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A 2-week Nitazoxanide-based quadruple treatment as a rescue therapy for *Helicobacter pylori* eradication

A single center experience

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Abstract

As there are increasing reports of fluoroquinolone resistance on use as a first- or second-line treatment for *Helicobacter pylori* (*H pylori*), we aimed at evaluation of the efficacy and safety of nitazoxanide-based regimen as a rescue regimen in Egyptian patients whose previous traditional treatment for *H pylori* infection failed.In total, 100 patients from the outpatient clinic of the Tropical medicine department, Tanta University hospital in whom the standard triple therapy (clarithromycin-based triple therapy) failed were enrolled in the study. Nitazoxanide (500 mg bid), levofloxacin (500 mg once daily), omeprazole (40 mg bid), and doxycyclin (100 mg twice daily) were prescribed for 14 days. Eradication was confirmed by stool antigen for *H pylori* 6 weeks after the end of treatment. Among the patients enrolled in the study, 44% of patients were men and the mean age for the participants in the study was 46.41 ± 8.05, 13% of patients were smokers, and 4% of patients had a previous history of upper gastro-intestinal bleeding. A total of 94 patients (94%) completed the study with excellent compliance. Only 1 patient (1%) discontinued treatment due to intolerable side effects and 5 patients (5%) did not achieve good compliance or were lost during follow up. However, 83 patients had successful eradication of *H pylori* with total eradication rates 83% (95 % CI 75.7–90.3%) and 88.30% (95 % CI 81.8–94.8%) according to an intention-to-treat and per-protocol analysis, respectively. Adverse events were reported in 21% of patients: abdominal pain (6%), nausea (9%) and constipation (12%), (2%) headache, and (1%) dizziness. A 2-week nitazoxanide-based regimen is an effective and safe rescue therapy in Egyptian patients whose previous standard triple therapy has failed.

Abbreviations: CI = confidence interval, GI = gastrointestinal, H pylori = Helicobacter pylori, ITT = intention-to-treat, n = number, PFOR = pyruvate-ferredoxin oxidoreductase, PP = per protocol, PPI = proton pump inhibitors.

Keywords: helicobacter, nitazoxanide, rescue therapy

1. Introduction

Helicobacter pylori (*H pylori*) is an organism that has been recognized as a major cause of gastritis and is associated with duodenal ulcer disease, gastric ulcer disease, gastric lymphoma, and gastric cancer in humans.[1,2] Therefore, it is of the utmost importance to eradicate the pathogen to reduce *H pylori*-related complications.[3]

The worldwide increasing resistance of *H pylori* towards different antibiotics may affect therapeutic management in different countries.[4] This will necessitate trials on new antibiotic combinations.

There is growing rates of treatment failure with observed marked decline in the eradication rates of triple therapy over the past few decades.[5]

Escalating percentages of people who are infected with *H pylori* strains resistant to standard antibiotic therapy necessitated adding another groups or searching for substitutes as the bismuth colloid containing quadruple regimen.[6–8]

So, there is considerable interest in evaluating new rescue regimens with high eradication rates >85%. This is an important target of prevailing research.[9,10]

The quadruple regimen comprising of proton pump inhibitor, tetracycline, metronidazole, and bismuth is the most commonly used as alternative therapy when failure occurs[3] but despite being cheap and with a success rate of 70%,[11] it has a lot of limitations as lack of compliance of the patients who refuse taking a lot of pills with repeated doses every day in addition to other adverse events. So, recent researches are performed targeting other substitutes.[12,13]

So, guidelines recommend a salvage triple therapy using levofloxacin 500 mg once daily together with PPI and amoxicillin 1 g twice daily.[12] Yet, recently the efficacy of levofloxacin-based

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second-line therapy seems to be decreasing due to an increasing levofloxacin resistance.[14] A study by Mégraud et al 2013 on >2000 European patients with *H pylori* infection showed resistance rates of 14.1% for levofloxacin, 17.5% for clarithromycin, and 34.9% for metronidazole.[15] A recent study by Liou et al 2016 has found that efficacy of levofloxacin triple therapy has fallen below 80% in the second-line treatment of *H pylori*. In Taiwan,[16] Liang et al 2014 reported that the 7-day levofloxacin-containing triple therapy provides an unacceptable per-protocol report card as the second-line treatment for anti-*H pylori* eradication in Taiwan and recommended modification by either extending the duration to 10 to 14 days or seeking other regimens.[17]

In the hopes of addressing some of these issues, we conducted this study using a second-line regimen with the addition of a fourth component and with an extended duration. We evaluated a nitazoxanide-based quadruple rescue therapy, composed of nitazoxanide (500 mg bid), levofloxacin (500 mg once daily), omeprazole (40 mg bid), and doxycyclin (100 mg twice daily) prescribed for 14 days in an attempt to improve the eradication rate and relatively decrease the number of pills and the frequent side effects.

