Original Article

Efficacy of a bismuth-based quadruple therapy regimen for *Helicobacter pylori* eradication in Saudi Arabia

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Abstract

Background/Aim: The treatment efficacy of *Helicobacter pylori* (*H. pylori*) has been decreasing over time due to resistance to multiple antimicrobial therapies. The most effective treatment regimen for Saudi Arabian patients infected with *H. pylori* is still unknown. We aimed to study the eradication rate of 10 days of quadruple therapy; bismuth subcitrate potassium 140 mg, metronidazole 125 mg, and tetracycline 125 mg for *H. pylori* infection in a Saudi population.

Patients and Methods: This was a prospective, open-label, non-randomized controlled trial. Patients with *H. pylori* infection were diagnosed by upper gastrointestinal (GI) endoscopy and rapid urease test (RUT) or histology. Patients who tested positive were recruited. Eligible patients were prescribed a 10-day course of quadruple therapy and received three capsules 4 times daily for 10 days along with omeprazole 20 mg twice daily. *H. pylori* was considered eradicated if the urea breath test (UBT) was negative after 6 weeks of completing the treatment.

Results: Ninety-two patients with *H. pylori* infection were recruited. Three patients withdrew from the trial and another seven patients lost follow-up. We analyzed 82 patient's data as per-protocol analysis, of whom 66 (80%) were naive to *H. pylori* treatment. Four patients had failed previous treatment with the sequential regimen and 12 patients had treatment with clarithromycin-based triple therapy. The post-treatment UBT for *H. pylori* infection was negative by per-protocol analysis in 72/82 patients (87.8%), and 72/92 (78.3%) by intention-to-treat analysis. There was no correlation between previous treatment failure and treatment response to the bismuth-based quadruple therapy (*P* value = 0.28).

Conclusions: Treatment with a bismuth-based quadruple therapy was effective in eradicating *H. pylori* infection in 78.3% of Saudi patients with an ITT analysis and in 87.8% as per-protocol analysis.

Keywords: Bismuth quadruple, *helicobacter pylori* eradication, quadruple therapy, Saudi Arabia

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INTRODUCTION

Helicobacter pylori is a gram-negative spiral organism, which is linked to gastritis, peptic ulcer disease, gastric adenocarcinoma, and mucosa-associated lymphoid tissue (MALT) lymphoma.[1] By eradicating *H. pylori* infection we can cure gastritis, and alter its progression to development of complications.[2]

Till today, the most commonly prescribed treatment regimen in Saudi Arabia for the eradication of *H. pylori* is the combination of amoxicillin, clarithromycin, and a proton pump inhibitor[3] but the eradication rate from this regimen has been decreasing in different parts of the world, including Saudi Arabia.[3,4]

The eradication rate for *H. pylori* in the Saudi population has been reported to be 62.3% with sequential therapy and 67.6% with standard triple therapy. Moreover, reported *H. pylori* resistance for different antibiotics were: 48.5% for metronidazole, 23.3% for clarithromycin, 14.8% for amoxicillin, 11.1% for levofloxacin, and 2.3% for tetracycline.[5] The *H. pylori* eradication rate for a levofloxacin-based treatment in Saudi Arabia was reported to be 39.22% (per-protocol analysis) and 36.36% by intention-to-treat (ITT) analysis.[6]

According to recent guidelines, in regions where clarithromycin and metronidazole resistance is more than 15%, bismuth-quadruple based therapy is recommended as first-line therapy for *H.pylori*[1] in agreement with the Maastricht guidelines.[1] The American College of Gastroenterology also recommends a bismuth-based quadruple therapy or concomitant therapy consisting of a proton pump inhibitor, clarithromycin, amoxicillin, and metronidazole as first-line therapy for most patients infected with *H. pylori*. Clarithromycin containing triple therapy is recommended only for patients with no previous history of macrolide exposure and who reside in areas where clarithromycin resistance amongst *H. pylori* isolates is known to be low.[7]

Previously, no studies have been reported from Saudi Arabia that tested the efficacy of a bismuth-based quadruple therapy for *H. pylori*. Hence, we conducted a prospective, open-label, non-randomized trial aiming to assess the eradication rate of a bismuth-based quadruple therapy (Pylera®) for 10 days in naïve and previously treated patients infected with *H. pylori*.

PATIENTS AND METHODS

The study was conducted in a tertiary care teaching hospital in Riyadh, Saudi Arabia. The enrollment for the study started from April 9, 2017 to May 14, 2018. Patients were prospectively screened for *H. pylori* infection in the age group from 16 to 70 years who were attending gastroenterology clinics or who underwent endoscopy for various reasons. The diagnosis of *H. pylori* was made if they had *H. pylori* organisms in the gastric biopsy from the histology or rapid urease test (RUT) from the gastric tissue (HpOne. GI supply™, PA, USA).

