

Comparison Between 10- and 14-Day Hybrid Regimens for *Helicobacter pylori* Eradication: A Randomized Clinical Trial

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Abstract

Background: *Helicobacter pylori* (*H. pylori*) eradication has always been a concern. In our previous study, 14-day hybrid regimen showed ideal results. Based on these findings, we decided to compare the efficacy of 10- and 14-day hybrid regimens for *H. pylori* eradication.

Methods: Two hundred and seventy patients with peptic ulcer disease and *H. pylori* infection were enrolled in the study. One hundred and thirty-four patients received 10-day hybrid regimen (PACT-10): pantoprazole, 40 mg, and amoxicillin, 1 g, both twice daily for 10 days; plus clarithromycin, 500 mg, and tinidazole, 500 mg, both twice daily just during the last 5 days. One hundred and thirty-six patients received 14-day hybrid regimen (PACT-14): pantoprazole, 40 mg, and amoxicillin, 1 g, both twice a day for 14 days; plus clarithromycin, 500 mg, and tinidazole, 500 mg, both twice daily just for the last 7 days. Eight weeks after treatment, ¹⁴C-urea breath test was performed to evaluate *H. pylori* eradication.

Results: Two hundred and fifty patients (124 patients in PACT-10 and 126 patients in PACT-14 regimens) completed the study. The intention-to-treat eradication rates were 77.6% (95% confidence interval (CI): 70.6–84.6%) and 86% (95% CI: 80–92%) for the two regimens, respectively ($p = .17$). Per-protocol eradication rates were 83.8% (95% CI: 80–86%) and 92.8% (95% CI: 88–96%), respectively ($p < .01$). There were no significant inter-group differences in compliance to treatment or discontinuation of therapy due to severe side effects.

Conclusion: Ten-day hybrid regimen could not achieve acceptable eradication rate. However, 14-day hybrid regimen seems to be an acceptable option for *H. pylori* eradication in Iran.

The global prevalence of *Helicobacter pylori* infection is more than 50%. *H. pylori* infection is associated with peptic ulcer disease, gastric cancer, and mucosa-associated lymphoid tissue lymphoma [1,2]. Therefore, *H. pylori* eradication has always been a concern.

Standard clarithromycin-containing triple therapy and 10-day sequential therapy are now effective only in special populations [3] and should be considered obsolete as empiric therapies [4]. Some studies have shown the superiority of the sequential regimen over the standard triple therapy, but the result of both regimens has been suboptimal [5,6]. A recent meta-analysis performed by Gatta et al. showed a mean cure rate of 84% for 10-day sequential therapy. The rate was

superior to 7-day triple therapy and marginally superior to 10-day triple therapy, but not superior to 14-day triple therapy [7].

Nonbismuth quadruple therapy, also termed as “concomitant” regimen, has been proposed as an alternative to the sequential therapy. It is less confusing for the patients and is more likely to facilitate compliance to treatment [3]. In several studies, this regimen could achieve *H. pylori* eradication rates above 90% [8–11]. Accordingly, concomitant therapy seems to be a superior alternative to sequential therapy.

Hybrid therapy, a combination of sequential and concomitant therapies, is a novel regimen with ideal results in related studies. It contains a proton pump

inhibitor (PPI) plus amoxicillin given for the first 7 days, followed by quadruple therapy including a PPI, amoxicillin, clarithromycin, and metronidazole (or tinidazole) for the last 7 days.

In 2014, Wu et al. compared the efficacy of 10-, 12-, and 14-day hybrid therapies for *H. pylori* eradication in Taiwan, an area of low clarithromycin resistance. Per-protocol eradication rates were 95, 95.1, and 93.4%, respectively [12]. Also, Hsu et al. [13] reported 99.1% per-protocol eradication rate by 14-day hybrid therapy in Taiwan.

In a study by Oh et al. in Korea, 14-day hybrid regimen was compared with 14-day sequential therapy. Per-protocol eradication rates were 85.9 and 82.0%, respectively, and did not show statistically significant difference [14].

