Triple and Quadruple Eradication Therapy for *H. pylori* in Iraqi Patients with Peptic Ulcer Disease a Comparative Study

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Authors’ contributions

This work was carried out in collaboration between all authors. Author YMKAH designed the study, wrote the protocol. Author ZAGMA wrote the first draft of the manuscript and managed the literature searches and analyses of the study. Author AAN together with author ZAGMA the experimental process, selection of the patients, treatment and follow-up. All authors read and approved the final manuscript.

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**ABSTRACT**

The eradication of *H. pylori* has become an important issue; since *Helicobacter pylori* infection can cause chronic gastritis, peptic ulcer, gastric cancer and (MALT) lymphoma. Standard triple therapy efficacy has decreased gradually worldwide during the last decade and quadruple therapy is recommended as an alternate treatment option for the management of *H. pylori*. The aim of this
1. INTRODUCTION

Peptic ulcer is a disruption of the mucosal integrity of stomach and/or duodenum leading to a local defect or excavation due to active inflammation [1]. Studies have confirmed a strong association between gastric antral infection with *H. pylori* and peptic ulceration [2].

During the late 1800s the prominent form was gastric ulcers (GUs) in young women.Duodenal ulcers (DUs) were rare until about 1900 and then became a prevalent condition during the first half of the 20th century.

Warren and Marshall [3]; showed that there was a relationship between *H. pylori* and peptic ulcer disease (PUD). In 2005, they were awarded the Nobel Prize in physiology or medicine for their work on *H. pylori* and PUD [4].

*H. pylori* is spiral-shaped, flagellated, Gram-negative bacillus [5]. It is microaerophilic bacterium i.e. it requires oxygen but at lower levels than those contained in the atmosphere [6]. It colonizes in the mucosa of stomach at which it has an important etiologic role in gastric diseases [7], such as chronic gastritis, peptic ulceration (90% of DU and 70% of GU) in addition to gastric cancer and it is a major cause of morbidity in infected patients) [8,9].

*H. pylori* are highly adapted to the gastric environment where it survives within or beneath the gastric mucous layer. The bacterium renders the underlying gastric mucosa more exposed to acid peptic damage by disrupting the mucous layer, liberating enzymes and toxins, and adhering to the gastric epithelium [10,11]. Several invasive (e.g. culture, histology, rapid urease testing) and noninvasive (e.g. the 13C-urea or 14C urea breath test (UBT), antibody detection, fecal antigen testing) methods are used to diagnose ulcers and detect *H. pylori* infection [12].

Regarding the treatment of PUD; triple therapy which consists of PPI (standard dose), amoxicillin (1 g), and clarithromycin (500 mg) twice daily for 7-14 d; is recommended as a first-line treatment option for the management of *H. pylori* [13]. Although their efficacy has decreased gradually worldwide during the last decade; this has been largely related to a worldwide increase of bacterial resistance, particularly against clarithromycin; the key antibiotic in the *H. pylori* treatment [14]. 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* [13]. Limited compliance due to the increased number of drugs and frequent dosing (four times daily) have led to the development of combination capsules containing bismuth, metronidazole, and tetracycline [15]. For example; a combination capsule (Pylera)® containing bismuth sub citrate 140 mg,
metronidazole 125 mg, and tetracycline 125 mg has been approved by the FDA [16].

1.1 Aim of the Study

To compare between triple and quadruple therapy for eradication of H. pylori in patients with peptic ulcer disease, and to treat relapsed patients after triple therapy. In addition to that; response to therapy (triple and quadruple) have been evaluated according to the Body Mass Index (BMI).

2. PATIENTS AND METHODS

2.1 Patients

This is a prospective case control study involved newly diagnosed patients (in and outpatients) with peptic ulcer disease (PUD). The study is carried out in Baghdad medical city during the period from September 2013 to August 2014. Patients undergoing esophageal-gastro-duodenoscopy (OGD) in the endoscopy unit of the hospital as well as in private clinic, patients were selected by a senior physician. 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 if they were smoker, alcoholics, NSAID users, gastric cancer, severe gastro esophageal reflux disease, or history of gastric operation, lactating or pregnant women, drug history over the past month which mimic those used in the present study and finally patients allergic to the study medications.

According to these criteria; 60 patients (34 male and 26 female) with a mean of age 36.61 years (range between 15 and 70 years) were chosen. Fourteen patients were presented with gastric ulcer and 46 patients were suffering from duodenal ulcer.

2.2 Diagnosis of Helicobacter pylori Infection (Sample Collection)

2.2.1 Diagnosis of PUD

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 known cases of peptic ulcers with positive H. Pylori infection confirmed by (histology [17,18], stool antigen test [19,20] and anti-H. pylori IgG antibody test [19,21]. Patients were considered to be H. pylori infected if all the three tests were positive.

