

Eradication Rate of *Helicobacter pylori* using a Two-week Quadruple Therapy: A Report from Southern Iran

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ABSTRACT

BACKGROUND

The use of quadruple therapy for *Helicobacter pylori* (*H. pylori*) eradication is a highly efficacious, gold standard regimen. However, according to a number of studies, this regimen has numerous compliance problems and adverse effects. In the current study we have evaluated the *H. pylori* eradication rate following a quadruple therapy that included omeprazole, bismuth subcitrate, amoxicillin, and metronidazole in Hormozgan, the most southern province in Iran. Hormozgan Province has high rates of *H. pylori* infection and its related disorders.

METHODS

A total of 100 patients diagnosed with dyspepsia and *H. pylori* infection as documented by the (13)C-urea breath test (UBT) or rapid urease test (RUT) were treated with the following quadruple regimen: bismuth subcitrate (120 mg, 2 tablets/q12h), amoxicillin (500 mg/q8h), metronidazole (250 mg/q8h) and omeprazole (20 mg/q12h) for a two-week period. Our primary efficacy outcome was *H. pylori* eradication as established by a negative UBT at least four weeks after the end of treatment.

RESULTS

Eradication rates were 79% and 82.3%, respectively, based on the intention-to-treat and per-protocol analyses. Quadruple therapy had a similar effect in women (81%) and men (83.3%) for the eradication of *H. pylori*, which was not statistically significant. *H. pylori* eradication rates according to age groups were: 16-20 years (100%), 21-40 years (81%), and 41-60 years (77.8%; $p=0.001$). There was no significant difference in *H. pylori* eradication rate between genders in those less than 20 years of age and the middle age group. However in the older group the eradication rate was significantly higher in women (100%) compared to men (66.6%).

CONCLUSION

A two-week quadruple therapy that includes omeprazole, bismuth subcitrate, amoxicillin and metronidazole is a highly effective treatment for *H. pylori* infection. This treatment has an acceptable eradication rate in Southern Iran. The eradication rate appears to be lower in older men compared with younger men or in women.

KEYWORDS

Helicobacter pylori; Treatment; Iran

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INTRODUCTION

Eradication of *Helicobacter pylori* (*H. pylori*) infection is a clinically important issue because of its association with benign and malignant diseases of the upper gastrointestinal tract as well as the presence of an increasing antibiotic resistance.¹⁻³ Despite different regimens for its eradication, complete *H. pylori* eradication is difficult because the bacterium lives beneath the gastric mucus, adhering to the gastric epithelium, where antimicrobial drugs have restricted access to this area.³ Additionally, *H. pylori* is resistant to commonly used antimicrobial agents.⁴ This high resistance has required the development of a new mode of treatment protocols. The ideal therapy for *H. pylori* eradication has not yet been clearly defined, but it should be simple, safe, and free from side effects, with 100% efficacy and low cost.¹ Some studies have shown a decline in the success rate of common therapies, in particular triple regimens whose success rate has plummeted to 25%–60%.⁵⁻⁷ The numerous causes of this decline are varied, but include poor compliance, high antibiotic resistance, high gastric acidity, high bacterial loading, and polymorphism.⁷ Recently, the use of quadruple therapy for *H. pylori* eradication has been considered a highly efficacious, gold standard regimen.⁸⁻¹⁰ However some studies have suggested that quadruple therapy is related to increased compliance problems and adverse effects compared with simpler regimens. In a study by de Boer et al., despite limitations, 98% of *H. pylori* eradication has been reported by using a quadruple regimen that included omeprazole, bismuth, and two types of antibiotics.¹¹

In current study, we evaluated the *H. pylori* eradication rate following a quadruple therapy of omeprazole, bismuth subcitrate, amoxicillin, and metronidazole in Hormozgan, the most southern province in Iran. This province has high rates of *H. pylori* infection and its related disorders.

