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A Comparison between 10-day and 12-day Concomitant Regimens for *Helicobacter Pylori* Eradication: A Randomized Clinical Trial

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ABSTRACT

BACKGROUND

Helicobacter pylori (*H. pylori*) infection is one of the most common bacterial infections worldwide, which is associated with peptic ulcer disease and gastric cancer. In this study, we compared the efficacy of 10-day versus 12-day concomitant therapy as the first-line treatment for *H. pylori* eradication in Iran.

METHODS

218 patients with peptic ulcer disease and naïve *H. pylori* infection, were randomly divided into two groups to receive either 10-day or 12-day concomitant regimens, composed of pantoprazole 40 mg, amoxicillin 1000 mg, clarithromycin 500 mg, and metronidazole 500 mg, all given twice daily. Eight weeks after treatment, *H. pylori* eradication was assessed by 14C- urea breath test. The trial was registered in the Iranian Registry of Clinical Trials (code: IRCT20170521034070N2).

RESULTS

212 patients completed the study. According to the intention to treat analysis, the eradication rates were 83.6% (95% CI: 76.6-90.5) and 88.8% (95% CI: 82.8-94.7) in 10-day and 12-day concomitant therapy groups, respectively ($p = 0.24$). Per-protocol eradication rates were 85.9% (95% CI: 79.3–92.4) and 92.6% (95% CI: 87.6–97.5), respectively ($p = 0.19$). The rates of severe side effects were not statistically different between the two groups (3.6% vs. 8.1%; $p = 0.428$).

CONCLUSION

12-day concomitant therapy could achieve ideal eradication rates by both intention to treat and per-protocol analyses. In order to reduce the cost of drugs and the rate of adverse effects of therapy, among 10-day and 12day regimens, 12-day concomitant therapy seems to be a good alternative to 14-day concomitant therapy that has been suggested by international guidelines.

KEYWORDS:
Helicobacter pylori, Peptic ulcer disease, Eradication, Concomitant

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INTRODUCTION

Almost half of the world population is infected with *Helicobacter pylori* (*H. pylori*). The infection is associated with peptic ulcer disease and gastric malignancies including adenocarcinoma and lymphoma. [1] During recent decades, multiple studies tried to find an ideal regimen to eradicate *H. pylori*. Standard clarithromycin-containing therapy has been used during previous years in many countries, but the success rate of this regimen has fallen to below 80% in many regions. [2]

According to the Maastricht V consensus report, a 14-day concomitant regimen can be considered as a suitable first-line *H. pylori* eradication regimen if the prevalence of dual resistant strains to clarithromycin and metronidazole is less than 15%.[3] Concomitant therapy is a novel treatment consisted of concomitant administration of a proton pump inhibitor (PPI), amoxicillin, metronidazole, and clarithromycin. Previous studies from different countries have mostly reported suitable *H. pylori* eradication rates by 14-day concomitant therapy.

Although the recommended duration of therapy with the concomitant regimen is 14 days, shorter treatment course can be favored by lower rates of adverse effects. Furthermore, according to the Maastricht V consensus report, shorter durations of concomitant therapy can be used if proven to be effective locally.[4] Accordingly, we decided to compare the effects of 12-day versus 10-day concomitant therapies for first-line *H. pylori* eradication in the north of Iran.

MATERIALS AND METHODS

218 patients with peptic ulcer disease and no previous treatment for *H. pylori* infection were randomly divided into two groups to receive either 10-day or 12-day concomitant regimens, consisting of pantoprazole 40 mg, amoxicillin 1000 mg, clarithromycin 500 mg, and metronidazole 500 mg, all given twice daily. The diagnosis of *H. pylori* infection was made by rapid urease test and histological assessment of gastric biopsy samples.

In order to randomize patients, block randomization was used. Accordingly, patients were classified in 5-patient blocks regarding their age and sex. The exclusion criteria were pregnancy, breastfeeding, and history of gastrointestinal surgery or gastrointestinal malignancy, and using anticoagulant drugs or anticonvulsant drugs.

Patients were given information about the regimens and they were asked to call the physician in case of any severe adverse effect. All patients had a follow-up visit in 2 weeks to assess the compliance to treatment and to record any adverse effect. Compliance with treatment was assessed through interviews and was assumed excellent if the patient used more than 90%, good if the patient took 70-90%, and poor if the patient used less than 70% of the medications. Also, adverse effects of therapies were classified as mild, if they did not interfere with daily activities, moderate if they partially interfered with daily activities, and severe, if they interrupted daily activities. Eradication of *H. pylori* was assessed using 14C-urea breath test (UBT) at 8 weeks after completion of the treatments.

This study was approved by the Ethics Committee of Mazandaran University of Medical Sciences (REC.1397.1540) and written informed consent was obtained from all patients. Also, the trial was registered in the Iranian Registry of Clinical Trials (code: IRCT20170521034070N2).