We recruited naïve patients and those previously treated with either 14 days of triple therapy as mentioned in our earlier study,[4,6] which includes esomeprazole 20 mg, clarithromycin 500 mg, and amoxicillin 1000 mg, each twice a day for 14 days or 10 days course of sequential therapy that includes esomeprazole (20 mg twice a day for 10 days), amoxicillin (1000 mg for 5 days), then clarithromycin 500 mg and tinidazole 500 mg, both twice a day for 5 days.

We excluded pregnant and lactating females, patients with previous gastric surgeries or advanced medical illnesses, and those who previously took bismuth-based quadruple therapy.

Ethical consideration

The research proposal (#2161-096) was approved by the hospital research and ethics committee. The research was conducted with the following hospital policies entrusted by the research and ethics committee. We conducted the research according to the Declaration of Helsinki and Good Clinical Practice guidelines.

Upper endoscopy

All patients were consented and underwent upper gastrointestinal endoscopy. Gastric tissue was obtained; two from the antrum and two from the body of the stomach for RUT and histology.

Bismuth-based quadruple regimen (Pylera)

Subjects infected with *H. pylori* were given three capsules of Pylera (containing; bismuth, metronidazole, and tetracycline) four times daily (after meals and at bedtime). In addition, they were given pre-meals omeprazole 20 mg twice daily. The total duration of the treatment was 10 days. Patients were instructed to swallow the capsules with a full glass of water (200–250 mL). Ingestion of adequate amounts of fluid was recommended to reduce the risk of tetracycline induced esophageal irritation and ulcers. Subjects were informed of the common adverse effects of the study drugs.

Eradication of *H. pylori*

Patients were asked to abstain from proton pump inhibitors and bismuth-containing agents for 2 weeks and antibiotics

for at least 4 weeks prior to the test. UBT was performed using Carbon 14 bound urea (3 μCi of C14) as the source of radiolabeled carbon dioxide. Patients underwent urea breath test (UBT) after 6 weeks of completing the treatment and if they tested negative on UBT, eradication of *H. pylori* was confirmed.

Statistical calculation

The primary efficacy endpoint was the *H. pylori* eradication rate. Mean, median, standard deviation, minimum, and maximum were calculated for the continuous data and frequency counts and percentages for the categorical data. *P* values of less than 0.05 were considered significant. The eradication rate was calculated with the ITT, which included all enrolled subjects who took at least one dose of study medication. The per-protocol population included all subjects who completed the study. Proportions were compared by chi- square test with continuity correction or a Fisher's exact test when appropriate. Data, only of patients who completed the study were used for calculating the differences between *H. pylori* eradicated and those who failed eradication.

Sample size calculation

The sample size was calculated for two-tailed alpha (significance) level of 5%, 80% power, 75% therapeutic response to standard concomitant therapy, 90% therapeutic response to (Pylera®) plus omeprazole therapy (a difference in eradication rate of 15%); minimum of 120 patients were required. As the probability of loss to follow-up was estimated at around 5%, the final size of the sample was estimated as 126 patients. Unfortunately, we were unable to recruit more than 92 patients due to limitations in supply of (Pylera®).

RESULTS

After screening 248 patients, a total of 92 patients were enrolled. The mean age of patients was 46.5 years (standard deviation (SD) 15.1 years) and 53 (57.6%) were females. The diagnosis of *H. pylori* was made from either UBT or histopathology. In 81/92 (88%) patients UBT was positive and in 80/92 (87%) the organism was identified on histology of the gastric mucosa. From the 92 patients, seven patients did not show up for the post-treatment UBT, and three patients had withdrawn from the trial due to either side effects or intolerance to (Pylera®). The flow diagram of recruited patients is shown in Figure 1.

Per-protocol and Intention-to-treat analysis

The results of 82 patients who completed the treatment and post-treatment UBT were included for the per-protocol analysis. The results of post-treatment UBT

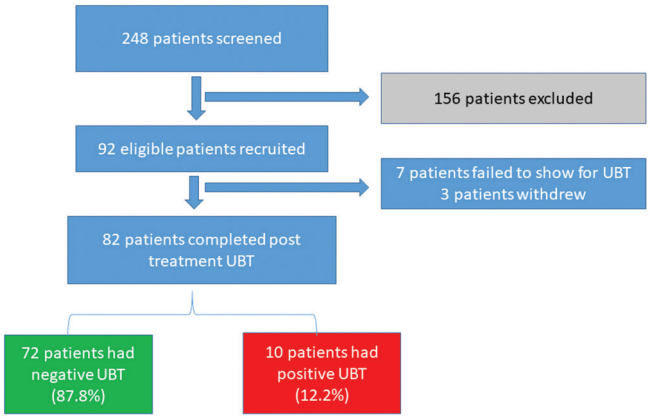

Figure 1: The flow diagram of recruited patients

of 82 patients (per-protocol analysis) showed, 72 (87.8%) patients became negative after the treatment and the remaining 10 (12.2%) were still infected (UBT was positive). *H. pylori* eradication according to the ITT analysis was in 72/92 (78.3%) patients and treatment failure was in 20/92 (21.7%) patients [Figure 2].

