Helicobacter Pylori Treatment Eradication in Egypt: Standard Clarithromycin-based Triple versus Quadruple Regimen Therapy

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Background and study aim: Absence of adequate treatment for Helicobacter pylori (H. pylori) infection leads to prolonged life time colonization which is responsible for complications. Antibiotics resistance is the main cause of eradication failure in H. pylori infection, thus our study aimed to evaluate the efficiency and tolerability of standard triple therapy vs. quadruple regimen therapy in H. pylori eradication in Egypt.

Subjects and Methods: Our study enrolled 140 patients (65 males,75 females) who attending to Gastroenterology clinic in Internal medicine & Tropical medicine departments, Zagazig University Hospitals from (June 2018 - June 2019), aged from 20 - 60 years, complained of recurrent non-specific dyspepsia and epigastric pain & proved to be positive for H. pylori stool antigen test. The patients distributed into two groups: group (1), 70 patients given Clarithromycin triple therapy [Clarithromycin 500 mg + Amoxicillin 1gm + Pantoprazole 40 mg, each twice daily]. Group (2), 70 patients given quadruple therapy [Levofloxacin 500 mg once daily + Nitazoxanide 500mg (twice daily)+ Doxycycline 100 mg (twice daily)+ Pantoprazole 40 mg (twice daily)] for 14 days.

Results: H. pylori eradication rate was statistically significant higher in patients who received quadruple therapy compared to those who received Clarithromycin-based triple therapy (85.7% vs. 67.1 % & P = 0.001 respectively).While, statistically insignificant regarding the treatment side effects in both groups (11.4 % vs. 14.3 %, P= 0.33 respectively).

Conclusion: Quadruple therapy is preferable to Clarithromycin-contained triple therapy in tolerability and eradication of H. pylori in Egypt.

INTRODUCTION

H. pylori is a gram negative bacilli in which infection is obtained during early adulthood, and transmitted to relatives but with lack of treatment early, it will build up prolonged life time colonization that is responsible for varieties of gastrointestinal disorders [**1-2**]. The severity of clinical symptoms related to H. pylori infection is associated to several virulence factors such as Vac A, Cag A, Ure A, Dup A, and etc. Vac A is a virulent gene that induce virulent factor leading to vaculation of the host cells [**3**]. The virulence factor causes induction of apoptosis through a certain specialized protein that causes depolarization of the cell membrane, disturbance in mitochondrial function, and suppression of T cell function [**3**].

Cag A gene encodes a high immunogenic protein that has been used to identify H. pylori. Cag A destructs the intracellular constituents of gastric epithelium via release of pro-inflammatory cytokines [4]. Attachment of H. pylori to the gastric epithelium facilitates persistence of infection, initiates colonization, release of virulence factors and the organism has the ability to protect itself from mucus , acidic PH , and peeling [**5-6**].

H. pylori is the most common infectious human pathogen, infecting more than half of populations worldwide & is responsible for varieties of upper GI symptoms including dyspepsia, gastritis, and even gastric cancer [**7**]. Gastric cancer is the fifth most common

cancer worldwide particularly in Asia [**8-9**], & the third most common cause of cancer-related mortality, because the preliminary diagnosis is usually at an advanced stage[**10**]. H. pylori infection is definitely carcinogenic, and the risk of gastric cancer development for an infected individual is approximately1-2 %[**11**].

The role of H. pylori infection in the pathogenesis of iron deficiency anemia is already validated and more than 60 % of the patients showed complete recovery from anemia after treatment eradication, and those patients who suffering ITP showed normalizing platelet count only after successful H. pylori eradication [**12**,**13**]. The risk of acute coronary artery disease has increased with H. pylori infection, because H. pylori can initiate a persistent chronic inflammatory process inside the gastric epithelium and can also cause systemic inflammatory impacts [**14-15**].

Stool antigen test (SAT) is more proper than Urea breath test (UBT) for mass analyses. It may provide more accurate results in detecting H. pylori infection when compared with serological tests, that are typically utilized for screening[**16**]. Both UBT as well as SAT are recommended by guidelines to assess the efficacy of eradication therapy one month after the treatment end[**17**].