Nitazoxanide is a first-line choice for the treatment of illness caused by *Cryptosporidium parvum* or *Giardia lamblia*.[18] Moreover, nitazoxanide (NTZ) is an antibiotic with microbiological characteristics similar to those of metronidazole, of comparable cost, and no discernible resistance.[19] The use of a traditional triple therapy for *H pylori* achieves an eradication rate below 80%. This rate has been surpassed by a 7 days course using 500 mg of levofloxacin once daily, 500 mg nitazoxanide twice daily, 100 mg doxycycline twice daily, plus 40 mg esomeprazole twice daily, with a 90% cure rate.[20]

Nitazoxanide, a nitrothiazole benzamide compound notable for its activity in treating both intestinal protozoa and helminthic infections, with a low range adverse effects, is believed to interfere with the pyruvate-ferredoxin oxidoreductase (PFOR) enzyme-dependent electron transfer reaction, which is essential to anaerobic energy metabolism.[21,22]

Broad spectrum of activity against microaerobic and anaerobic bacteria, anaerobic protozoa, and helminths supports the selection of nitazoxanide.[23]

An in vitro study carried out on nitazoxanide proved its potent anti-*H pylori* effect against metronidazole resistant strains.[24]

Nitazoxanide was included in a multidrug treatment regimen for pediatric *H pylori* infection, where patients were exposed to nitazoxanide for 3 days plus azithromycin, and cefixime for 7 to 10 days, plus a proton pump inhibitor for 30 days, with a success rate of 89.2%.[25]

The antibacterial mechanism of levofloxacin is attributed to its effect on bacterial DNA gyrase.[26] Levofloxacin has been tried as a rescue therapy in many trials.[27] However, there is much concern about levofloxacin increasing resistance especially in areas where this drug is commonly prescribed.[8]

Doxycycline exerts its bacteriostatic action through inhibition of protein synthesis.[28] The little to no resistance rate for doxycycline favors its inclusion in our study.[29]

So, the aim of this study was to evaluate the efficacy and safety of this nitazoxanide-based regimen as a rescue regimen in Egyptian patients whose previous traditional treatment for *H pylori* infection failed, as until now there are no actual similar reported trials in Egypt.

2. Methods

2.1. Study design and settings

This open-label trial started with patients complaining of dyspepsia and attending the outpatient clinics of the Tropical Medicine department, Tanta University hospital between January 2014 and December 2014. Those found to be positive for *H pylori* infection were given first-line standard triple regimens (PPI twice daily, 500 mg clarithromycin twice daily and either 1 g amoxicillin or 500 mg metronidazole twice daily for 2 weeks). Patients failing the first-line standard regimen were then enrolled in the study.

Our study was approved by the ethical committee of faculty of medicine, Tanta University. The research team recruited potential participants and explained to each patient the aim of the research, and side effects of the treatment. A written consent was obtained from all participants in the study. A 100 patients aged 18–65, attending the outpatient clinic of the Tropical medicine department, Tanta University Hospital, in whom the standard triple therapy failed, were enrolled in the study.

Patients suffering from major illnesses such as liver cirrhosis, renal impairment, and gastrointestinal malignancies were excluded from the study. Pregnant and lactating women were not entered into the study. Patients with contraindication or allergy to any of the drugs included in our study were excluded as well as those taking PPI and antibiotics during the 6 weeks prior to entry in the trial.

Nitazoxanide (Nitclean, Western pharmaceuticals, Egypt) 500 mg bid, levofloxacin (Venaxan, Sedico pharmaceuticals, Egypt) 500 mg once daily, omeprazole (Pepzole, Hikma pharmaceuticals, Egypt) 40 mg bid and doxycycline (Doxymycin, Nile pharmaceuticals, Egypt) 100 mg twice daily were prescribed for 14 days.