MATERIALS AND METHODS

This clinical trial was performed in 2010 at Shahid Mohammadi Hospital in Hormozgan Province,

Iran. Eligible patients were aged 16 years or older who had confirmed *H. pylori* and dyspepsia or peptic ulcers. Patients were excluded if they had recently used antibiotics to eradicate an adequately recorded *H. pylori* infection or if they had used antibiotics four weeks prior to study entry. Written informed consent was obtained from all patients before enrollment. Our protocol and one amendment were approved by the Research Ethics Committee of the Hormozgan University of Medical Sciences and the study was undertaken in accordance with the Principles of the Declaration of Helsinki.

For participation, patients had to be positive for *H. pylori* by the (13)C-urea breath test (UBT) or rapid urease test (RUT). Eligible patients received the quadruple therapy regimen of bismuth subcitrate (120 mg, 2 tablets/q12h), amoxicillin (500 mg/q8h), metronidazole (250 mg/q8h), and omeprazole (20 mg/q12h) for a two-week period.

Our primary efficacy outcome was *H. pylori* eradication as established by a negative UBT at least four weeks after the end of treatment.

RESULTS

A total of 100 patients were enrolled in the study, of which 72% had a positive UBT, 28% had a positive RUT and 8 patients were diagnosed with peptic ulcers. Of these, 96 patients that were assigned to receive quadruple therapy completed the study. Patient loss was due to either the lack of treatment compliance or not undergoing the UBT. The mean age of participants was 34 years (range: 16-58). Patients were divided into the following age groups: 16 to 20 years (n=8), 21 to 40 years (n=74), and 41 to 58 years (n=18). Males comprised 42% of the study population. After completion of the *H. pylori* eradication regimen, all patients underwent a UBT between 4 to 24 weeks (mean: 14 weeks) after the end of treatment. The per-protocol eradication rate was 82.3% and intent-to-treat eradication rate was 79%. Quadruple therapy results for *H. pylori* eradication were similar between women (81.0%) and men (83.3%). This difference was statistically insignificant. However, the *H. pylori* eradication rates with quadruple therapy were better in the younger

age group. The eradication rates according to age category were: 16 to 20 years (100%), 21 to 40 years (81%), and 41 to 58 years (77.8%; $p=0.001$). Figure 1 compares eradication rates between men and women in each age group. As shown, there was no significant difference in *H. pylori* eradication rate between genders in the age groups less than 20 years and the middle age group, however in the older group the eradication rate was significantly higher in women than men (100% V/S 66.6%; $p=0.001$). The most common adverse effects to treatment were metallic taste, diarrhea, dyspepsia, nausea/vomiting and abdominal pain. All adverse effects were mild. Although no severe adverse effects were observed, however two patients discontinued treatment due to non-compliance.

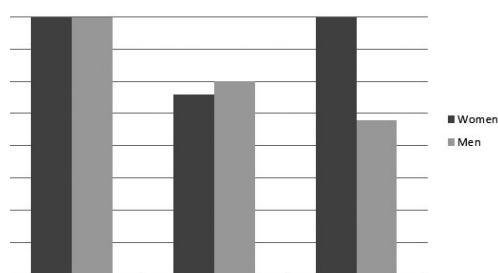


Fig.1: Compares eradication rates between men and women in each age group.

DISCUSSION

In different clinical settings triple therapy is considered to be the first choice for treating *H. pylori*, however the eradication rate with triple therapy has gradually decreased to less than 80% and as low as 70%. Bismuth-containing quadruple therapy has been attempted in an effort to resolve the high resistance to antibiotics, particularly resistance to clarithromycin in the former regimens. Malfertheiner and colleagues¹² showed that bismuth-containing quadruple therapy was effective and acceptable for a first-line therapy to eradicate *H. pylori* in regions with high levels of clarithromycin resistance. In their study, eradication rates were 80% with quadruple therapy and 55% with triple therapy. In other studies, relatively good results with this quadruple regimen were empirically prescribed, with a mean eradication rate of 77%.¹³⁻²¹ However, most of these

studies prescribed tetracycline, which appeared to be less effective than the amoxicillin used in this study.

