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RESPONSE TO FIRST- LINE QUADRUPLE AND SECOND – LINE QUADRUPLE *H PYLORI* ERADICATION THERAPY IN IRAQI PATIENTS WITH PEPTIC ULCER DISEASE

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ABSTRACT

Because the high prevalence and serious health burden of *H. pylori* infection, it is crucial to use a highly effective and well tolerated eradication regimen. The overall prevalence is high in developing countries and lower in developed countries and within areas of different countries. This prospective study involved newly diagnosed patients aged 15-70 years with peptic ulcer (DU or GU) confirmed by endoscopy and positive for *H. pylori* by (histological examination, stool antigen test and antibody test). Thirty patients received first line quadruple therapy (triple capsule (Pylera)®; with esomeprazole 20 mg) for 10 days, and 20 patients who failed for previously treatment with triple therapy were treated with second- line quadruple therapy for 10 days. The higher incidence *of H. pylori* positive was in male gender. Approximately 26% had family history of peptic ulcer disease. The per protocol analysis revealed 90% eradication rates in patients treated with first- line quadruple therapy, and 85% with second- line quadruple therapy. Better *H. pylori* eradication rates were in younger adult patients < 50 years after both first- line and second- line regimen, and was significantly less successful in women compared to men after both regimen. According to the data obtained from Iraqi population we can conclude that second- line *H. pylori* eradication quadruple therapy is as effective as first- line quadruple therapy that can be used as a rescue therapy after failure of triple *H. pylori* regimen.

KEYWORDS: *H. pylori*, Peptic Ulcer Disease, Gastric Ulceration, Duodenal Ulceration, Per-protocol intention to treat, Quadruple *H. pylori* regimen, Three-in-one capsules (pylera)®

1. INTRODUCTION

H. pylori infection is untill now one of the world's most recurrent infections and accounts for high risk of morbidity and mortality.[1]

The prevalence of *H pylori* infection worldwide is more than 50%. The overall incidence is high in developing countries and lower level in developed countries, and within areas of different countries.[2]

In peptic ulcer disease and gastric cancer, about 20% of subjects infected with the bacterium will develop complications of the *H. pylori* infection [3] , and because the high prevalence and serious health burden of such infection, it is necessary to use a highly effective and well tolerated eradication regimen.[2]

Several studies showed a higher rate of eradication with quadruple therapy.[4]In the ACG (American college of gastroenterology) guidelines, quadruple therapy is recommended as an alternate first-line treatment option for the management of H. pylori. H_2-receptor antagonist (H2RA) could be substituted for the proton pump inhibitor (PPI), however, PPIs are considered to be more efficacious at suppressing acid production.[4]

Recently, the Maastricht IV consensus recommends for first-line empirical treatment of *H. pylori* infection a combination of a PPI, clarithromycin, and amoxicillin or metronidazole for 7–14 days in areas with low clarithromycin resistance, and a combination of a PPI, bismuth, metronidazole, and tetracycline for 10–14 days in areas with high clarithromycin resistance.[5] The Maastricht III consensus has accepted a bismuth-based quadruple regimen as an alternative first-line therapy, and has been used as the second-line therapy after triple (PPI-clarithromycin-amoxicillin) therapy failure, to be the recommended 'rescue' regimen. This regimen achieved a better eradication rate compared to the PPI-based triple regimen as a first-line eradication for *H. pylori*.[6]

Upon examination of the components of the regimen, resistance to bismuth and tetracycline is rare, but repeated or recent metronidazole use increases the potential for metronidazole resistance.[7]Unlike clarithromycin, resistance to metronidazole can be overcome by using higher doses of metronidazole, treatment for a longer duration of time (i.e.14 days), or using

a PPI in the regimen.[8] A combination capsule (Pylera) ® containing bismuth subcitrate 140mg,metronidazole 125mg, and tetracycline 125mg has been approved by the FDA.

