



Effects of Clarithromycin-Containing Quadruple Therapy on *Helicobacter Pylori* Eradication after Nitroimidazole-Containing Quadruple Therapy Failure

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ABSTRACT

BACKGROUND

Several large clinical trials and meta-analyses have shown about 20% failure to eradicate *Helicobacter pylori* (*H.pylori*), necessitating investigations for second-line treatments. The aim of this study was to evaluate the effects of clarithromycin-containing quadruple regimen after nitroimidazole-containing quadruple therapy failure.

METHODS

Thirty two patients who had failed 10-day *H.pylori* treatment with omeprazole, amoxicillin, bismuth subcitrate, and metronidazole (OABM) regimen and 31 patients who had failed 10-day treatment with omeprazole, amoxicillin, bismuth subcitrate, and furazolidone (OAMF) regimen entered the study. They all received omeprazole (20 mg), amoxicillin (1 gr), bismuth subcitrate (240 mg) and clarithromycin (500 mg) twice a day for 10 days. Eight weeks after treatment, *H. pylori* eradication was assessed by ¹⁴C-urea breath test.

RESULTS

Totally 61 patients completed the study. According to intention to treat (ITT) analysis, eradication rates by second-line OABC regimen were 84.37% (95% CI= 71.7–96.9%) in OABM group and 77.41% (95% CI= 62.71–92.11%) in OABF group ($p=0.756$). Per-protocol (pp) eradication rates were 87.09% (95% CI= 75.2–98.8%) and 82.75% (95% CI= 79.4–96%), respectively ($p=0.638$). Also the cumulative eradication rates by OABC regimen were 80.9% (95% CI= 71.2–90.6%) and 85% (95% CI= 75.9–94%) according to ITT and PP analyses, respectively. Severe side effects were reported in 3.1% of the patients.

CONCLUSION

Regarding ideal eradication rate (>80%) and very low adverse effects, it seems that clarithromycin-containing quadruple therapy can be an encouraging regimen after nitroimidazole-containing regimen failure.

KEYWORDS

Helicobacter pylori; Clarithromycin; Metronidazole; Furazolidone

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INTRODUCTION

Helicobacter pylori (*H.pylori*) infection is a global health problem and almost half of the population worldwide is infected by the organism.¹ *H.pylori* infection is associated with peptic ulcer disease, gastric

adenocarcinoma, and lymphoma.¹

Although many investigators have tried to introduce regimens with ideal eradication rates, several large clinical trials and meta-analyses have shown about 20% failure to eradicate the infection, necessitating investigations for second-line treatments.²⁻⁵

According to Maastricht IV Consensus Report, in areas of low clarithromycin resistance (<20%), clarithromycin-containing triple therapy or bismuth-containing quadruple regimen is recommended as the first line treatment. In case of failure, either a bismuth-containing quadruple regimen (if not used previously) or levofloxacin-containing triple therapy is recommended. On the other hand, in areas of high clarithromycin resistance, bismuth-containing quadruple regimen is the first-line option and in case of unavailability, sequential therapy or any non-bismuth-containing quadruple regimen can be used. However, after failure, levofloxacin-containing triple therapy is recommended.⁶

As a general rule, second-line regimen should include at least one different antibiotic than what was previously prescribed.⁷ However, the global rise in antibiotic resistance for *H.pylori* eradication and unavailability of new effective antibiotics have led to use different combinations of the currently available antibiotics.

In Iran, resistance to metronidazole has been growing during the previous years and rates as high as 70% have been reported.⁸ Therefore, use of quadruple therapy, replacing metronidazole for furazolidone, is a frequent strategy. However, in case of failure, very few studies have evaluated the second-line options for *H.pylori* eradication.⁹⁻¹¹ Therefore, we designed a study to evaluate the effects of clarithromycin-containing quadruple regimen on two groups of patients who had failed their previous treatment with a nitroimidazole- (metronidazole or furazolidone) containing quadruple therapy.

MATERIALS AND METHODS

Sixty three patients with positive test for *H.pylori* and peptic ulcer disease or gastric/duodenal erosions entered the study to receive a second-line *H.pylori* eradication regimen. Thirty two of the pa-

tients had been previously treated with omeprazole 20 mg, amoxicillin 1 g, bismuth subcitrate 240 mg, and metronidazole 500 mg (OABM), all twice a day, for 10 days and the remaining 31 patients had previously received omeprazole 20 mg, amoxicillin 1g, bismuth subcitrate 240 mg, and furazolidone 200 mg (OAMF) twice a day for 10 days. All the patients had failed their first-line *H.pylori* eradication regimen, confirmed by ¹⁴C-urea breath test (UBT) 8 weeks after treatment (using urea composition made by Helicap Institute of Isotopes, Budapest, Hungary and a cartridge made by Heliprobe breath card, Kibion Uppsala, Sweden).

The exclusion criteria were: age less than 18 years, significant underlying liver/cardiac/pulmonary or renal diseases, pregnancy, breast feeding, any kind of malignancy, previous gastric surgery, coagulopathy, and previous history of allergic reactions to any of the medications used in this protocol and recent proton pump inhibitor or antibiotic consumption.

