

A Two-Week Nitazoxanide-Based Quadruple Treatment as a Rescue Therapy for Helicobacter Pylori Eradication

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ABSTRACT

Introduction: Helicobacter pylori is the most common prevalent chronic human bacterial infection estimated in 50% of the global population but only induces clinical diseases in 10-20% of infected individuals. These include peptic ulcers, acute and atrophic gastritis, intestinal metaplasia, gastric adeno-carcinoma and gastric B-cell lymphoma. H. pylori infection has become highly resistant to traditional first-line treatment regimens because of antibiotic resistance coupled with poor patient compliance with completing the treatment course. Many clinical studies proved that nitazoxanide (NTZ) was found to be well tolerated by humans, with an encouraging rate of eradication when it was administered with omeprazole.

Aims: The aim of the work is to compare between the efficacy of traditional triple therapy and nitazoxanide-based quadruple therapy in treatment of H. pylori and to evaluate the efficacy of nitazoxanide-based regimens as a rescue regimen for H. pylori eradication in resistant patients.

Methodology: This study was carried out on 85 Helicobacter pylori (H. pylori) infected patients; Patients were classified in to 3 groups: Group 1: 60 patients with positive H. pylori Ag taking 14 days triple therapy composed of amoxicillin (1 gm twice daily), clarithromycin (500 mg twice daily) and omeprazole (40 mg once daily).; Group 2: 25 patients with positive H. pylori Ag (naïve: not having previously taken or received a particular treatment for H. pylori) taking 14 days quadruple therapy composed of nitazoxanide (500 mg twice daily), in addition to triple therapy.; Group 3: 22 patients with positive H. pylori Ag after treatment (resistant for triple therapy from group 1) taking 14 days nitazoxanide-based quadruple therapy.

Results: This work recorded the best results for H. pylori eradication (92%) in group II who received nitazoxanide based quadruple therapy compared with group I eradication rate (63.3%), who received traditional triple therapy regimen and better results (77.3%) in group III (resistant patients from group I).

Conclusion: This study could state that, using nitazoxanide can overcome traditional triple therapy resistance; in addition to its efficacy in treating naïve patients who didn't take any medical treatment for H. pylori.

Recommendations: Nitazoxanide (NTZ) based regimen namely NTZ/ clarithromycin / PPIs and amoxicillin is a recommended H. pylori therapeutic regimen in our community.

Keywords: Helicobacter-Pylori, Nitazoxanide.

INTRODUCTION

Helicobacter pylori (H. pylori) is a small, Gram-negative spirochete inhabiting the mucous layer overlying the gastric epithelial cells in humans. It is the most common prevalent chronic human bacterial infection estimated in 50% of the global population⁽¹⁾.

H. pylori only induces clinical diseases in 10-20% of infected individuals. These include peptic ulcers, acute and atrophic gastritis, intestinal metaplasia, gastric adeno-carcinoma and gastric B-cell lymphoma⁽²⁾.

Furthermore, according to the World Health Organization, H. pylori is classified as a type 1 carcinogen and is the primary cause of peptic ulcer disease, gastric carcinoma, and mucosa-associated lymphoid tissue lymphomas (MALT)⁽³⁾.

Current H. pylori infection preferred treatment involves; proton pump inhibitor (PPI)-based triple or quadruple regimens⁽⁴⁾.

However, a study based on the Maastricht EQ guidelines, indicated that treatment with a PPI-based triple regimen as first-line therapy will fail in ~30% of patients on an intention-to-treat (ITT) basis, and will fail in ~ 50 % of patients who are treated with PPI-based triple regimen with Metronidazole⁽⁵⁾.

H. pylori infection has become highly resistant to traditional first-line treatment regimens because of emerging antibiotic resistance coupled with poor patient compliance with completing the treatment course that decrease H. pylori eradication rates. So there is a considerable interest in evaluating new antibiotic combinations and regimens⁽⁶⁾.

Nitazoxanide (NTZ) is an antibiotic with microbiological characteristics similar to those of metronidazole with nearby cost. It was settled as a therapy having a broad spectrum of activity against micro-aerobic and anaerobic bacteria, anaerobic protozoa, and helminthes⁽⁷⁾.