2. PATIENTS AND METHODS

2.1 Patients

This prospective randomized controlled study involved newly diagnosed patients with peptic ulcer disease (PUD). Patients were selected by a senior physician while undergoing esophageal gastroduodenoscopy (OGD) in the endoscopy unit of the hospital as well as in private clinic. Ethical clearance to conduct the research was sought and obtained from the patients. Data were collected through direct interview with the patient with the following inclusion criteria.

Patients aged 15-70 years, patients with peptic ulcer (DU or GU) confirmed by endoscopy and positive for *H. pylori* by (histological examination, stool antigen test and antibody test). The exclusion criteria includes :smokers, alcoholics, NSAID users, gastric cancer, severe gastro esophageal reflux disease, history of gastric operation, lactating or pregnant women, drug history over the past month which mimic those used in the present study, and patients allergic to the study medications.

A total of 50 patients (27 male and 23 female), age range between 15 and 70 years were chosen. Eleven patients were presented with gastric ulcer and 39 patients were suffering from duodenal ulcer.

Patients were divided randomly into two groups. Group I includes 30 patients received first line quadruple therapy for 10 days. Group II include 20 patients treated with second- line quadruple therapy for 10 days. The latter group of patients was failed for previously treatment with triple therapy.

Patient's compliance was evaluated at the end of the treatment by counting the number of pills used from the packet, and was considered acceptable if more than 90% of the medication had been taken.

2.2 Methods

The endoscopic examination was performed to verify the diagnosis of peptic ulcer disease; distinguish between the gastric ulcer and duodenal ulcer and to take a biopsy from the ulcer. All participants were confirmed for *H. Pylori* positive infection by histological examination

of the biopsy, stool antigen test, and anti-*H. pylori* IgG antibody test. Patients were considered to be *H. pylori* infected if all the three tests were positive.

2.3 Sample collection

2.3.1 Biopsy samples

Two gastric antral biopsy specimens were taken from every patient. Biopsy specimen was fixed in 10% formal buffer saline for histological diagnosis, embedded in paraffin sectioned on glass slides. Paraffin sections were stained with Hematoxylin and Eosin and modified Giemsa to examine the presence/absence of curved rod shaped *H. pylori* on the mucosal surface.[9] Sections were reviewed by two experienced histopathologists who were blinded to the endoscopic findings. The pathologist characterized the presence of spiral bacteria in the superficial mucous layer or along the luminal surface of the gastric epithelial cells as a positive test.

2.3.2 Stool sample

Stool are collected from each patient after endoscopy using sterile plastic covered cup and examined for the presence of *H. pylori* antigen.

Stool samples were collected from each patient before and after treatment. The stool antigen test was performed based on the principle of *H. pylori* Antigen Test Device (feces) [10], manufactured by ABON Biopharm (Hangzhou), China. The test utilizes antibodies specific for *H.pylori* antigen to selectively detect *H. pylori* antigen in human feces specimens.

2.3.3 Blood samples

Blood samples were drawn from all patient groups. Three milliliters of venous blood was drawn from the patients using 5mls syringe. Patients serum or plasma were screened for the presence of *H. pylori* IgG antibodies. Blood samples were collected immediately after endoscopy, then *H. pylori* test performed based on the principle of *H. pylori* Antibody rapid test device (Serum/Plasma) [11], manufactured by ABON Biopharm (Hangzhou), China.

2.4 Study therapeutic regimen

A 10-day quadruple regimen, three-in-onecapsules were taken four-times daily (after mealsand at bedtime), and swallowed whole with 250 mL of water. And esomeprazole capsule was taken with (pylera)® capsules before morning andevening meals.

Three-in-one capsules (pylera)® containing 140 mg bismuth sub citrate potassium, 125 mg metronidazole, and 125 mg tetracycline hydrochloride (Aptalispharma, Canada).

The clinical outcome for *H. pylori* eradication was confirmed with negative stool antigen test 8 weeks after completion of anti *H. pylori* therapy [12], while a treatment failure was considered ata positive stool antigen (non-eradicated *H. pylori*patients). The incidence of adverse effects associated with different *H. pylori* eradication therapy has been evaluated as well.