Eradication of H. pylori infection is challenging, and the resistance to antibiotics is the major cause of eradication failure. Regardless of various examinations, the ideal therapeutic regimen has not yet been defined [**18**]. The clarithromycin-based triple therapy is still suggested in zones with low occurrence of clarithromycin resistance and in patients without history of macrolides experience [**19**]. Concomitant therapy includes clarithromycin-based triple therapy plus metronidazole 500mg for 14 days, anyway the frail point in this routine, it loses efficiency in the sight of resistant H. pylori strains to both clarithromycin and metronidazole [**20**].

A second line treatments including levofloxacin-based triple therapy (PPI 40mg (twice daily) + levofloxacin 500 mg (once daily) + amoxicillin 1 g (twice daily) for 2 weeks is recommended by guidelines [**21**]. However, the efficacy of levofloxacin-based second-line therapy seems to be reducing due to growing levofloxacin resistance [**22**]. Nitazoxanide is (NTZ) is similar to metronidazole, in price, and no recognizable resistance [**23**], however, it has a potent anti-H pylori effect against metronidazole resistant strains [**24**]. The aim of this study is to assess the efficacy and tolerability of the standard Clarithromycin-contained triple therapy versus Quadruple regimen therapy in H. pylori infection eradication in Egypt.

SUBJECTS AND METHODS

Study design

Our study was cross-section comparative study designated on patients who attending to Gastroenterology clinic in Internal medicine &Tropical medicine departments, Zagazig University Hospitals during the period from June 2018 to June 2019. Those patients were complaining of recurrent non-specific dyspeptic symptoms and epigastric pain. The study included 140 patients out of 200 patients were examined and found to be positive for stool antigen test for H. pylori infection. We excluded 60 patients before initiation of the study because of their non-compliance and they had recent history of medications for H. pylori eradication. The inclusion criteria composed of patients' ages ranged from 20-60 years old who did not previously receive any treatment regimen for H. pylori infection, no history of ulcer related dyspepsia, or past history of peptic ulcer disease. Meanwhile, the exclusion criteria composed of pregnant or lactating women, history of previous allergic reaction to antibiotics and/or PPIs, any contraindication to treatment drugs, advanced chronic liver disease or renal disease, history of gastro-intestinal bleeding and finally, no history of receiving antibiotics or PPIs within the preceding last month.

All included patients subjected to full clinical examination, full blood count, liver & kidney function tests, abdominal ultrasound, and proved to be positive for stool antigen test . The study protocol has gained an approval by the institution's board of Medicine, Zagazig University Hospitals, and all participants had assigned a written permission. The treatment regimen was explained in details with benefits and probable side effects before initiation of the study to all participants. Also, phone numbers were taken for follow up. They were distributed into 2 groups. Group (1) composed of 70 patients were given Clarithromycin-contained triple therapy in the form of (Clarithromycin 500 mg twice daily, Amoxicillin 1gm twice daily, Pantoprazole 40 mg twice daily for 2 weeks).

Group (2) included 70 patients were given Quadruple therapy in the form of (Levofloxacin 500 mg once daily, Nitazoxanide 500mg twice daily, Doxycycline 100 mg twice daily, Pantoprazole 40 mg twice daily for 2 weeks).

During treatment; follow up of the patients to study their compliance to treatment and the probable side effects of the medications, that may include abdominal distension, abdominal pain, unpleasant taste, constipation, dizziness, epigastric pain, lethargy, halitosis, headache, diarrhea, lack of appetite, nausea, vomiting, oral ulcer, & skin eruption. The response to treatment was evaluated 4 weeks after cessation of therapy. Instructions were given to patients not to receive any antibiotics or PPI for four weeks before retesting there stool for H. pylori antigen.

Method

Stool antigen test retested for all included patients 4 weeks after cessation of therapy by using rapid test cassette for qualitative detection of H. pylori antigen in human stool samples giving results within 10 minutes. It is a rapid chromatographic immunoassay, in which the membrane is pre-coated with anti-H. pylori antibodies on the test line region during testing the specimen. This blend migrates upward on the membrane by capillary action to react with anti-H. pylori antibodies on the membrane and created a colored line. The presence of this colored line in the test region indicates a positive result, while its absence indicates a negative result. To serve as a procedural control, a colored line will always appear in the control line region indicating that proper volume of the specimens has been used and membrane wicking has happened. Invalid result means that the colored line fails to appear. Comparison will be done between both groups to assess the efficacy and tolerability of both regimens.