Statistical analysis:

Data were analyzed using SPSS software (version 16; SPSS Inc., Chicago, IL, USA). Pearson Chi-square test, t test, and logistic regression analyses were used as appropriate. All participants were included in the intention-to-treat analysis. Only those patients who completed the treatment protocol with more than 90% compliance to treatment were included in the per-protocol analysis. Also, p values less than 0.05 were considered to be statistically significant. The statistician was blind to the assignments.

RESULTS

218 patients entered the study. 110 patients were randomized to receive 10-day concomitant therapy and 108 patients received a 12-day concomitant regimen. The mean ages of the patients of the two groups were 46.5 years and 44.4 years, respectively. Demographic characteristics and endoscopic findings of the patients are shown in table 1.

Of the 218 enrolled patients, 212 completed the study. According to the intention-to-treat analysis, the eradication rates were 83.6% [95% confidence interval (CI): 76.6–90.5] and 88.8% (95% CI: 82.8–94.7) in 10-day and 12-day concomitant groups, respectively (p = 0.24). Two patients in the 10-day protocol and seven patients in the 12-day regimen stopped treatment due to severe adverse effects of therapy (p = 0.1). Also, compliance with treatment was excellent in 97.2% of the patients in 10-day protocol and 87.9% of the patients in the 12-day regimen groups (p = 0.03). Accordingly, per-protocol eradication rates were 85.9% (95% CI: 79.3–92.4) and 92.6% (95% CI: 87.6–97.5) in 10-day and 12-day groups, respectively (p = 0.19) (Figure 1). In logistic regression analysis, none

Table 1: Demographic characteristics and endoscopic findings of the patients in both groups

Patients' characteristics	10-day concomitant therapy N (%)	12-day concomitant therapy N (%)	*p* value
Male / Female	48 / 62	48 / 60	0.99
Mean age ± SD (years)	46.5 (±14) years	44.4 (±13)	0.35
Current Smoking (%)	13 (11.8%)	8 (7.4%)	0.99
History of gastrointestinal bleeding (%)	7 (6.3%)	6 (5.5%)	0.99
Non-steroidal anti-inflammatory drugs consumption	10 (9.1%)	12 (11.1%)	0.65
Endoscopic findings			
- Duodenal ulcer - Gastric ulcer - Gastric + duodenal ulcer - Gastric cancer in 1st degree relative - Gastric adenomatous polyp	47 (42.7%) 16 (14.5%) 2 (1.8%) 5 (4.5%) 1 (0.9%)	61 (56.4%) 15 (13.8%) 3 (2.7%) 2 (1.8%) 2 (1.8%)	0.24

Table 2: Frequency and severity of side effects of therapy in both groups

Side effects	10-day concomitant therapy N (%)	12-day concomitant therapy N (%)	*p* value
Diarrhea	1 (0.9%)	6 (5.4%)	0.277
Bitter taste	15 (13.5%)	18 (16.2%)	
Anorexia	2 (1.8%)	0	
Dizziness	1 (0.9%)	1 (0.9%)	
Nausea and vomiting	2 (1.8%)	6 (5.4%)	
Rash	1 (0.9%)	0	
Epigastric pain	5 (4.5%)	3 (2.7%)	
Bloating	1 (0.9%)	0	
Headache	2 (1.8%)	1 (0.9%)	
Malaise	5 (4.5%)	3 (2.7%)	
Abdominal cramp	1 (0.9%)	1 (0.9%)	
Dry mouth	0	1 (0.9%)	
Palpitation	0	2 (1.8%)	
Severity of side effects			
- Mild - Moderate - Severe	14 (12.6%) 18 (16.2%) 4 (3.6%)	17 (15.3%) 16 (14.4%) 9 (8.1%)	0.428

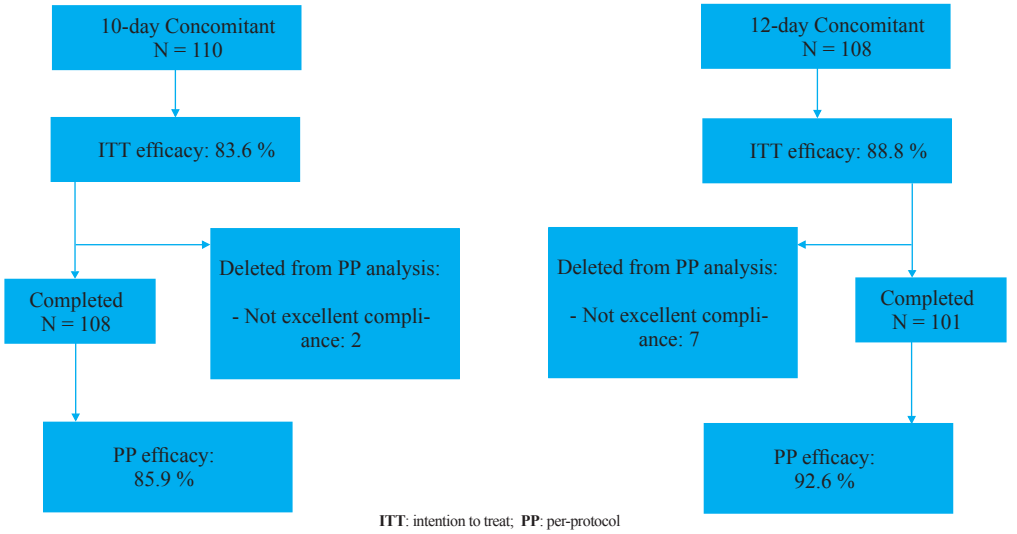
of the demographic or endoscopic factors was found to be associated with treatment success.