Many clinical in vivo and in vitro studies proved that Nitazoxanide (NTZ) was found to be well tolerated by humans, with an encouraging rate of eradication of *H. pylori* when it was administered with omeprazole⁽⁸⁾.

NTZ was used as a mono-therapy, as it was a new drug that was unlikely to be affected by the antibiotic resistance of strains in patients who had previous failed therapies. The partial success of NTZ as a single-agent therapy would be an excellent base for further studies of combination therapy⁽⁹⁾.

AIM OF THE WORK

The aim of the work is to compare between the efficacy of traditional triple therapy and nitazoxanide-based quadruple therapy in treatment of *H. pylori* and to evaluate the efficacy of nitazoxanide-based regimens as a rescue regimen for *H. pylori* eradication in resistant patients.

PATIENTS AND METHODS

This work was carried out on 115 patients with dyspeptic symptoms (patients selected within two months) who were enrolled from Tropical Medicine Department at El-Hussein and El- Sayed Galal University Hospitals.

Selection of patients in whom *H. pylori* induced GIT disease was confirmed by positive (+ve) *H. pylori* monoclonal stool antigen test and positive *H. pylori* biopsy (Giemsa stain) on upper GIT endoscopy.

Firstly the enrolled 115 patients were tested for *H. pylori* prevalence recording a high *H. pylori* prevalence rate (105/115, 91.3%).

The recorded high frequency of *H. pylori* infection in this study, with upper gastrointestinal tract related symptoms and documented gastritis could be due to the fact that El-Hussein and El- Sayed Galal University Hospitals are receiving a wide range of population with a relatively poor socioeconomic status and overcrowded conditions.

Then 20 *H. pylori* cases were excluded; 12 refused the participation, and 8 cases didn't meet the inclusion criteria (History of previous *H. pylori* treatment, pregnant women and known allergy to medication included in the study).

Eighty five *H. pylori* patients were included in the research and randomly distributed into two groups according to the received regimens of therapy for *H. pylori*.

Group I (60 patients) who received the traditional treatment regimen of amoxicillin (1gm twice daily), clarithromycin (500 mg twice daily) and omeprazole (40 mg once daily) for 14 days. A case of clarithromycin allergy appeared within the study as a dermatological rash, stopped treatment and replaced with another case.

A case of amoxicillin associated diarrhea (for 5 days) appeared within the study, stopped treatment and replaced with another case.

Group II (25 patients) who received *H. pylori* treatment regimen of nitazoxanide (500 mg twice daily), omeprazole (40mg once daily), clarithromycin (500 mg twice daily) and Amoxicillin (1gm twice daily) for 14 days.

Regarding sex and age; 48 males and 37 females were included in the study with males were slightly more than females. Sex distributions among the three studied groups were (35 males and 25 females) in group I and (13 males and 12 females) in group II.

Inclusion criteria: 1. Patients with dyspeptic symptoms undergoing upper gastrointestinal tract (GIT) endoscopy selecting HP infected patients to be recruited for the study. 2. Patients must have had *Helicobacter Pylori* infection confirmed by *H. pylori* monoclonal stool antigen.

Exclusion Criteria: 1. Active GIT bleeding. 2. Recent use of antibiotics (within 6 weeks). 3. Pregnancy and lactating women. 4. Previous treatment for HP. 5. Recent use of PPI within 2 weeks. 6. Allergy to any medication included in the study.

Initial evaluation: All the studied subjects were subjected to: Complete history taking and clinical assessment: Stressing on symptoms of upper gastrointestinal tract (GIT) disorders e.g. nausea, vomiting, epigastric pain, heart burn, eructation, fullness, dyspepsia, hematemesis or melena. Full general and abdominal examinations. 2- Laboratory evaluation: Complete blood count (CBC). Liver function tests: alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin, prothrombin time and INR. Renal function tests: S. urea and S. creatinine. 3- Stool *H. pylori* antigen: The test was done at start of study and 6 weeks after completion of therapy for both groups (1 and 2). 4- Esophagogastroduodenoscopy and biopsy was taken for histopathology for detection of *H. pylori* infection: The endoscopy was done at start of study and 6 weeks after completion of therapy for both groups (1 and 2). 5- Urea Breath Test: The test was done 6

weeks after completion of therapy for group 3 (patients in whom triple therapy failed).