Statistical analysis

Data collected throughout history, basic clinical examination, laboratory investigations and outcome measures coded, entered and analyzed using Microsoft Excel software. Data were then imported into statistical package for the social sciences (SPSS version 20.0) software for analysis. According to the type of data, qualitative data represented as number and percentage, & quantitative data represented by mean ± SD , the following tests were used to test differences for significance. Differences that are associated of qualitative variable by Chi square ($\chi 2$) test. Differences between quantitative independent groups by t-test. P-values less than 0.05 were considered as statistically significant. P value >0.05 insignificant, P<0.05 significant, P<0.01 highly significant.

RESULTS

The study was enrolled 140 patients that were distributed into 2 groups. Our findings showed no significant difference detected between Clarithromycin-contained triple therapy and Quadruple regimen group regarding age, sex and also laboratory investigations (Table 1, 2).The side effects for the treatment were 8 cases (11.4%) in Quadruple group while 10 cases (14.3%) in Clarithromycin group (Table 3).The response to treatment (Table 4),the Quadruple group vs. Clarithromycin group was (85.7% vs. 67.1%, highly significant P <0.01).

Table (1): Distribution of the patients regarding age and sex (n=140).

parameter	Triple therapy Group (70)	Quadruple therapy Group (70)	t	P value
Age (years) (Mean ± SD)	43.01 ± 10.9	44 ± 13.21	1.85	0.06*
Male %	35 (50 %)	30 (42.8%)		
Female %	35 (50%)	40 (57.2%)		0.39*

SD: Standard deviation P: Probability value *: non-significant (P > 0.05)

Table (2): Laboratory investigations of the studied patients (n=140).

parameter	Triple therapy Group (70) Mean ± SD	Quadruple therapy Group (70) Mean ± SD	P value
HB (gm/dl)	12.6 ± 1.67	12.83 ± 1.56	0.4 *
WBCs mm^3	7.81 ± 1.21	7.57 ± 1.87	0.36 *
Platelet mm^3	234 ± 60.3	235.8 ± 69.02	0.87*
ALT u/l	32.1 ± 5.0	33.2 ± 3.5	0.13 *
AST u/l	36.8 ± 4.0	36.2 ± 3.2	0.33 *
Bl. Urea (mg/dl)	24.9 ± 4.4	26.3 ± 5.5	0.09 *
S. Cr. (mg/dl)	0.99 ± 0.03	0.98 ± 0.03	0.08 *

HB : hemoglobin WBCs : white blood cells ALT : alanine aminotransferase
AST : Aspartate aminotransferase Bl. urea : blood urea S. Cr : serum creatinine
*: non-significant (P > 0.05).

Table (3): Side effects of treatment of the two studied groups.(n=140).

		Triple therapy Gr (70)	Quad. therapy Gr(n=70)	Total n=140	χ2	P value
Abdominal pain N (%)		1 1.4%	1 1.4%	2 1.4%	0.25	0.61 *
Taste disturbance N(%)		2 2.8%	1 1.4%	3 2.1%		
Bloating N(%)		1 1.4%	2 2.8%	3 2.1%		
Diarrhea N(%)		3 4.2%	1 1.4%	4 2.8%		
Nausea N(%)		3 4.2%	3 4.2%	6 4.2%		
Total SE	**yes**	10 (14.3%)	8 (11.4%)	18 (12.9%)		
	No	60(85.7%)	62(88.6%)	122 (87.1%)		
Total N (%)		70 100%	70 100%	140 100%		

SE: side effect χ2: Chi square (χ2) test *: non-significant(P > 0.05).

Table (4): Response to treatment of H. pylori infection in both regimens.