Patients' telephone numbers were taken and 6 weeks after completion of therapy, they were called and testing for *H pylori* infection was performed using a stool *H pylori* antigen. The test used was ImmunoCard STAT! HpSA.

Compliance was determined through asking the patients and recovery of empty medication envelopes.

2.2. Outcomes

The rate of eradication of the *H pylori* infection confirmed by a negative stool *H pylori* antigen test was considered the primary outcome of the study. Patient compliance and incidence of side effects were the secondary outcomes recorded at the end of the study.

2.3. Statistical analysis

The *H pylori* eradication rates were evaluated by intention-to-treat (ITT) and per protocol (PP) analyses. Per-protocol analysis was defined as the patients who completed the whole treatment course and received *H pylori* follow-up. The demographic characteristics, the eradication rates, and presence of side effects to treatment were calculated by the chi-square test.

The ClinicalTrials.gov registration identifier is NCT: NCT02621359.

3. Results

A 370 patients infected with *H pylori* received the standard triple therapy. Eradication was successful in only 223 patients

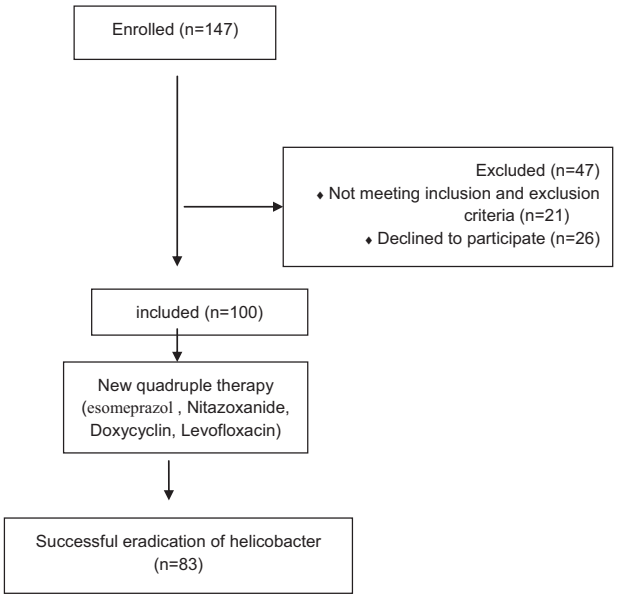

Figure 1. Flow diagram of quadruple therapy.

(60.27%) raising questions if *H pylori* is still responding to standard triple therapy. Then eradication-failure patients (147 patients) were invited and assessed for participation in the study. However, 47 patients were excluded from the study (21 were not meeting inclusion and exclusion criteria and 26 declined or refused to participate in the study). Finally, a total of 100 patients with persistent *H pylori* infection were enrolled in this study (the flow diagram of the study is shown in Fig. 1).

Among the patients enrolled in the study, 44 patients (44%) were men. The mean age for the participants in the study was 46.41 ± 8.05. 13 patients were smokers. Four patients had a previous history of upper gastro-intestinal (GI) bleeding. The initial eradication regimen was PPI, clarithromycin and amoxicillin in 42 patients, and PPI, clarithromycin, and metronidazole in 58 patients. The baseline demographic data of the participants is shown in Table 1.

3.1. Helicobacter pylori eradication rates with quadruple therapy

Ninety-six patients (94%) completed the study with excellent compliance. Only 1 (1%) patient discontinued treatment due to intolerable side effects (severe nausea and diarrhea), 2 (2%) did not achieve good compliance, and 3 (3%) were lost during follow up. Successful eradication of *H pylori* was achieved in 83 patients (83%).

H pylori eradication rates were 83% (95 % CI 75.7–90.3%) and 88.30% (95 % CI 81.8–94.8%) according to an intention-to-treat and per-protocol analysis, respectively.

Table 1

Baseline demographic data of the participants.

Age	46 ± 8
Sex	56 (56%) females, 44 (44%) males
Smoking	13 (13%) smokers
Previous upper GI bleeding	4 (4%) with previous upper GI bleeding
Initial eradication regimen	42 (42%) PPI, clarithromycin, amoxicillin
	58 (58%) PPI, clarithromycin, metronidazole

3.2. Compliance and adverse effects

The regimen was well tolerated by all the patients enrolled in the study. Mild side effects were reported in 21 patients (21%); 6 patients (6%) had abdominal pain, 9 (9%) had nausea, 12 (12%) had constipation, 2 (2%) had headache, and 1 (1%) complained of dizziness.