Ethical Aspects:

I. Approving protocol: Current protocol was approved by Committee of Tropical Medicine Department and Committee of Faculty of Medicine at Al-Azhar University, and then by the ethical committee at Al-Azhar University.

II. Patient Consent: All patients that were included in current study signed an approved consent from Al-Azhar University Ethical Committee.

Statistical Analysis:

Data were analyzed using Statistical Program for Social Science (SPSS) version 15.0. Quantitative data were expressed as mean±standard deviation (SD). Qualitative data were expressed as frequency and percentage. Probability (P-value). P-value <0.05 was considered significant. P-value <0.001 was considered as highly significant. P-value >0.05 was considered insignificant.

RESULTS

Table (1): Main clinical data in all dyspeptic patients in the studied groups.

Mean Clinical data	Group (I) [N=60]	Group (II) [N=25]	p-value
Regurgitation	20 (33.3%)	7 (28%)	>0.05
Nausea/ vomiting	17 (28.3%)	6 (24%)	>0.05

This table shows no statistically significant difference between groups according to mean clinical data.

Table (2): Pretreatment endoscopic findings in the studied groups.

Endoscopic findings	Group (I) [N=60]	Group (II) [N=25]	p-value
Pan-gastritis	40 (66.7%)	18 (72%)	>0.05
Duodenal ulcer	12 (20%)	5 (20%)	>0.05
Gastric ulcer	8 (13.3%)	3 (12%)	>0.05

This table shows no statistically significant difference between groups according to endoscopic findings.

Table (3): Comparison between groups according to post treatment H. pylori stool antigen results.

Post treatment H. pylori stool antigen results	Group (I) [N=60]	Group (II) [N=25]	p-value
Positive	22 (36.7%)	2 (8%)	<0.008*
Negative	38 (63.3%)	23 (92%)	

*p-value <0.05 S

This table shows statistically significant difference between groups according to post treatment H. pylori stool antigen results.

Table (5): Comparison between groups according to endoscopic findings post treatment.

Endoscopic findings	Group (I) [N=60]	Group (II) [N=25]	p-value
Pan-gastritis	23 (38.3%)	3 (12%)	0.016*
Duodenal ulcer	8 (13.3%)	1 (4%)	>0.05
Gastric ulcer	3 (5%)	1 (4%)	>0.05

*p-value <0.05 S

This table shows statistically significant difference between groups according to pan-gastritis.

Table (6): Comparison between groups according to post therapeutic regimens clinical data.

Post therapeutic regimens clinical data	Group (I) [N=60]	Group (II) [N=25]	p-value
Dyspepsia	25 (41.7%)	5 (20.0%)	>0.05
Nausea/ vomiting	13 (21.7%)	2 (8.0%)	>0.05
Regurgitation	7 (11.7%)	2 (8.0%)	>0.05

This table shows no statistically significant difference between groups according to dyspepsia.

Table (7): Post treatment urea breath test results distribution in the group III.

Post treatment urea breath test results	Group (III) [22]	
	No.	%
Positive (Resistant)	5	22.7%
Negative (Cured)	17	77.3%

This table shows that the positive (22.7%) and negative (77.3%) of post treatment urea breath test results.

Table (8): Post therapeutic regimen clinical data in Group (III).

Post therapeutic regimen clinical data	Group (III) [22]	
	No.	%
Dyspepsia	6	27.3%
Nausea/ vomiting	3	13.6%
Regurgitation	3	13.6%

This table shows that the dyspepsia (27.3%), nausea/vomiting (13.6%) and regurgitation (13.6%) of post therapeutic regimen clinical data.

Table (9): Comparison between groups according to (Results).

	Group (I) [N=60]	Group (II) [N=25]	Group (III) [22]	p-value
Positive (Resistant)	22 (36.7%)	2 (8%)	5 (22.7%)	0.022*
Negative (Cured)	38 (63.3%)	23 (92%)	17 (77.3%)	

*p-value <0.05 S

This table shows statistically significant difference between groups according to ((RESULTS)), while group II and III non-significant.