2.2.2 Sample collection

2.2.2.1 Biopsy samples

Two gastric antral biopsy specimens were taken from every patient. Biopsy specimen was fixed in 10% formal buffer saline for histological diagnosis [17], 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 [18].

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.

2.2.2.2 Blood samples

Blood samples were drawn from all the studied 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) [19,21]. Manufactured by ABON Biopharm (Hangzhou), China.

2.2.2.3 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) [19,20]. 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.

Patients were divided randomly into three groups. The first group received triple therapy for two weeks. The second group received quadruple therapy for 10 days. While the third group involved patients in responding to triple therapy treated with second-line quadruple therapy for 10 days.

Group one includes 38 patients and second group include 22 patients and from the first group 16 patients not responding to triple therapy and 13 from them retreated with quadruple therapy.

Patient’s compliance was evaluated at the end of the treatment by pill count from the packet of the drugs, and was considered acceptable if more than 90% of the medication had been taken.

2.2.2.4 The study drugs were

-The 14 days standard triple regimen, one capsule of esomeprazole, one amoxicillin, and one of clarithromycin were taken twice daily.

-The 10-day quadruple regimen, three-in-one capsules were taken four-times daily (after meals and at bedtime), and swallowed whole with 250 mL of water. And esomeprazole capsule was taken with (pylera) capsules after morning and evening 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 [22], while a . treatment failure was considered at a 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.

A per-protocol analysis was performed to compare the eradication for all patients who finished the course of treatment.

**2.2.3 Statistical Analysis**

Data were analyzed by using SAS 2012 (Statistical Analysis System), User’s Guide. Statistical. Version 9.1th ed. SAS. Inst. Inc. Cary. N. C. USA. The Statistical Analysis System-SAS (2012) was used to effect of different factors in study parameters. Chi-square test was used to significant compare between percentage of demographic variables such as gender and age, the others were the rate of eradication, the presence of adverse events, and patient compliance. 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. RESULTS AND DISCUSSION

In this study, the eradication rates of the first line quadruple therapy using triple capsule (Pylera), with PPI (esomeprazole 20 mg) for 10 days was found significantly higher (*p<0.01*) than standard triple therapy using (esomeprazole 20 mg amoxicillin 1.0 g and clarithromycin 500 mg) for 14 days.

Based on triple protocol, the *H. pylori* eradication rate of the standard triple therapy was only 57.89%, as shown in (Table 1) which was less than the 85-90% threshold that most consensus guidelines recommend [23,24].

On the other hand, failure rates with standard triple therapy were found in this study to be 42.02%. This result is consistent with that reported in Europe by De Francesco V et al. [25] and Megraud F et al. [26] who showed a failure rates with standard triple therapy of about 40% of patients and continue to increase.

Considering the quadruple therapy; this study achieved an 88.57% eradication rate as shown in (Table 1), which was similar to (88-93%) eradication rates in previous studies using the same three-in-one capsule with 20 mg omeprazole twice daily for 10 days [15,16,27].

Furthermore, Lu H et al. [28] Dore MP et al. [29] and Zheng Q et al. [30] were reported a success rate of bismuth-containing quadruple therapy of >90% in different parts of the world.

*H. pylori* eradication rate of the standard triple therapy in this study was 57.89%. This is consistent with recent meta-analysis containing subgroup analysis in one group where quadruple therapy achieved eradication in 82.5% of patients, whereas triple therapy achieved an eradication rate of 57.7%. Thus, quadruple
therapy was shown to be more effective than triple therapy [31].

Polat Z et al. [32] had recorded eradication rate of 57% using amoxicillin 1,000 mg bid. and clarithromycin 500 mg bid. esomeprazole 40 mg bid. for 14 days. Also Kadayifci A et al. [33] reported a 55.3% H. pylori eradication with the triple-therapy regimen which was similar to the results of this study.

So, quadruple regimens is more effective than standard triple therapy in this study the reasons for this fall in efficacy of triple regimens are uncertain but may be related to the increasing incidence of clarithromycin-resistant strains of H. pylori [26,34-36].

Also the novel combination (pylera)® with PPI have shown good efficacy and adds a relevant asset for both first- and second-line H. pylori eradication therapy, in agreement with the Maastricht IV consensus [23].

The presence of bismuth compounds in this combination has a mucosal cytoprotective and ulcer healing effects, in addition to that bismuth compounds have some complex actions on H. pylori, such as inhibition of ATP and protein synthesis and membrane function. They can suppress H. pylori in vivo when they are used alone. However, their combination with two antibiotics significantly increases their efficacy on H. pylori and may overcome antibiotic-resistance in vivo and in vitro [37-41].

