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INCREASING RATES OF TREATMENT FAILURES WITH THE STANDARD TRIPLE THERAPY FOR HELICOBACTER PYLORI: A UNIQUE AND ALTERNATIVE TREATMENT OPTION IS URGENT

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Keywords:

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Abstract

Background: The triple treatment including Proton pump inhibitor (PPI) - clarithromycin and amoxicillin or metronidazole was proposed 30 years ago at the first Maastricht conference to treat helicobacter pylori (H. pylori) infection and since that time, it has become the universal and standard treatment for helicobacter pylori. However, the efficacy of this triple regimen has been seriously challenged, and they are gradually becoming ineffective.

Aim: to assess the response of patients with H. pylori to the standard triple therapy in Nile delta.

Patients and Methods: Patients who visited the outpatient clinics in tropical medicine department Tanta university hospital between January 2012 and June 2015 complaining of dyspepsia were tested for H. Pylori and H. pylori infected patients received first-line eradication therapies with standard triple regimens (PPI twice/day, 500 mg of clarithromycin twice/day and 1 g of amoxicillin twice/day or 500 mg metronidazole twice/day for two weeks). 6 weeks after completion of therapy, eradication of H. pylori infection was assessed using stool helicobacter pylori antigen.

Results: one thousand and ninety patients infected with helicobacter pylori received the standard triple therapy. Eradication rates were 59.36% and 62.03% according to an intention-to-treat and per-protocol analysis, respectively raising questions if H. Pylori is still responding to standard triple therapy.

Conclusions: There is growing rates of treatment failure with standard triple therapy. The efficacy of standard eradication therapies is expected to further decrease in the next years. So, development of unique and alternative treatment regimens with high eradication rates is urgent.

Introduction

Helicobacter pylori (H. pylori) represents one of the most common and medically prominent infection worldwide **[1]**.

Epidemiological studies in Egypt revealed that H. pylori infection was more common in men of rural origin, low socio-economic standard, low educational levels and crowded places **[2]**. The prevalence in Egypt is about 50% in children ≤ 3 years and 90% in adults **[3]**.

Infection with H - pylori is a an important factor in the development of three important upper gastro-intestinal diseases: duodenal or gastric ulcers (reported to develop in 1 to 10% of infected patients), gastric cancer (in 0.1 to 3%), and gastric mucosa-associated lymphoid-tissue (MALT) lymphoma (in <0.01%) and the risk of these disease outcomes in infected patients varies widely among populations **[4]**.

According to current guidelines, standard triple therapy containing a proton pump inhibitor (PPI) and two antibiotics; amoxicillin and clarithromycin or metronidazole, is still the preferred first-line regimen for treatment of

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H. pylori infection. However, the efficacy of this triple therapy has been seriously challenged, and they are gradually becoming ineffective **[5]**.

Growing rates of treatment failure are observed worldwide and the eradication rate of triple therapy has declined over the past few decades. Helicobacter pylori infection has become increasingly 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]**.

Antibiotic resistance is the major cause of treatment failure **[7]**. The prevalence of antimicrobial resistance in H. pylori shows regional variation both within and between countries.

Due to the rising prevalence of antimicrobial resistance, mainly to clarithromycin, efficacy of standard triple therapies has declined to unacceptably low levels in most parts of the world This treatment resistance is also an issue warranting the investigation of other agents **[8]**.

The aim of the study was to assess the response of patients with H. pylori to the standard triple therapy in Nile delta.

Patients and methods

The study was carried out on patients who visited the outpatient clinics of tropical medicine in Tanta university hospital between January 2012 and January 2015 complaining of dyspepsia. Test for helicobacter pylori infection was done for these patients and H. pylori infected patients received the standard triple therapy (PPI twice daily, 500 mg of clarithromycin twice daily and 1 g of amoxicillin twice daily or 500 mg metronidazole twice daily for two weeks).

Patients with previous gastric or duodenal operations or malignancy were excluded from the study. Also patients with active GIT bleeding and pregnant women were excluded from the study. Patients with previous treatment for helicobacter pylori infection or with recent use of antacids, PPI or antibiotics were also excluded from the study. Finally, patients with allergy to any medications in the study were excluded from the study.

The duration of the study was 36 months. The study was approved by Ethical Committee of the Faculty of Medicine, Tanta University. A written consent was taken from all participants in this research. A code number for each patient was used, and kept in a special file to maintain Patients' privacy during the research.