Multiple drugs and combination of a PPI-based regimen have been evaluated in the therapy of *H. pylori*. Combination quadruple therapy for 14 days provides the greatest efficacy than PPI-based triple regimen but may be associated with a relatively higher incidence of drug induced adverse effects.

The duration of treatment with bismuth-containing quadruple therapy is an important consideration that influences compliance rate, which is controversial. In the present study, we have used a similar regimen and longer treatment duration of 14 days, compared to the Malfertheiner study.¹² We had a higher eradication rate compared with their study. However, in support of the current study, a Korean study²² that prescribed quadruple therapy for 14 days was more effective than a 7-day regimen. Per-protocol analysis showed a 77% (7 day treatment) versus a 94% (14 day treatment) eradication rate as second-line treatment for *H. pylori* when empirical triple therapy had failed. One of the most common regimens prescribed in Iran consist variable combination of bismuth, omeprazole, metronidazole and amoxicillin.

In a study by Saberi-Firoozi et al., the eradication rate was only 35% with omeprazole (2 x 40 mg) plus amoxicillin (4 x 500 mg) that was prescribed for two weeks.²³ In one study, the combination of omeprazole, amoxicillin and metronidazole was administered to pediatric patients for 14 days and resulted in a 78.9% per-protocol and 73% intention-to-treat eradication rate.²⁴ In a study by Sun et al., patients with peptic ulcers received the triple therapy combination of omeprazole (20 mg), amoxicillin (1000 mg) and metronidazole (400 mg) twice daily for seven days. The eradication rate of *H. pylori* for the per-protocol analysis was 84.1%. Based on the intention-to-treat analysis, the eradication rate of *H. pylori* was 82.2%.²⁵ In another Iranian study an intention-to-treat analysis showed eradication rates of 62.5% after a two-week administration of amoxicillin (1 g bid), metronidazole (500 mg bid), bismuth subcitrate (240 mg bid) and

ranitidine (300 mg bid).²⁶

In another report from Iran, eradication was assessed by the C-urea breath test four weeks after the end of a ten-day treatment period with omeprazole, amoxicillin, metronidazole and bismuth citrate. Eradication rates were 84% according to the per-protocol approach and 68.8% in the intention-to-treat approach.²⁷ In the Mousavi et al. study, patients received a combination of omeprazole, bismuth subcitrate, amoxicillin, and metronidazole twice daily for a two-week period. In this study, the eradication rate was 70.4% for intention-to-treat and 75.7% for per-protocol analysis.²⁸ A quadruple-drug regimen that consisted of bismuth, a PPI, amoxicillin and metronidazole showed a 68% intention-to-treat eradication rate.²⁹⁻³⁰ Aminian et al. have reported an eradication rate of 84.1% in intention-to-treat and 85.7% for per-protocol analyses after omeprazole, amoxicillin, metronidazole and bismuth were prescribed twice daily for two weeks.³¹ Thus, it seems that 14 days of bismuth-containing quadruple therapy might be more appropriate than other regimens with different treatment durations.

In our study, we noted that the eradication rate was associated with some baseline variables such as patients' age and gender. Older women had a higher eradication rate compared with men in the same age group. Additionally, the eradication rate gradually decreased with increasing patients' age. In a study by Cai et al.,³² occupation, gender and protocol compliance were positively associated with eradication rate. Lower eradication rates were observed in farmers and women. In another study by Silva,³³ no significant difference was observed regarding sex, tobacco use, alcohol consumption, and NSAID use for *H. pylori* eradication. However for elderly patients the difference was meaningful. According to our findings, it appeared that older men compared with other sex-age groups had a lower *H. pylori* eradication rate. Factors that affect this rate such as poor compliance, high antibiotic resistance, high gastric acidity, high bacterial loading, and some polymorphisms might be highlighted more in older males. This should be studied further.

In summary, quadruple therapy including

omeprazole, bismuth, amoxicillin and metronidazole results an acceptable eradication rate for *H. pylori* in Southern Iran. The eradication rate seems to be lower in older men compared to young men or women.

CONFLICT OF INTEREST

The authors declare no conflict of interest related to this work.

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