The rates of adverse effects of treatment were 32% and 38% in 10-day and 12-day regimens, respectively. However, most of the side effects were mild and only 3.6% and 8.1% of the patients reported severe side effects in the two groups, respectively. These rates were not statistically different between the two groups. The most common side effect was a bitter taste (table 2).

DISCUSSION

According to the results of our study, 85.9% of the patients in the 10-day regimen group and 92.6% of the patients in the 12-day protocol could eradicate *H. pylori* by per-protocol analysis.

The ideal regimen for *H. pylori* eradication is a regimen that can eradicate *H. pylori* in more than 90% of cases. [4] However, according to the Toronto consensus report, regimens with more than 85% per-protocol eradication rates are also acceptable.[5] Therefore, although 12-day concomitant therapy could achieve an ideal eradication



ITT: intention to treat; **PP**: per-protocol

Fig.1: Method of follow up & treatment efficacy

rate, a 10-day regimen is also acceptable.

Studies from other countries have mostly reported accep eradication rates by either 14-day or shorter durations of concomitant therapy. In 2013, Zullo and colleagues reported 85.5% *H. pylori* eradication rate by 5-day concomitant therapy in Italy.[6] At the same year, Molina-Infante reported 91.3% eradication rate by 14-day regimen in Spain.[7]

In 2014, the rate was increased to 86.3% by 14-day concomitant therapy in Italy [8] and remained 91% in a prospective multicenter study in Spain.[9] Studies from Asian countries also, have reported ideal eradication rates by concomitant therapies with different durations.[10] In 2014, Heo and co-workers reported 88.7% and Kim and colleagues reported 94.4% per-protocol *H. pylori* eradication rate by 10-day concomitant therapy in South Korea.[11]

In 2017, Park and others reported 95.6% and 98.5% per-protocol eradication rates by 10-day and 14-day concomitant regimens in Korea, respectively.[12] Also, another study in 2018 reported a 95.5% per-protocol *H. pylori* eradication rate by 10-day concomitant therapy in Korea.[13] Studies from Taiwan, a country with high *H. pylori* resistance rate, have also shown acceptable *H. pylori* eradication rates by 7-day, 10-day, and 14-day concomitant regimens.[14-16]

According to the Maastricht V Consensus Report, concomitant therapy is the most effective non-Bismuth quadruple therapy and can be used if the prevalence of dual resistant strains to clarithromycin and metronidazole is less than 15%.[3] Also, the recommended duration of concomitant therapy is 14 days, unless shorter durations of therapies are proven to be locally effective.[3]

In our geographic area, the rate of *H. pylori* resistance to antibiotics, especially to metronidazole, is high. Recent studies have mostly reported more than 15% resistance rate to clarithromycin. But the rate of dual resistance is not defined.[17] According to the results of our study, both 10-day and 12-day concomitant regimens can be used as first-line treatment for *H. pylori* eradication in this geographic area and the results may be attributable to regions with the same pattern of resistance to antibiotics.

Another important issue in the treatment of *H. pylori* is the rate of severe adverse effects. The ideal regimen should have less than 5% severe side effects. In our study, although the rates of severe adverse effects of treatments were not statistically different between the two groups, 10-day concomitant therapy was associated with less than 5% severe side effects. Therefore, it seems to be a suitable option in this region.

A limitation of our study was the unavailability of *H. pylori* culture. Also, it would be better to have an arm of 14-day concomitant therapy that has been introduced as the standard of care. However, this study has a strong point. This is the first study evaluating the effects of 10-day and 12-day concomitant therapies for first-line *H. pylori* eradication in Iran.

In conclusion, both 10-day and 12-day concomitant therapies seem to be effective for first-line *H. pylori* treatment even in regions with high resistance to antibiotics. Although the eradication rates and the rates of side effects were not statistically different, the 10-day regimen has numerically lower side effects and 12-day therapy has more ideal eradication rate.

ETHICAL APPROVAL

There is nothing to be declared.

CONFLICT OF INTEREST

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

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