Also, demographic information, history of previous upper gastrointestinal bleeding (GIB), smoking habits, and drug history including non-steroidal anti-inflammatory drugs (NSAIDs) consumption were recorded in questionnaires.

All the 63 patients received omeprazole (20 mg), amoxicillin (1 gr), bismuth subcitrate (240 mg), and clarithromycin (500 mg) (OABC) twice a day for 10 days. The protocol was approved in the Ethics Committee of Mazandaran University of Medical Sciences and written informed consents were obtained from all the patients.

During the treatment course, the patients recorded side effects of medications each day and were advised to call the doctor in case of severe side effects. After the treatment course, they were visited and were asked about their compliance to treatment and side effects of the treatment. The severity of side effects were classified as: no side effect, mild (not interfering with daily activities), moderate (partially interfering with daily activities), and severe (abandoning daily activities). The compliance to treatment was considered as: excellent if the patient had used more than 90% of the prescribed drugs, good if the patient had used 80-90% of the

medications, and poor in case of taking less than 80% of the prescribed drugs. Eight weeks after the second-line treatment, *H.pylori* eradication was reassessed using ¹⁴C-UBT.

Data were analyzed using SPSS software (version 16). To calculate the intention to treat eradication rate, all the patients who entered the study were considered and to calculate per-protocol eradication rate, only those who completed the entire protocol with more than 90% compliance to treatment were considered for analyses. Also t test, fisher exact test, and univariate logistic regression analyses were used as appropriate. *p* values less than 0.05 were considered as statistically significant.

RESULTS

In the initial study, 510 patients with *H.pylori* infection had entered the study. They were all naïve to *H.pylori* treatment. Two hundred and sixty patients had received the mentioned OABF regimen and 250 patients had received OABM. The per-protocol eradication rates were 87.4% and 82.7%, respectively. Out of those patients who had failed treatment with either OABF or OABM therapies, 63 patients were enrolled in the present second-line treatment.

Thirty two patients were previously treated with OABM and 31 had previously received OABF. The mean ages of the patients were 45.6 ± 8.7 years and 45.8 ± 12.5 years in the two groups, respectively. Baseline demographic and clinical characteristics of the patients were not significantly different between the two groups (table 1). Sixty one patients completed the study. One patient from each group was lost to follow-up due to not performing UBT. Furthermore, one of the patients from OABF group discontinued treatment because of severe metallic taste and nausea.

Compliance to treatment was excellent in 100% of the patients in OABM group and 96.8% of the patients in OABF group. The compliance rates were not statistically different between the two groups.

According to intention to treat (ITT) analysis, eradication rates were 84.37% (27/32)(95% CI= 71.7–96.9%) in the group that had previously received OABM, and 77.41% (24/31) (95% CI=

62.71–92.11%) in OABF group (*p*=0.756). Per-protocol (pp) eradication rates were 87.09% (27/31) (95% CI= 75.2–98.8%) and 82.75% (24/29) (95% CI= 79.4–96%), respectively (*p*=0.638) (figure 1). Also the cumulative eradication rates by OABC regimen were 80.9% (95% CI= 71.2–90.6%) and 85% (95% CI= 75.9–94%) according to ITT and PP analyses, respectively.

Totally, eight patients (12.6%) reported side effects of the treatment, but they were mostly mild (table 2). Two patients (3.1%) reported severe side effects, one of whom stopped treatment because of severe metallic taste and nausea.

DISCUSSION

An ideal second-line *H.pylori* eradication regimen is a regimen that can achieve more than 80% per-protocol eradication rate with less than 5% severe adverse effects.¹² In our study, the clarithromycin-containing quadruple therapy could achieve more than 80% per-protocol eradication rates in both treatment arms and the cumulative eradication rate was 85%. Also, the total rate of severe side effects was 3.1%. Furthermore, 98.3% of the patients had excellent compliance to treatment.

Second-line *H.pylori* eradication regimen must be chosen according to the patterns of regional antibiotic resistance and the type of first-line eradication regimen. It is recommended that if the first-line strategy was a nitroimidazole-containing quadruple regimen, a second-line clarithromycin-based regimen may be used afterwards, and vice versa.¹³⁻¹⁶ The absence of cross reaction between clarithromycin and nitroimidazole supports this concept.