Parameter		Triple	Quadruple	Total	χ2	P value
Negative result (treatment success)	N	47	60	107	6.7	0.009***
	%	67.1%	85.7%	76.4%		
Postive result (treatment failure)	N	23	10	33		
	%	32.9%	14.3%	23.6%		
Total N (%)	N	70	70	140		
	%	100%	100%	100%		

χ2: Chi square (χ2) test. ***: highly significant(p<0.01)

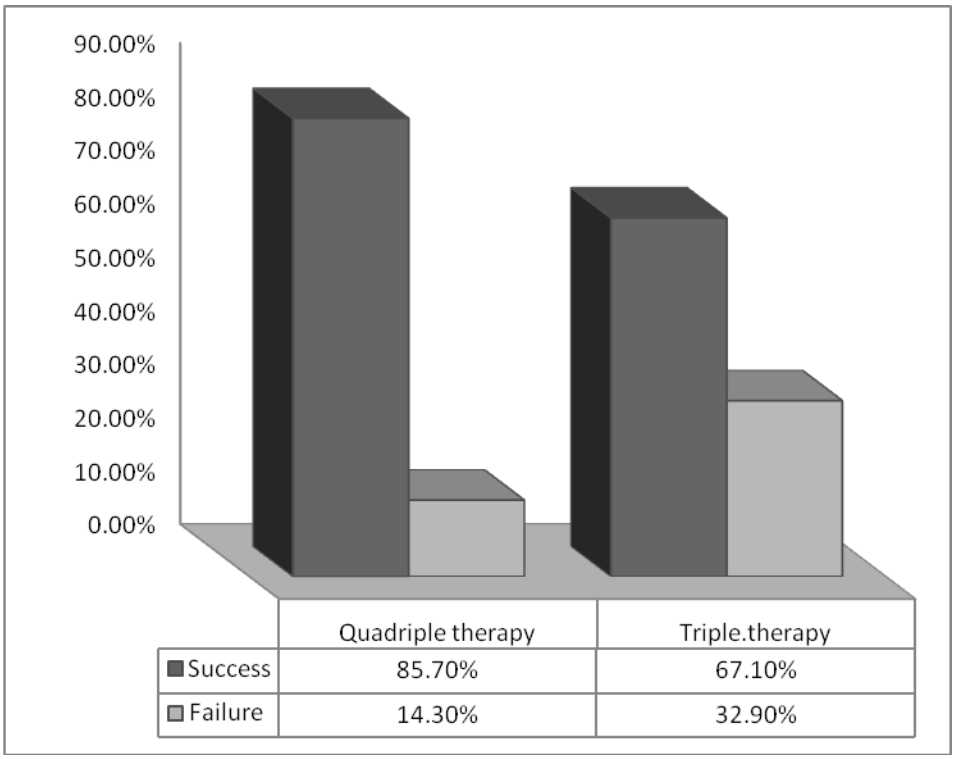

Figure (1): Response to quadruple versus triple based regimen therapy.

DISCUSSION

H. pylori is a definite carcinogenic pathogen that affects the gastric mucosal layer and the epithelial lining of the stomach, & build up a prolonged colonization in the stomach mostly during childhood [**25,26**]. Approximately 90 % of infection remains subclinical and can persist all life if not treated, while 10 % of infected individuals develop obvious clinical disease [**27**].

The resistant strains and non-compliance of patients are the main causes of treatment failure in obliteration of H. pylori infection [**28,29**]. The higher prevalence of H. pylori was in developing than in developed countries [**25,29**]. Egypt is considered one of the highest prevalence areas for H. pylori infection and higher resistance to antibiotics owing to the abuse of antibiotics. The prevalence in Egypt was 90 % in adults while 60-90% in middle east as reported by the World Gastroenterology Organization (WGO) [**30**].

Regarding the age and sex, there was no significant statistical differences between two groups clarithromycin - based triple therapy and quadruple therapy (43.01 ± 10.9 vs.44 ± 13.21, P= 0.06 respectively) as shown in (Table 1). Also, the study showed that relative mild degree of anemia as hemoglobin in both groups triple and quadruple was (12.6 ± 1.6 vs.12.8 ± 1.5,P=0.4 respectively) **,** however, the statistical analysis was insignificant (P> 0.05).

The overall adverse effects in all enrolled patients were 12.9%. The patients on quadruple regimen therapy exhibited lower adverse effects (11.4%) compared to patients on clarithromycin-based triple therapy (14.3%) however, no statistical significant difference between both group (11.4% vs 14.3%,P= 0.61). The recorded adverse events included taste disturbance, diarrhea, nausea, abdominal pain and distension in tiny percentages. The quadruple regimen therapy showed lower incidence in taste disturbance**,** abdominal pain**,** and diarrhea compared to clarithromycin-based triple therapy. There are many studies are consistent with our findings [**31,32,33**].