Bismuth salts have a short-term effect and acts topically that appears to be more like an antiseptic [42]. It exerts its antibacterial action by decreasing mucin viscosity, binding toxins produced by H. pylori, preventing bacteria colonization and adherence to gastric epithelium [43].

3.1 Eradication Efficacy According to the Patient's Gender

A correlation between the rate of eradication of triple therapy and gender among the patients involved in this study was 63.64 and 50.00% in men and women respectively as shown in (Table 2). This is consistent with the study of Masjedizadeh AR et al. [44] with an eradication rate of (68.1% and 57%) in men and women respectively.

Therapy was significantly less successful in women; we have reported this previously but the reasons for this finding were unclear, but there may be gender differences in acid output and gastric blood flow that influence treatment success [45].

Considering the quadruple therapy, the results showed that there was no significant difference in the eradication rate for H. pylori in both male and female (88.89%, 88.23%) respectively as shown in (Table 2). This may be comparable with the study of Masoodi M et al. [46] reported an (83.3% and 81%) eradication rate in men and women respectively using quadruple therapy. It is possible that males and females are equally exposed to the bismuth combination capsule and achieve the same response.

| Treatment protocol       | Patients number | Eradication rate |
|--------------------------|-----------------|-----------------|
| Frist line triple regimen| 38              | 22              | 57.89%          |
| Quadruple regimen        | 35              | 31              | 88.57%          |
| Chi-Square (χ²)          | ---             | 8.926 **        |

** (P<0.01) High significant

Table 2. Eradication efficacy of triple and quadruple regimens according to the patient's gender

| Patients gender | Triple regimen | Quadruple regimen |
|-----------------|---------------|-------------------|
|                 | Patients number | Eradication efficacy | Eradication efficacy |
| Male            | 22             | 14                | 63.64%               | 18             | 16             | 88.89%         |
| Female          | 16             | 8                 | 50.00%               | 17             | 15             | 88.24%         |
| Chi-Square (χ²) | ---            | 4.638 *           | ---                 | 0.093 NS       |

* (P<0.05) significant, ** (P<0.01) High significant, NS: Non-significant
3.2 Eradication Efficacy of Triple Regimen According to the Patient's Age

The results of this study showed an eradication failure with the first-line triple regimen occurred more frequently in patients aged less than 50 years, while a good success rate was observed among elderly patients as shown in (Table 3).

The easy H. pylori eradication with first-line triple regimen experienced by elderly patients may be related to the contribution of different factors. Elderly patients are frequently infected with H. pylori for a longer period of time, present with enlarged atrophic gastritis, and progress to intestinal metaplasia. In addition, the gastric mucosa becomes more atrophic in elderly patients in comparison to younger patients, and elderly patients also display gastric acid hypo secretion. This can compromise their ability to inactivate the amoxicillin and clarithromycin [47].

Dark stool occur due to the presence of bismuth salt in the quadruple regimen bismuth will react with hydrogen sulfide and forms bismuth sulfide in the colon, which blackens the stools [52].

Educating patients about the possible common side effects and the importance of complete eradication will provide a very high curerate as.

Regarding the adherence to the regimens, all patients in this study, (except three; one in the triple group and two in the quadruple group) have complied with the eradication therapies and took more than 90% of the assigned tablets.

Malferttheiner P et al. [15] had reported a good compliance rate above 95% which was similar to compliance rate with quadruple therapy in this study using the same three in one capsule. Studies have suggested that quadruple therapy has a similar magnitude of adherence and adverse effects compared to triple therapies [16,53].

In this study the adherence was similar in both regimens but the adverse effect occurred significantly higher with quadruple therapy, as shown in study that reported the adverse effects were significantly higher in the quadruple regimen [54].

3.3 The Incidence of Adverse Effect Associated with h. pylori Eradication Therapy According to Different Regimens

The most common adverse effects observed in patients treated for H. pylori eradication include abdominal discomfort, diarrhea, nausea, vomiting, headache and weakness; furthermore, these symptoms have an impact on treatment compliance [48].

In this study the most frequently reported side effects in standard triple therapy include gastrointestinal (GI) upset, headache, this was consistent with Alahdab YO et al. [49].

While in quadruple regimens, the reported side effects include gastrointestinal (GI) upset, black stool, Malaise as shown in (Table 4), and this result agreed with those of Luther J et al. [50].

Systematic review and meta-analysis conclude that bismuth for the treatment of H. pylori is safe and well-tolerated. The only adverse event occurring significantly more commonly was dark stools. Other specific individual adverse events with bismuth or bismuth-containing regimen include: abdominal pain, diarrhea, dizziness, headache, nausea and/or vomiting [51].