Previous treatment for *H. pylori*

From the 82 patients, 66 patients were naive to *H. pylori* treatment, four had received treatment with a sequential regimen in the past, and 12 had treatment with triple therapy amoxicillin, clarithromycin, and proton pump inhibitor for 14 days. Out of 10 patients who failed eradication, seven were naive to any *H. pylori* treatment and three had failed a triple regimen for *H. pylori*. There was no correlation between previous treatment and response to a bismuth-based quadruple therapy (*P* value = 0.28). The eradication rate of *H. pylori* infection was not different between different genders (*P* value = 0.45) or for previous treatment exposure (*P* value = 0.63). The results are shown in Table 1.

Adherence and adverse events

A research coordinator helped in recruiting the patients, follow-up of the results, contacted the patients for their

Table 1: Characteristics of individuals enrolled in the study and the outcomes of therapy

	Enrolled patients (*n*=92)
Age (Mean)	46.5 years
Males	39 (42.4%)
Females	53 (57.6%)
Naive to *H. pylori* treatment	73 (79.3%)
Received sequential regime in the past	4 (4.3%)
Received triple therapy	15 (16.3%)
Diagnosis made by urea breath test	81 (88%)
Diagnosis made by histology	80 (87%)
Outcomes of therapy	
Eradication achieved	72 (78.3%)
Failed eradication	10 (10.9%)
Lost to follow up	10 (10.9%)

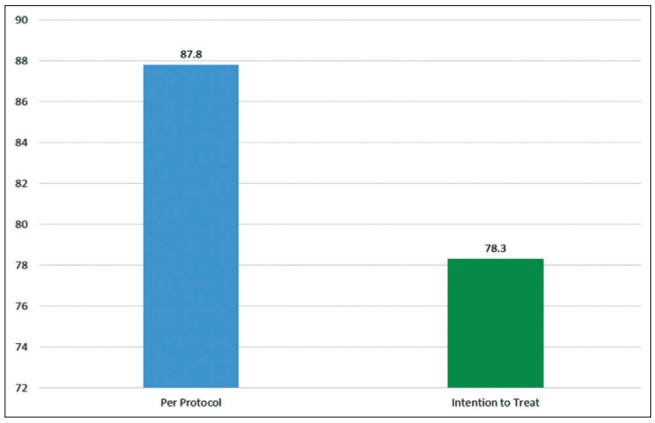

Figure 2: The eradication rates of H. pylori with a bismuth-based quadruple therapy based on per-protocol and intention-to-treat analysis

compliance with treatment and if any side effects of the medications to be reported by the patient as mild, moderate, or severe. Adherence to the bismuth-based quadruple therapy treatment was known in 80 patients, and 73 of them were 100% adherent to treatment, and overall 97.6% of the patients had treatment adherence of 80% and above.

Three patients withdrew from the trial (one patient developed severe vomiting from the first (Pylera®) dose, one patient refused to take the medicine for no clear reason, and one patient refused to take it because of psychological vomiting prior to starting the treatment). Of those who completed the trial, the most common serious adverse events were nausea, fatigue, followed by abdominal pain. Adverse events are given in Table 2.

DISCUSSION

Different treatment regimens are used for the treatment of *H. pylori*, with the most popular among them being a clarithromycin-based regimen. Recently, the eradication rate of *H. pylori* worldwide has decreased; this is mainly attributed to clarithromycin resistance.[8] In a recent meta-analysis, the primary and secondary resistance rates to clarithromycin, metronidazole, and levofloxacin were equal to or more than 15% in all the World Health Organization (WHO) regions, except primary clarithromycin resistance in America [10%; 95% confidence interval (CI), 4–16%) and Southeast Asia (10%; 95% CI, 5–16%) and primary levofloxacin resistance in the European region (11%; 95% CI, 9–13%).[9]

In Saudi Arabia, the primary resistance of *H. pylori* to different antibiotics has been reported as following: Metronidazole (48.5%), clarithromycin (23.3%), amoxicillin (14.8%), levofloxacin (11.1%), and tetracycline (2.3%).[4] In addition, a recent study from Saudi Arabia that used molecular methods for resistance genes variants showed that overall clarithromycin resistance among *H. pylori*-positive patients was considered high (39.9%), and the resistance was significantly higher (48.2%) among the secondary resistance group.[10]