Our study showed the quadruple regimen was generally well-tolerated with mild transient adverse events like taste disturbance, despite four medications included in this regimen. Also, it has been noticed that no patients had discontinued the treatment or was lost to follow up.

Eradication of H. pylori was found to be significantly higher in patients who received quadruple regimen when compared to those who received the standard clarithromycin-based triple

regimen in (85.7% vs. 67.1% , P=0.009).These differences indicate that quadruple therapy is more effective than clarithromycin-based triple therapy in eradication of H. pylori infection. Comparable results have been reported in study by Gopal et al. and another study by Cheng H et al. who compared the standard clarithromycin triple therapy to levofloxacin-contained triple therapy with eradication rates lower than our results [**34,35**].

Our results are similar to those obtained by a study of Basu et al. who reported in a randomized study of 270 patients conducted in United States, underwent to quadruple therapy that contained levofloxacin 250mg once daily, omeprazole 40 mg once daily, nitazoxanide 500 mg twice daily and doxycycline 100 mg once daily given for 7 or 10 days, produced high eradication rates of 90% when compared with 73% with 10 days course of lansoperazole, amoxicillin, and clarithromycin regardless of the duration of therapy [**36**].

In spite of using higher concentrations of levofloxacin 500mg once daily , doxycycline 100 mg twice daily , lanzoprazol 40 mg twice daily and the same dose with nitazoxanide 500mg twice daily and with longer period in treatment (14 days) in our study to ensure adequate eradication, The eradication rate of quadruple-based therapy 7 or 10 days that reported in the study by Basu et al. (90% vs.73%) was higher when compared with eradication rate that obtained in our findings (85.7% vs. 67.1%). The decrement in our results may be explained by the reduction in number of included patients and progressing bacterial resistant strains in our locality even with levofloxacin [**36**]. The higher rates of H. pylori antibiotic resistance in recent years could be explained by the frequent antibiotics usage [**37**]. A study done in Egypt by Elrazky et al. [**38**] detected a high incidence of H. pylori resistant strains to clarithromycin (71%), whereas resistance patterns were less towards levofloxacin (23.2%).

In the present study, quadruple-based therapy containing levofloxacin, NTZ and doxycycline surpassed standard clarithromycin-based triple therapy regarding efficacy (85.7% vs. 67.1% P= 0.009) however, with equal tolerability (mild transient side effects).Regarding relative higher cost of levofloxacin-contained quadruple regimen, this issue may partly affect in the decision to select this regimen and may prevent the use of levofloxacin-contained quadruple regimen as the primary line of empiric treatment for H. pylori eradication. To our knowledge, bismuth-based regimen is not available in Egypt. So, we had to experience another regimen to fulfill the same purpose, improve the eradication rate and produce little side effects.

CONCLUSION

Quadruple-based therapy is preferable to clarithromycin-contained triple therapy in H. pylori infection eradication particularly in countries like Egypt with great clarithromycin resistance. This is at least until we can get the bismuth in our country. Recently, the increasing concepts about levofloxacin resistance and decreasing efficacy as a second line treatment directed us towards thinking in levofloxacin-contained quadruple therapy including doxycycline and NTZ as alternative line of regimen therapy for better H. pylori eradication in our country . Further studies are needed on larger scale of patients, and culture and sensitivity tests are frequently required to evaluate the resistant emergent bacteria. Although culture and sensitivity might not be carried out, the detection of mutations by molecular methods provides an alternative way in which we can relay in the future.

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Conflict of interest: The authors declared that there are no conflict of interest.

Ethical approval: The work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. Ethical approval from the ethical committee for Medical Research in the Faculty of Medicine, Zagazig University was obtained prior the study.

A written informed consent was taken from all participants after explaining details and benefits before sharing in the study.

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Authors' contributions:

SAA, NGE & SSA collected patients' samples and clinical data from outpatient clinic of Internal medicine & Tropical medicine departments, Zagazig University Hospitals , Zagazig, Egypt and prepared sample for laboratory investigations. All laboratory assessment was supervised by RHE in Medical Microbiology & Immunology Department , Zagazig University Hospitals , Zagazig, Egypt. Statistical analysis, interpretation of data, and writing the manuscript was done by SAA, and NGE. Critical revision of the manuscript was performed by all of the authors. All authors have read and approved the final manuscript.

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