4. Discussion

Several "rescue" therapies have been recommended, but they still fail to eradicate *H pylori* in >20% of the cases.[30]

Failure of 2 following treatment courses containing clarithromycin and metronidazole is indicative of a single or double resistance of the *H pylori* organism, and the use of bismuth salts in treatment regimens is hindered by its worldwide lack of availability. These factors render a great challenge to current management of first-line eradication failures.[31]

Our study was conducted in hope of treating patients who failed to eradicate *H pylori* infection following clarithromycin-based triple therapy.

Guidelines recommend a salvage triple therapy using levofloxacin 500 mg once daily together with PPI and amoxicillin 1 gram twice daily.[12] Yet, recently the efficacy of levofloxacin-based second-line therapy seems to be decreasing due to an increasing levofloxacin resistance.[32]

Levofloxacin is an antibiotic that is commonly used to treat different types of infections. Its use as a single agent in patients with *H pylori* is unexpected to clear the infection and may exert pressure on the organism resulting in the development of fluoroquinolone-resistant strains.

Previous administration of fluoroquinolone use and the number of courses taken in the last 10 years has been associated with the presence of Levofloxacin-resistant strains.[33]

Therefore, in our study, a new nitazoxanide-based regimen including nitazoxanide (500 mg bid), levofloxacin (500 mg once daily), omeprazole (40 mg bid), and doxycyclin (100 mg twice daily) was prescribed for 14 days as a rescue regimen in Egyptian patients whose previous traditional treatment for *H pylori* infection had failed. In total, 83 patients had successful eradication of *H pylori*, with total eradication rates 83% (95 % CI 75.7–90.3%) and 88.30% (95 % CI 81.8–94.8%) according to an intention-to-treat and per-protocol analysis, respectively.

Molina-Infante et al 2015 also found that high-dose acid suppression and 14-day duration of treatment can improve eradication rates by up to 10%.[33]

These results are parallel to those of the study by Basu et al[20] on treatment naive *H pylori*-infected patients, where they compared the efficacy of LOAD (levofloxacin, 250 mg once daily); omeprazole, 40 mg once daily; nitazoxanide 500 mg twice daily with meals; doxycycline, 100 mg once daily) for 7 or 10 days to LAC (lansoprazole 30 mg; amoxicillin 1 g twice daily; clarithromycin 500 mg, twice daily for 10 days.

The eradication rate of LOAD 10 and 7 reported in the Basu et al 2011 study (90% and 89.4%) seems to be higher than the eradication rate achieved in our study (83%) despite using higher doses of levofloxacin 500 mg once daily and doxycycline 100 twice daily and longer treatment duration (14 days) in our study. This difference may be attributed to the difference of sample size and that their study was conducted on naive patients with diminished probability of bacterial resistance. On the other hand, the increasing rate of fluoroquinolone resistance may explain the lower eradication rate detected in our study.[33]

Regarding the safety of this regimen, adverse events were reported in 21% of patients: abdominal pain (6%), nausea (9%) and constipation (12%), (2%) headache, and (1%) dizziness.

In the study by Basu et al, the adverse events were limited in 8 patients of LOAD 7 and 10 and were in the form of gastro intestinal distress (n = 6), dizziness (n = 1), and palpitation (n = 1).[20]

The higher doses of levofloxacin and doxycyclin and longer treatment duration may explain the more evident adverse effects in our patients. This fact makes adjusting the doses and duration of consideration in future trials.

However, this new nitazoxanide-based regimen improves the eradication rate and relatively decreases the number of pills and the frequent side effects with bismuth-based regimen.

Our study has some limitations. This was a single center study of a tertiary care setting, raising the question of generalizability. Also, larger studies on larger groups of patients are needed to confirm the results. Testing of levofloxacin resistance may be taken in consideration in future studies to decrease the failure rate.

5. Conclusion

A 2-week nitazoxanide-based regimen is an effective and safe rescue therapy in Egyptian patients whose previous standard triple therapy for *H pylori* infection has failed.

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