Follow up of the patients at the end of therapy was done and compliance was assessed through asking the patients and recovery of empty packs. Patients' telephone numbers were taken and 6 weeks after completion of therapy, they were called and eradication of H. pylori infection was assessed using a stool helicobacter pylori antigen.

Outcomes: The primary outcome measured was the total eradication rate for helicobacter pylori (h. pylori) infection as assessed by the stool helicobacter pylori antigen. Successful eradication of H. pylori was confirmed by a negative result 6 weeks after the end of treatment.

Statistical analysis: The H. pylori eradication rates were evaluated by intention-to-treat (ITT) and per-protocol (PP) analyses. Per-protocal analysis was defined as analysis of 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.

Results

The study included one thousand, two hundred and forty nine patients who visited the outpatient clinics in tropical medicine department Tanta university hospital between January 2012 and June 2015 complaining of dyspepsia. Those patients were tested for H. Pylori. 159 patients were excluded from the study (134 were not meeting inclusion

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and exclusion criteria and 25 declined or refused to participate in the study). One thousand and ninety patients were enrolled in the study and received the standard triple therapy.

Our patients had average age 46.13 ± 9.53. 567 (52.02%) of our patients were men. 187 (17.16%) of patients enrolled in the study were smokers. 47 (4.31%) patients had previous history of upper gastro-intestinal (GI) bleeding.

Eradication rates with standard triple therapy: One thousand and forty three six patients (96.05 %) of patients completed the study. Twelve patients did not complete treatment due to side effects of treatment (severe diarrhea in three patients, severe nausea and vomiting in four patients ,epigastric pain in two patients, urticaria and skin rash in three patients) while nineteen patients did not achieve good compliance and sixteen patients were lost during follow up.

647 patients achieved successful eradication as proved by stool helicobacter pylori antigen 6 weeks after completion of triple therapy. H.pylori eradication rates were 59.36% and 62.03% according to an intention-to-treat and per-protocol analysis, respectively.

Side effects of treatment: side effects were reported in 46 (4.22%) of patients and they were mild in most patients as 12 patients had abdominal pain, 11 patients had nausea, 7 patients had constipation, 5 patients had urticaria or skin rash. 4 patients had vomiting, 4 patients had headache, 3 patients had diarrhea and 3 patients had dizziness.

Discussion

Helicobacter pylori (H. pylori) represents a medically prominent infection worldwide **[1]**. The commonly used first-line treatment regimen for Helicobacter pylori (H. pylori) eradication for many years in the world is the standard triple therapy, in the form of a proton pump inhibitor, plus amoxicillin and clarithromycin **[9]**.

Effective antimicrobial therapy for Helicobacter pylori infection should achieve cure rates greater than 90%-95%, which are no longer met by Standard triple therapy in most settings worldwide **[5]**.

In a trial to estimate the response of patients with H. pylori to the standard triple therapy in Nile delta our study was designed. Of the one thousand and ninety who completed the study, 647 patients achieved successful eradication as proved by stool helicobacter pylori antigen 6 weeks after completion of triple therapy. H.pylori eradication rates were 59.36% and 62.03% according to an intention-to-treat and per-protocol analysis, respectively. Side effects were reported in 46 (4.22%) of patients.

The eradication rate obtained from the study is lower than expected which trigger thinking of possible explanation with drug resistance may be one of the most powerful reasons. Especially, among patients in Nile delta where multiple uncontrolled misuse of antibiotic intake is observed, which is also a common problem in many developing countries. Similar results were demonstrated in a study was carried out in Uruguay in a duration of 14 years divided into five years groups The overall eradication rate was 66.6% in 548 patients of 823 with ascending decrease of eradication rates through years **[10]**.

The increasing rate of bacterial resistance is supported by an in vitro Italian study where Resistance towards at least one antibiotic was detected in 111 (76.6%) isolated, and multiple antibiotic resistance in 35.2% of cases. Primary resistance towards clarithromycin, metronidazole, and levofloxacin was detected in 51 (35.2%), 86 (59.3%), and in 32 isolated (22.1%), respectively **[11]**.

Another in vitro study in Vietnam observed high incidence of resistance to clarithromycin (33%) and mitronidazole (69.9%) and suggests that standard triple therapies may not be useful as first-line treatment **[12]**.

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The low eradication rate which was noticed in our study open the way to try new strategies for therapy and enrolment of more numbers of patients with associated in vitro microbial studies to detect anti microbial resistance may clearly through the light on the problem in Nile Delta.

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