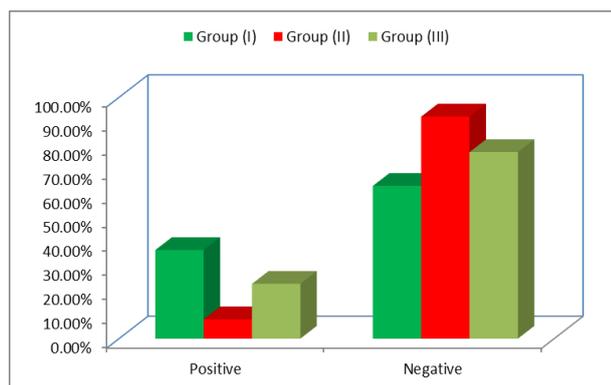


Fig (1): Bar chart between groups according to ((Results)).

DISCUSSION

Helicobacter pylori is one of the most common, medically prominent infection worldwide and one of the major causative factor of peptic ulcer disease. So, eradication of *H. pylori* is effective in healing ulcers and reducing the ulcer recurrence, eliminating the need for maintenance therapy⁽¹⁰⁾.

Besides being a major etiological factor in peptic ulcer disease, there is some evidence that it may also be associated with other gastric diseases, and also was listed as a class 1 carcinogen⁽¹¹⁾.

H. pylori is not easy to eradicate. Factors such as the bacterial resistance and difficulty achieving bactericidal concentrations in the gastric mucosa contribute to the variable response to antibiotic therapy. As a result, triple and quadruple pharmacotherapy regimens are now used to ensure high eradication rates⁽¹²⁾.

Epidemiological studies have indicated that the incidence of new infections in developing countries is 3 to 10 percent of the population per year. Overcrowding, poor sanitation, and low economic standards are the risk factors for *H. pylori* infection, which is inversely correlated with the socioeconomic status⁽¹³⁾.

There are several methods available to detect *H. pylori* infection including invasive methods based on gastric biopsies and non-invasive methods like serology, urea breath tests (UBTs), and stool antigen tests. Stool antigen tests, which have been used in this study, have recently been welcomed with great expectations as they are convenient to the patients and can be easily performed even in small laboratories with a reported high accuracy⁽¹⁴⁾.

H. pylori eradication reduces the lifetime risk of peptic ulcer disease and possibly of gastric cancer. Patients with active gastric or duodenal

ulcers or a documented history of ulcer should be tested for *H. pylori* infection and treated if found to be infected. First-degree relatives of those with a gastric cancer history should also be tested and treated if positive. Testing for and treatment of *H. pylori* infection are recommended for low-grade gastric MALT lymphoma and following resection of early gastric cancer⁽¹⁵⁾.

The wide spread and sometimes indiscriminate use of antibiotics in developing countries has resulted in a higher prevalence of *H. pylori* treatment failure depending on antimicrobial resistance⁽¹⁶⁾.

Nitazoxanide, is a cheap compound with a spectrum of activity similar to that of metronidazole but without the problem of resistance⁽¹⁷⁾.

In this study, we tried to determine the prevalence of *H. pylori* as well as comparing between the current and new nitazoxanide (NTZ) - based therapeutic regimens for *Helicobacter pylori* (*H. pylori*) infection to overcome the problem of resistance with the current regimens.

On history taken from the studied groups, the reported suspected injurious agents for their GIT disorders were out door fast food, smoking, non-steroidal anti-inflammatory drugs (NSAIDS) and caffeine with percentages of (30%, 25%, 21.7%, 15%) in group I and (24%, 8%, 24% & 12%) in group II without statistically significant difference between the studied groups.

These reported suspected injurious agents for the studied patients' disorders are agreed with *Laine et al.* and *Begovic and Selmani*^(18,19).

The patients' endoscopic appearance was pan-gastritis, duodenal ulcers and gastric ulcers with a percentage of (66.7%, 20% & 13.3%) in group I and (72%, 20% & 12%) in group II, *H. pylori* infection almost always causes chronic active gastritis.

Helicobacter pylori eradication results as evaluated by *H. pylori* monoclonal stool antigen, 6 weeks post therapeutic regimens reported that eradication rate was 63.3% (38 patients) in group I and 92% (23 patients) in group II with statistically significant difference between the studied groups.