2.5 Statistical Analysis

Data were analyzed by using SAS 2012 (Statistical Analysis System).[13] Chi-square test was used to compare between demographic variables and disease characteristics. Analysis of *H. pylori* eradication efficacy was performed on an "intention-to-treat" basis (included all eligible patients enrolled into the study) and on a "per-protocol" basis (excluded patients with poor compliance of therapy, and patients with unavailable data after therapy or patients loss due to adverse effects). A *p* value of less than 0.05 was considered statistically significant.

3. RESULT AND DISCUSSION

Helicobacter pylori (*H. pylori*) infection is a worldwide problem with a significant morbidity and mortality.[14,15] Since the discovery of *H. pylori*, several studies have been conducted to select therapeutic regimen. This study is another attempt in this respect considering Iraqi patients (though at a smaller scale).

3.1 Demographic data and disease characteristic

In the present study, the mean age of PUD patients was matched in both study groups (37.9, 33.07) years respectively, which was similar to that reported by Masjedizadeh*et al* (36.26) years.[16] Or it could be older (43-50) years.[17,18]

The male: female ratio for *H. pylori* positive patients was also matched for both study groups. The higher incidence was in male gender of approximately 1.14:1 (16 males and 14 females) and 1.22:1(11 males and 9 females), respectively. This finding was close to that of Hajiani*et al*. where male gender showed only a marginal predominance.[19] Another study by Yasir *et al*. in 2014 showed predominance of male gender over female in *H. Pylori* positive patients.[20] This may be due to a significant higher infection rates in men than in women and the literatures regarding the relationship between both sex and *H. pylori* infection is

conflicting. It is possible that women are more likely to have infection eradicated with antimicrobials that used for other gynecological illnesses.[21]

Studies showed that the majority of infections occur within families through close person-to-person contact.[22] Therefore, *H. pylori* infection in individuals with a family history have high risk of developing gastro duodenal diseases.[23] In this study approximately 26% of *H. pylori* positive patients had family history of peptic ulcer disease. This finding was close to that of Shokrzadeh *et al.*, who reported that family history of peptic ulcer disease about 24% in *H. pylori* positive patients.[23]

Peptic ulcer patients presented in this study were suffering predominantly of epigastric pain (83.3% vs75 %), heart burn (76.6 %vs 70%), vomiting (43.3.% vs 55%) for both groups respectively. Epigastric pain is the major compliance of PUD patients[17,20,24], and considered as the most frequent symptoms in (70.3%) of patients, followed by heart burn (50.2%) and vomiting (14.8%).[23] Demographic data and disease characteristic of the present study were shown in table (1).

3.2 H pylori eradication rate of first- line quadruple versus second- line quadruple regimens

In the present study, the per protocol analysis revealed 90% eradication rates in patients treated with first- line quadruple therapy using triple capsule (Pylera)®; with PPI (esomeprazole 20 mg) for 10 days(table 2), which was comparable to (88–93%) eradication rates in previous studies when used the same three-in-one capsule with 20 mg omeprazole twice daily for 10 days.[25,26,27] Saleem *et al*. reported that when given the triple capsule with omeprazole, achieved eradication rates between (84%-97%), and it is the same for clarithromycin- and metronidazole-resistant strains.[28] Additionally, the present study is consistent with a pilot study revealed a 97.7% eradication rare effectiveness for bismuth quadruple therapy.[29]

As a general rule, the therapeutic regimens that have a per-protocol eradication rate ≥ 90% for *H. pylori* infection gives the optimum therapeutic outcome.[30] And many studies reported a success rate of > 90% for bismuth-containing quadruple therapy in different parts of the world [31- 34], but, up to our knowledge, this is the first one in Iraq.