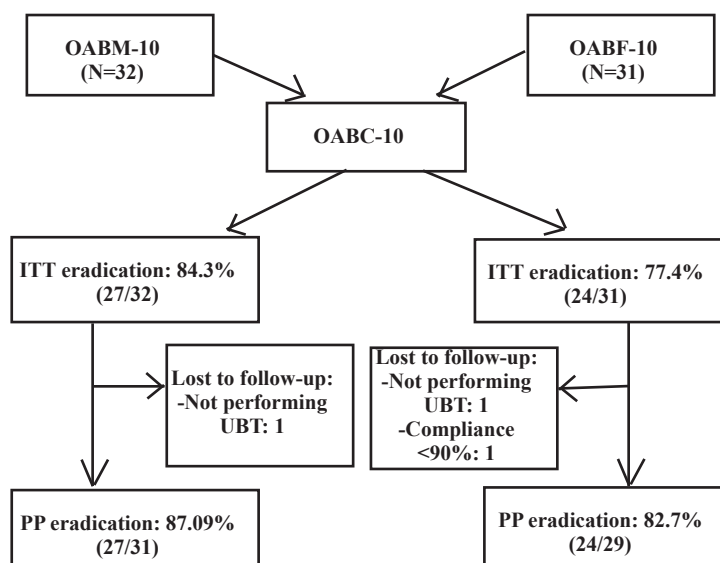
Amongst very few reports evaluating second-line eradication regimens in Iran, the only study that has evaluated the effects of second-line clarithromycin-containing quadruple regimen was conducted by Minakari and colleagues in 2010. In the mentioned study, 220 patients who had failed treatment with OABM were randomized to receive either OABC or OBAzOf (az: Azithromycin, Of: ofloxacin). Per-protocol eradication rates were 74.7% and 86.7%, respectively.⁹

There are other reports in favor of substituting

Table 1: Baseline demographic and clinical characteristics of the patients in the two groups

Variables	OABM group (N= 32)	OABF group (N=31)	p-value
Age (years)	45.6±8.7	45.8±12.5	0.92
Sex (Male/Female)	17/15	19/12	0.51
History of GI bleeding (%)	1 (3.12)	0	0.98
History of NSAIDs consumption (%)	1 (3.12)	1 (3.22)	0.99
History of smoking (%)	2 (6.25)	2 (6.45)	0.98
Endoscopic findings (%)	Gastric Erythema	2 (6.2)	1 (3.2)
	Duodenal ulcer	14 (43.7)	25 (80.6)
	Gastric ulcer	4 (12.5)	2 (6.4)
	Erosive duodenopathy	2 (6.2)	0
	Erosive gastropathy	4 (12.5)	3 (9.6)
	Erosive gastro-duodenopathy	1 (3.1)	0
	Familial history of gastric cancer	4 (12.5)	0
Gastric polyp	1 (3.1)	0	

GI: gastrointestinal, NSAID: Non-steroidal anti-inflammatory drug

**Fig. 1:** Flow chart of treatment protocol and eradication rates

clarithromycin for metronidazole in case of failure to treat *H.pylori*. In this regard, Gisbert could achieve 85% eradication rate,¹⁷ Reilly and co-workers reported 86%,¹⁸ and even Lerang and colleagues reported 100% *H.pylori* eradication rates by second-line clarithromycin-containing regimen after metronidazole failure.¹⁹ However, they all had used clarithromycin-containing triple therapy as the second-line strategy. But clarithromycin-containing triple therapy has shown disappointing results in our country,²⁰⁻²³

therefore, we used clarithromycin-containing “quadruple” regimen as the second-line treatment.

Furazolidone-containing quadruple regimens have also been evaluated as the first-line option in Iran and the reported results have mostly been ideal.²⁴⁻²⁸ However, in case of furazolidone failure, second-line studies are scanty. According to a review of different first-line or second-line *H.pylori* eradication regimens in Iran performed by Malekzadeh and co-workers, it is suggested that if a

Table 2: Frequency of adverse effects and their severity during treatment

Variables	Frequency (%)	
Diarrhea	1 (1.5)	
Bloating	1 (1.5)	
Metallic taste	3 (4.7)	
Nausea	2 (3.1)	
Vomiting	2 (3.1)	
Headache	1 (1.5)	
Malaise	1 (1.5)	
Anorexia	1 (1.5)	
Epigastric pain	1 (1.5)	
Sleepiness	1 (1.5)	
Total patients with side effects	Mild	5 (7.9)
	Moderate	1 (1.5)
	Severe	2 (3.1)

furazolidone-containing regimen was used initially, a clarithromycin-based regimen can be used afterwards.²⁹ Furthermore, since clarithromycin is an expensive drug in Iran, it seems better to keep this drug for second-line strategies.

The main limitation of our study was the unavailability of *H.pylori* culture. However, the resistance rates to clarithromycin have been less than 20% in most studies performed in Iran.³⁰⁻³⁵ Another limitation was the small sample size in each arm of the treatments. In fact, we had treated more than 700 patients with positive *H.pylori* test to achieve the present sample size.

In conclusion, since nitroimidazole-containing quadruple regimens are commonly used as first-line therapies in Iran, introducing a second-line regimen with ideal eradication rate and few adverse effects is worth considering. Accordingly, regarding ideal eradication rate (>80%), excellent compliance to treatment and very low adverse effects, it seems that clarithromycin-containing quadruple therapy can be an encouraging regimen after nitroimidazole-containing regimen failure in Iran. We suggest further studies to evaluate the effects of other combinations of clarithromycin-containing regimens (such as concomitant or hybrid therapies) after nitroimidazole-containing regimen failure. Also, we suggest culture-guided strategies for sec-

ond-line *H.pylori* treatment.

CONFLICT OF INTEREST

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

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