Zullo et al. conducted a study in Italy in which 14-day hybrid regimen was compared with 5-day concomitant and 10-day sequential therapies. Per-protocol eradication rates were 85.7% by hybrid regimen, 91.6% by the concomitant therapy, and 92.1% by the sequential regimen. However, differences were not statistically significant [15].

In 2014, De Francesco et al. evaluated the efficacy of 14-day hybrid regimen, 5-day and 10-day concomitant therapies and 10-day sequential regimen. According to intention-to-treat analysis, sequential therapy achieved the highest eradication rate. However, the success rate did not statistically differ among the sequential and either 14-day concomitant (90 vs 86.3%) or hybrid therapies (90 vs 82.7%) [16].

Molina-Infante et al. compared the efficacy of 14-day hybrid regimen with 14-day concomitant therapy in 2013. Per-protocol eradication rates were 92 and 96.1%, respectively. In the mentioned study, 23.5% of patients had *H. pylori* strains resistant to clarithromycin, 33% were resistant to metronidazole, and 8.8% were resistant to both drugs. Although the rates of resistance to clarithromycin and metronidazole were high, both regimens could achieve more than 90% eradication rate [17].

In Iran, only one study has been performed to evaluate the efficacy of hybrid regimen in *H. pylori* eradication: Sardarian et al. [18] reported 92.9% per-protocol eradication rate by 14-day hybrid therapy.

Although the rate of clarithromycin resistance is high in Iran, considering the acceptable eradication rate by hybrid regimen in the previous study performed in Iran and other countries, we designed this study to compare the efficacy of 10- and 14-day hybrid regimens for *H. pylori* eradication. Our goal was to assess whether decreasing the duration of therapy would lower the rate of side effects while increasing compliance rates and maintaining the efficacy.

Methods

Two hundred and seventy patients with *H. pylori* infection and endoscopically confirmed peptic ulcer disease or gastric/duodenal erosions were enrolled in the study. *H. pylori* infection was documented by antral biopsy for pathology (Giemsa staining) and/or rapid urease test (RUT; Shim-enzyme, Tehran, Iran).

Upper GI endoscopy and antral biopsies were performed using Pentax upper endoscopes (Video gastro-scope HD EG-2990i with Video processor HDEPK-i, Tokyo, Japan, 2010 and Video gastro-scope EG-2985K with Video processor EPK-1000, Tokyo, Japan, 2011). All patients were naïve to *H. pylori* treatment. Also, written informed consents were obtained from all patients. The study was also approved in the ethic committee of Mazandaran University of Medical Sciences and was registered in Iranian Registry of Clinical Trials (IRCT number: 2013112415510N1).

The exclusion criteria were age <18 years, significant underlying diseases such as liver, cardiac, pulmonary or renal diseases, neoplasm, coagulopathy, history of gastric surgery, pregnancy, breast-feeding, previous history of allergic reaction to any medications used in this study, and recent PPI or antibiotic consumption.

Demographic information, history of nonsteroidal anti-inflammatory drugs (NSAIDs) consumption, smoking, previous upper gastrointestinal bleeding (GIB), and some endoscopic findings including duodenal or gastric ulcer/erosions, and the presence or absence of bulbar deformity were recorded in questionnaires. Ulcer was defined as a break in the lining of the mucosa, with appreciable depth at endoscopy, and erosions were defined as breaks in the surface epithelium that did not have perceptible depth.

The patients were randomly enrolled to either of the two groups. One hundred and thirty-four patients received PACT-10: pantoprazole 40 mg/bid and amoxicillin 1 g/bid for 10 days plus clarithromycin 500 mg and tinidazole 500 mg, both twice daily for the last 5 days. One hundred and thirty-six patients received PACT-14: pantoprazole 40 mg/bid and amoxicillin 1 g/bid for 14 days plus clarithromycin 500 mg and tinidazole 500 mg, both twice daily for the last 7 days.