As first-line quadruple therapy, the higher eradication rate (90%) of the present study was in agreement with many other studies which evaluate the bismuth-containing *H. pylori* eradication regimen[35-38], and has been considered a highly efficacious, gold standard regimen.[39,40] Especially when PPI-bismuth based quadruple therapy in the new regimen was used.[41, 42] This novel combination reduce complexity and improving compliance with a good efficacy and can be a candidate for a second-line *H. Pylori* eradication therapy, as stated by the (Maastricht IV consensus).[43]The combination capsule gives a chance to standardize the doses of antimicrobial drugs contrary to what occurs when the drugs are administered separately.[44]

The presence of bismuth compounds in this combination has a mucosal cytoprotective and ulcer healing effects, in addition, bismuth has some complex actions on *H. pylori*, such as the inhibition of ATP, inhibition of protein synthesis, and membrane function . *In vivo*, they can suppress *H. pylori* when used alone.[45] However, their combination with two antibiotics significantly increases their efficacy on *H. pylori* and may overcome antibiotic-resistance *in vivo* and *in vitro*.[35,46,47,48]It has a short-term effect and acts topically; and appears to be more like an antiseptic.[49] In the scope of *H. pylori* eradication, the doses of bismuth currently included in this combination was lower than previously administered leading to blood levels lower than 50 mg/l which is the threshold for potential bismuth toxicity.[50]

Quadruple *H. pylori* therapy is devised for a 10-day duration.[51,52] Extending the duration from 10 to 14 days would not increase the therapeutic efficacy. One randomized controlled trial compared 10 days versus14 days BMT(bismuth,metronidazole,tetracycline) therapy did not find any significant difference in respect to treatment duration.[53]

Bismuth-based quadruple therapy according to the Maastricht IV consensus recommendation is administered as a second-line[43] when *H. pylori* eradication failed with triple therapy.[54-57] Quadruple therapy using a single capsule preparation meets the proposed criteria for a second line treatment.[58] The treatment is not affected by clarithromycin resistance[59], also metronidazole resistance *in vitro* does not affect the outcome of quadruple therapy significantly.[60] Patient compliance with this regimen is high as in the present study. The regimen is effective in most parts of the world [61] Despite the number of pills taken per day and some adverse effect of the combination, the compliance was satisfactory.[62]

In this study, eradication rates with second- line quadruple therapy in patients failed the first-line triple regimens was 85%, which was similar results to that conducted in France, where a 10 days of omeprazole and quadruple (Pylera)® therapy achieved 84% *H. pylori* eradication when given as a second- line in patients who had failed at last 3 prior triple eradication therapies and had proven that *H. pylori* strains were resistant to clarithromycin, and metronidazole.[63] Also a 10 day bismuth-based quadruple therapy as a second -line choice produce a per protocol *H. pylori* eradication rates of 85.7% [64] And the very recent study in 2014, per protocol *H. pylori* eradication rates was (94.7% - 95.0%), after failure of one or more previous courses of standard triple therapeutic regimen.[65]

Collectively, many studies found that quadruple rescue therapy for patients failing first-line *H. pylori* eradication treatment was a standard second-line therapy for *H. pylori* infection and achieving an eradication rate of about 80%-90.8%.[66-69]

3.3 H pylori eradication rate of first- versus second- line quadruple regimens according to patient's age and gender

According to the results in table 3, the *H. pylori* eradication rates were better in younger adult patients < 50 years of age after treating with both first- line and second- line *H. pylori* eradication regimen. These results were agreement with recent studies.[70,71] and that the eradication failure occur in older age.[72] The possible explanation for treatment failure in elderly patients may be due to bad patient compliance due to poly pharmacy, which is frequently observed in elderly patients, *H. pylori* resistance to antibiotics [73, 74], or concomitant use of NSAIDs.[74]

H. pylori eradication therapy was significantly less successful in women compared to men after treating with both first- line and second- line *H. pylori* eradication regimen (table 4). There is no clear explanation to this result, but there may be gender variation in acid secretion and gastric blood flow that influence the success of treatment.[75] A very high resistance rates towards metronidazole have been reported, particularly in developing countries among female patients [76], which may be more likely due to the prior treatment with metronidazole for gynecological diseases.[77]