3.4 Eradication Efficacy According to Body Mass Index in Triple and Quadruple (First and Second Line) Regime

The eradication efficacy in patient having normal weight (BMI<25) were 53.84% and 87.5% in triple and quadruple regimen respectively and high significant difference (P<0.01) was obtained as shown in (Table 5), while in an overweight individual the eradication efficacy in triple and quadruple regimen were 56.25% and 100% also high significant difference (P<0.01) between the two groups was recorded, but it was 66.67% and 75% for triple and quadruple regimen in an obsess individual (BMI≥30) and significant difference (P<0.05) between triple and quadruple regimen.

In this study quadruple therapy produce higher eradication rate than triple therapy in (normal, overweight and obsess) patients although obsess patient have lower eradication in same quadruple regimen.
Table 3. Eradication efficacy of triple and quadruple regimen according to the patient's age

| Age range | Patients number | Eradication efficacy | Patients number | Eradication efficacy |
|-----------|-----------------|----------------------|-----------------|----------------------|
| <20       | 4               | 2                    | 5               | 100%                |
| 20-30     | 13              | 7                    | 9               | 77.78%              |
| 30-40     | 4               | 1                    | 6               | 100%                |
| 40-50     | 7               | 3                    | 7               | 100%                |
| 50-60     | 6               | 5                    | 4               | 66.67%              |
| ≥60       | 4               | 4                    | 2               | 100%                |

Chi-Square ($\chi^2$) ---- 16.728 ** ---- 8.610 **

** ($P<0.01$) High significant; Data presented as number and (%)

Table 4. Incidence of adverse effects of H. pylori eradication therapy according to regimens

| Adverse effects     | Triplen=38 | Quadruple n=35 | Chi-square value |
|---------------------|------------|----------------|------------------|
| Nausea              | 4(10.53%)  | 12(34.29%)     | 7.215 **         |
| Vomiting            | 1(2.63%)   | 2(5.71%)       | 0.942 NS         |
| Diarrhea            | 5(13.16%)  | 2(5.71%)       | 4.620*           |
| Headache            | 4(10.53%)  | 2(5.71%)       | 1.316 NS         |
| Dizziness           | 1(2.63%)   | 1(2.86%)       | 0.069 NS         |
| Epigastric pain     | 4(10.53%)  | 19(54.29%)     | 9.583 **         |
| Black tarry stool   | 0(0%)      | 33(94.29%)     | 14.372 **        |
| Malaise             | 0(0%)      | 1(2.86%)       | 0.194 NS         |
| Dyspepsia           | 4(10.53%)  | 41(11.3%)      | 0.0618 NS        |

** ($P<0.01$) High significant, * ($P<0.05$) significant, NS: Non-significant; Data presented as number and (%)

Table 5. Eradication efficacy according to body mass index in triple and quadruple (first and second line) regimen

| Body mass index | Body mass index | Eradication efficacy | Quadruple regimen | Eradication efficacy | Chi-Square ($\chi^2$) |
|-----------------|-----------------|----------------------|-------------------|----------------------|-----------------------|
| BMI<25          | 13              | 7                    | 16                | 14                   | 87.5%                 | 8.245 **               |
| BMI 25-30       | 16              | 9                    | 11                | 11                   | 100%                  | 8.958 **               |
| BMI >30         | 9               | 6                    | 8                 | 6                    | 75%                   | 4.612 *                |

Chi-Square ($\chi^2$) ---- 5.439 * ---- 8.217 ** ----

* ($P<0.01$) significant, ** ($P<0.01$)High significant; Data presented as number and (%)

The mechanisms by which obese patients have a poor eradication rate remain to be elucidated, it seems likely to be due to the following reasons leading to sub therapeutic drug concentrations. First, the physiological changes that occur in obesity, such as possible delayed gastric emptying [55], may lead to a decrease in the rate of drug absorption, regardless of the characteristics of the drug. Second, the volume of distribution of drugs may be altered in obese patients because the increased adipose tissue mass can influence medications with lipophilic properties [56,57].

Clearly, the need of a tailored eradication regimen for obese patients based on body weight arises, but no clinical trials have compared eradication therapy versus weight-based regimens.

4. CONCLUSION

According to the data obtained during this study we can conclude that:

Ten days quadruple therapy showed a higher eradication rate compared with common fourteen days triple for treatment of H. pylori infection in the Iraqi population, side effects are more common with quadruple therapy, patient education to the regimen were alternative options to improve compliance of the quadruple regimen.
CONSENT

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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