We tried in this study to introduce nitazoxanide as an anti-microbial drug to overcome *H. pylori* resistance to the currently used anti-microbial agents.

So the 22 resistant cases of group **I** were included in group **III** and received nitazoxanide based quadruple therapy composed of nitazoxanide (500 mg twice daily), omeprazole (40 mg once daily), clarithromycin (500 mg twice daily) and Amoxicillin (1 gm twice daily) for 14 days.

Helicobacter pylori eradication results in group **III** as evaluated by urea breath test, 6 weeks post therapeutic regimens reported that eradication rate was **77.3%** (17 patients).

Regarding post treatment complaints in group **III**; (27.3%) of patients remained having dyspepsia, (13.6%) had Nausea/vomiting and (13.6%) had regurgitation.

So this work recorded the best results for *H. pylori* eradication (92%) in group **II** who received **nitazoxanide based quadruple therapy** compared with group **I** eradication rate (63.3%), who received **traditional triple therapy regimen** and better results (77.3%) in group **III** (resistant patients from group **I**).

Group I who received clarithromycin, omeprazole and amoxicillin **regimen** achieved the least eradication rate (**63.3%**) with a lot of residual complaints.

These results agreed with *Yakoob et al.* ⁽²⁰⁾ who reported that patients were treated with omeprazole (40 mg daily), clarithromycin (CLR) (500 mg) and amoxicillin (AMX) (1g twice a day) for 14 days. A 14 C-urea breath test (14 C-UBT) was repeated four weeks after completion of treatment to confirm eradication. Triple therapy failure was seen in 30/92 (33%) patients. The resistance rates were: CLR 33% (30/92 and AMX 2% (2/92).

Also agreed with *Kobtan et al.* ⁽²¹⁾ who reported that A 370 patients infected with *H. pylori* received the standard triple therapy (PPI twice daily, 500 mg clarithromycin twice daily and either 1 g amoxicillin or 500 mg metronidazole twice daily for 2 weeks). Eradication was successful in only 223 patients (60.27%) raising questions if *H. pylori* is still responding to standard triple therapy.

The present results also agreed with *Malfratherner et al.* ⁽²²⁾ who stated that in areas of low clarithromycin resistance, including the United States, a 14-day course of "triple therapy" with an oral proton pump inhibitor, clarithromycin 500 mg, and amoxicillin 1 g (or, if penicillin allergic, metronidazole 500 mg), all given twice daily for 14

days, is still recommended for first-line therapy. This regimen only achieves rates of eradication in up to 70% of cases.

The present results are disagreed with the study reported by *Higuchi et al.* ⁽²³⁾ who stated that *H. pylori* eradication rates were 80% (116/145 patient) who received the high-dose group (omeprazole 40 mg/day + amoxicillin 2 gm/day + clarithromycin 800 mg/day).

Group II who received nitazoxanide, clarithromycin, omeprazole and amoxicillin **regimen** achieved the best eradication rate (**92%**) with a minimal residual complaints.

These results agreed with *Shehata et al.* ⁽²⁴⁾ who reported that the response to treatment of nitazoxanide was significantly higher than traditional treatment regimen. One hundred and six cases (94.6%) of 112 patients who completed the study showed complete cure, while only 63 cases (60.6%) of 104 patients (received triple therapy) showed the same response.

H. pylori infection has become highly resistant to the traditional first-line treatment regimens because of emerging antibiotic resistance coupled with poor patient compliance with completing the treatment course that decrease *H. pylori* eradication rates. So there is a considerable interest in evaluating new antibiotic combinations and regimens.

CONCLUSION

This study could state that, using nitazoxanide can overcome traditional triple therapy resistance; in addition to its efficacy in treating naïve patients who didn't take any medical treatment.

RECOMMENDATIONS

Improving the standard of living, socioeconomic status, environmental sanitation and personal hygiene are important for elimination and personal *H. pylori* infection.

H. pylori eradication should be confirmed to accelerate the healing and prevent relapse in PUD as well as GIT malignancies; as *H. pylori* is classified as a class 1 carcinogen by IARC and WHO.

Nitazoxanide (NTZ) based regimen namely NTZ/ Clarithromycin / PPIs and Amoxicillin is a recommended *H. pylori* therapeutic regimen in our community.

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