Table (1) Demographic data and disease characteristics

Variables	GI (n=30) n(%)	GII (n=20) n(%)	*P* value
Age (years)	37.9	33.07	0.254 NS
Gender Male Female	 16(53.3%) 14(46.7%)	 11(55%) 9 (45%)	0.185 NS
Type of ulcer Gu Du	 8(26.7%) 22(73.3%)	 3(15%) 17(85%)	0.002 **
Positive family history	10(33.3%)	3(15%)	0.014 **
Duration of symptoms <1 yr. 1-5 yr. ≥ 5yr.	 2(6.7%) 21(70%) 7(23.3%)	 3(15%) 12(60%) 5 (25%)	0.009 **
Presentation Epigastric pain Vomiting Heart burn Melena Hematemesis	 25(83.3%) 13(43.3%) 23(76.6%) 8(26.6%) 2(6.66%)	 15(75%) 11(55%) 14(70%) 5(25%) 2(10%)	0.0048 **

GI, first line quadruple regimen (pylera), GII, second line quadruple regimen(pylera)
Data presented as number (n) and percentage (%)
*Pearson Chi-Square p < 0.05 is significant , NS non significant results

Table (2) *H pylori* eradication rate of first- line quadruple versus second- line quadruple regimens

Eradication rate	GI (n=30) n(%)	GII (n=20) n(%)	*P* value
Intention to treat (ITT)	27/31(87%)	17/21(80.9%)	0.174 NS
Per protocol (PP)	27/30(90%)	17/20(85%)	0.369 NS
Compliance	30/31(96.7%)	20/21(95.2%)	0.882 NS
Adverse events	29/30(96.6%)	18/20(90%)	0.107 NS

GI, first line quadruple regimen (pylera), GII, second line quadruple regimen(pylera)
Data presented as number (n) and percentage (%)
NS =non significant results

Table (3) *H pylori* eradication rate of quadruple regimen (first –line versus second line) according to the patient's age

Age range	Patients Number	First line eradication efficacy		Patients Number	Second line eradication efficacy		Chi-Square(χ^2)
		Number	%		Number	%	
<20	3	3	(100%)	1	1	(100%)	0.00 NS
20-30	7	7	(100%)	4	4	(100%)	0.00 NS
30-40	8	8	(100%)	5	5	(100%)	0.00 NS
40-50	5	5	(100%)	3	3	(100%)	0.00 NS

50-60	**5**	**3 (60%)**	**4**	**3 (75%)**	**5.241 ***
≥60	**2**	**1 (50%)**	**3**	**1 (33.3%)**	**6.095 ****
Chi-Square(χ^2)	**---**	**9.752 ****	**---**	**12.861 ****	**---**

GI, first line quadruple regimen (pylera), GII, second line quadruple regimen(pylera)

Data presented as number (n) and percentage (%)

*Pearson Chi-Square $p < 0.05$ is significant, NS non significant results

Table (4) *H pylori* eradication rate of quadruple regimen (first –line versus second line) according to the patient's gender

Patient's gender	**Patients Number**	**First line eradication efficacy**		**Patients Number**	**Second line eradication efficacy**		**Chi-Square(χ^2)**
		Number	**%**		**Number**	**%**	
Male	**16**	**15**	**(93.7%)**	**11**	**11**	**(100%)**	**2.187 NS**
Female	**14**	**12**	**(85.7%)**	**9**	**6**	**(66.6%)**	**7.449 ****
Chi- Square(χ^2)	**---**	**4.297 ***		**---**	**9.361 ****		**---**

GI, first line quadruple regimen (pylera), GII, second line quadruple regimen(pylera)

Data presented as number (n) and percentage (%)

*Pearson Chi-Square $p < 0.05$ is significant, NS non significant results

4. CONCLUSION

According to the data obtained from Iraqi population we can conclude that a 10 days second-line *H. pylori* eradication quadruple therapy showed a similar eradication rate efficacy as in first- line quadruple therapy that can be used as a rescue therapy after failure of triple regimen. And the response rate was higher in men compared to women gender, especially in age < 50 years.

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