In parallel with increasing clarithromycin resistance, the treatment efficacy of *H. pylori* to clarithromycin-based treatment regimens has decreased globally at an alarming rate.[9] The recent ACG clinical guidelines recommended using clarithromycin triple therapy selectively to patients with no previous history of macrolide exposure who reside in areas where clarithromycin resistance amongst *H. pylori* isolates is known to be low. Most patients will be better served by first-line treatment with a bismuth-based quadruple therapy or concomitant therapy consisting of a proton pump inhibitor, clarithromycin, amoxicillin, and metronidazole. In agreement with the above guideline, the Maastricht V/Florence Consensus Report recommended bismuth-based quadruple therapy or concomitant non-bismuth containing quadruple therapy.[1] Studies from Saudi Arabia have demonstrated the high prevalence of *H. pylori* resistance to clarithromycin and metronidazole.[3,4,10] In addition, the efficacy of levofloxacin-based therapy for *H. pylori* from Saudi Arabia was disappointing.[4,6]

To date, there have been no studies reported from Saudi Arabia on the efficacy of bismuth-based quadruple therapy for *H. pylori*. The eradication rate of *H. pylori* in our study with a bismuth-based quadruple therapy is similar to others. Our study demonstrated *H. pylori* eradication rate to be 87.8% per-protocol and 78.3% in the ITT analysis. Our analysis did not show differences in eradication rates between naive patients versus treatment-experienced patients to clarithromycin-based triple therapy or sequential therapy. Our results are slightly better than previously reported as a secondary therapy.

The cure rates for secondary treatment of *H. pylori* with a bismuth-based quadruple therapy after failed initial triple

Table 2: Side effects from bismuth based quadruple therapy

Symptom severity	Abdominal pain	Diarrhea	Constipation	Anorexia	Nausea	Vomiting	Skin rash	Headache	Dizziness	Fatigue	Bad taste
None	43 (53%)	53 (61.6%)	78 (90.6%)	61 (70.9%)	38 (44%)	73 (84.88%)	79 (91.86%)	51 (59.3%)	56 (65%)	50 (58%)	52 (60.46%)
Mild	26 (30.23%)	28 (32.55%)	7 (8.13%)	17 (19.76%)	14 (34.88%)	7 (8.13%)	5 (5.81%)	23 (26.7%)	22 (25.58%)	13 (15.1%)	24 (27.9%)
Moderate	8 (10.57%)	3 (3.48%)	1 (1.1%)	5 (5.81%)	9 (10.4%)	3 (3.48%)	2 (2.32%)	7 (8.13%)	5 (5.81%)	14 (16.27%)	5 (5.81%)
Severe	8 (9.3%)	-	-	-	9 (10.46%)	3 (3.48%)	-	5 (5.81%)	3 (3.48%)	9 (10.46%)	5 (5.81%)

therapy has been reported to be around 78%.[11,12] Many patients had side effects, but they were not major. Most of our patients completed the treatment with adherence to the whole treatment regimen. We could not assess the efficacy of treatment in seven patients who completed the therapy because they failed to do a UBT after 6 weeks from the completion of the treatment.

The bismuth-based quadruple therapy lasting 10–14 days achieved ≥85% eradication rate as first-line therapy, even in areas with a high prevalence of metronidazole resistance.[1] From a meta-analysis of bismuth quadruple therapy versus clarithromycin triple therapy as first-line treatment for *H. pylori* eradication, the authors analyzed 12 randomized control trials and demonstrated that bismuth quadruple therapy achieved eradication in 77.6% of patients.[13]

Based on the recent recommendations, it was suggested that the aim for eradication of *H. pylori* in any clinical trial should be to achieve eradication in >90% of patients.[14] A recent retrospective analysis of the use of (Pylera®) for 10 days in a Spanish population (185 individuals) has almost similar results of eradication rate of 78% in the ITT and 86.6% per protocol with no statistically significant differences between naïve patients and those previously treated.[15] A multicenter, retrospective study of 349 patients in Italy, showed eradication rate using (Pylera®) for 10 days was 90.5% in the ITT and in 93.5% per-protocol population with no difference in the eradication rate between naïve and previously treated patients.[16] A limitation of our study is the small sample size and we were not able to recruit the calculated sample size. Also, the recruited patients were heterogeneous with regards to prior attempts at eradication of H pylori.

In conclusion, in line with international recommendations,[17] patients from Saudi Arabia treated with a bismuth-based quadruple therapy for 10 days as first-line treatment or as second-line therapy, based on per-protocol analysis, achieved *H. pylori* eradication rates of 87.8%. Most of the patients were adherent to the treatment even though many had some form of side effects from the medications.

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Conflicts of interest

There are no conflicts of interest.

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