatment	Group I (n = 50)		Group II (n = 50)			
	N	%	N	%	χ^2	*p*-value
Negative	46	92.0	42	84.0	0.758	0.384
Positive	4	8.0	8	16.0		

of these combinations has decreased globally[27]. Rossignol and Cavier[28] first described NTZ in 1975. Many researchers[29,30] have been convinced about the efficacy of NTZ as a single agent or in combination with other drugs in empiric pharmacologic therapy for *H. pylori* infection. This may be because of the observed wide range of activity and safety of NTZ.

NTZ reduces *H. pylori* infection through a variety of mechanisms. It interrupts the pyruvate ferredoxin oxidoreductase (PFOR) enzyme-dependent electron transfer pathway by targeting thiamine pyrophosphate (a cofactor of PFOR), thus impeding pyruvate oxidation and energy generation and resulting in the organism's death. Mutation-based drug resistance can be avoided through this mechanism. The enzyme systems nitroreductases and protein disulfide isomerases, which are crucial factors in anaerobic energy metabolism, are also disrupted by NTZ[31].

NTZ was used as a single agent therapy for *H. pylori* infection in several trials; however, the outcomes were poor. In an *in vitro* study, Yamamoto et al[32] found that NTZ is effective against MTZ-resistant strains of *H. pylori* and other anaerobes. Mégraud et al[33] reported that NTZ is a possible option for eradicating *H. pylori*, with no cross-resistance to MTZ. However, Guttner et al[20] discovered that although NTZ alone did not eradicate *H. pylori*, it may be used in conjunction with PPI to cure *H. pylori* infection.

In a multicenter randomized trial, Basu et al[34] found that a 7-10-day course of a four-drug (levofloxacin, omeprazole, NTZ, and doxycycline [LOAD]) regimen led to a significantly higher eradication rate of *H. pylori* than a standard three-drug (lansoprazole, amoxicillin, and clarithromycin) regimen (88.9-90% *vs.* 73%). Meanwhile, except for abdominal pain, which substantially less frequently occurred with the LOAD regimen, the adverse event rates were similar between the two groups.

In other investigations, NTZ was used as a combined treatment agent with a high eradication rate. Stuppy[35] investigated 11 individuals with previously failed *H. pylori* therapy and discovered that NTZ combined with sucralfate eradicated *H. pylori* in 82% of the patients. Sharma et al[36] used NTZ in individuals who had failed to respond to therapy and observed a 77.6% eradication rate.

In patients who failed a classical triple treatment (PPI, clarithromycin, and either amoxicillin or MTZ for 14 days), Abd-Elsalam et al[14] achieved an 83% *H. pylori* eradication rate with an NTZ-based regimen (NTZ, levofloxacin, omeprazole, and doxycycline for 14 days).

Shehata et al[18] found that patients treated with an NTZ-based regimen had a cure rate of 94.6% compared with 60.6% for those treated with the first-line MTZ-based regimen.

Other scholars[37] showed NTZ was effective in a two-drug regimen with a PPI or sucralfate and a three-drug regimen with a PPI and amoxicillin.

Ahmed et al[17] recently reported an *H. pylori* eradication rate of 90% with moxifloxacin-omeprazole-NTZ compared with 62.9% with standard triple therapy.

Only a few studies on NTZ-based treatment for *H. pylori* eradication in children have been published. Because chronic gastrointestinal disease in children causes feeding and nutritional issues, it is important to begin treatment as soon as possible[20]. Ramos-Soriano and Black[21] evaluated empiric treatment with NTZ twice daily for 3 days in combination with a third-generation cephalosporin (cefixime, ceftibuten, or cefdinir) and azithromycin for 7-10 days and a PPI for 30 days to treat endoscopically diagnosed *H. pylori* peptic ulcer and erosive disease in 111 pediatric patients aged 1-21 years. The cure rate was 89.2%, whereas 10% of the patients had minimal gastrointestinal adverse effects that were classified as mild to moderate. All 12 patients who had clinical failures reported mild to moderate abdominal pain, nausea, or vomiting during the trial period, and one patient also had a face rash.

The higher cure rates with NTZ-based treatments are dependent on the dose, concurrent drugs, and treatment duration. The effects of

NTZ on DNA synthesis in parasites are dose-dependent, although the specific mechanism is uncertain[34]. This shows that greater doses are more effective and have similar *H. pylori* eradication effects.

Using a PPI is preferable to reduce infection-related symptoms and adverse effects from concomitant medications and increase the possibility of *H. pylori* eradication[38]. NTZ is a new alternative drug for *H. pylori* eradication in children because it is well tolerated and synergistic with other antibiotics, especially in those with clinically suspected multidrug resistance to MTZ.

The present study was limited by the single-center design and the small number of enrolled patients. Therefore, larger multicenter investigations with a larger sample size are needed to confirm our findings.

Conclusions

The findings of this study suggest that NTZ-based triple therapy is a viable option for eradicating *H. pylori* infection in Egyptian children and adolescents. Although no statistically significant difference in cure rates was found between patients who received NTZ and those who received MTZ, children who received MTZ triple therapy had a greater failure rate than those who received NTZ triple therapy. Patients in the NTZ group had a 54% lower risk of developing a resistant illness than patients in the MTZ group.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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