Patients recorded side effects of medications on a daily basis and were advised to call the doctors if side effects were severe. All patients were visited at the end of therapy. They were asked about their compliance to treatment, number of remaining drugs (if any), and side effects. The severity of side effects was classified as: no side effect, mild side effects (no limitation in daily activities), moderate side effect (partial limitation in

daily activities), and severe side effect (profound limitation in daily activities). The compliance to treatment was considered as excellent if the patient had consumed more than 80% of prescribed medications, good for taking 60–80% of medication and poor for consuming <60%. Eight weeks after therapy, *H. pylori* eradication was assessed by ^{14}C -urea breath test (UBT). To perform UBT, patients swallowed 37 kBq (lCi) encapsulated ^{14}C -labeled urea compositions (Helicap Institute of Isotopes, Budapest, Hungary) with water. After 10 minutes, patients exhaled into a cartridge (Heliprobe breath card, Kibion, Uppsala, Sweden) until the indicator of the card changed from orange to yellow. The cards were inserted into a Geiger–Muller counter (Heliprobe Analyzer; Kibion AB), and radioactivity of samples was automatically measured after 250 seconds. Based on radioactivity, as count per minute (cpm), counts more than 50 cpm were considered infected with *H. pylori* (positive UBT).

Statistical Analysis

Sample size

Previous studies have mostly assessed the efficacy of 14-day hybrid regimens with eradication rates ranging from 82% in Italy to 92% in Iran. No study has assessed the efficacy of 10-day hybrid regimen in our geographic region. Accordingly, we assumed to have about 10% difference between the two regimens in their ability to eradicate *H. pylori*. Considering $\alpha = 0.05\%$ and $\beta = 0.2\%$ and the equation $n = 2(z_{1-\alpha/2} + z_{1-\beta})^2 + \bar{p}(1 - \bar{p})/(p_1 - p_2)^2$, the number of patients in each arm was calculated to be 110. But we assumed about 20% withdrawal rate; therefore, we included at least 132 patients in each arm.

The primary outcome variable was *H. pylori* eradication rate. Secondary outcome variables were the incidence of adverse drug reactions and compliance rate to treatment. Eradication rate was evaluated by intention-to-treat (ITT) and per-protocol (PP) analyses. To calculate the ITT eradication rates, everyone who entered the study was considered, and to calculate PP eradication rates, only those who completed the entire protocol with more than 80% compliance to treatment were considered. Data were analyzed using IBM SPSS software for windows (version 19.1; SPSS Inc., Chicago, IL, USA), and Pearson's chi-square test for qualitative parameters, *t*-test for quantitative parameters, and logistic regression analysis were used as appropriate. *p*-values <.05 were considered statistically significant. The statistician analyzer of the final results was blind to the assignment of patients.

Results

Two hundred and seventy patients with peptic ulcer disease and/or erosive gastritis or duodenitis were randomly enrolled in this study. One hundred and thirty-four patients (49.6%) received PACT-10 regimen, and 136 patients (50.4%) received PACT-14 regimen. Mean age in PACT-10 regimen was 46.42 ± 13.59 and in PACT-14 regimen was 45.43 ± 12.88 ($p = .41$). Demographic, clinical, and endoscopic findings were not statistically different between the two groups (Table 1).

Compliance to treatment was excellent: 96.3% of patients in PACT-10 and 95.6% in PACT-14 groups. Seven patients (2.5%) were lost to follow-up due to not performing UBT (four patients in PACT-10 and three patients in PACT-14 group). The per-protocol eradication rates were 83.8% (95% CI: 80–86%) and 92.8% (95% CI: 88–96%) in PACT-10 and PACT-14 groups, respectively ($p < .05$) (Fig. 1, Table 2).

Furthermore, none of the baseline demographic variables were associated with UBT results in univariate logistic regression analysis, neither among the whole group of patients nor within any of the two treatment groups.

Adverse drug reactions are shown in Table 3. The most common side effect was metallic taste in both groups: 31 patients (23.1%) in the PACT-10 and 38 patients (27.9%) in the PACT-14 groups. However, the overall rate of side effects did not significantly differ between the two groups.

Table 1 Demographic characteristics, clinical and endoscopic findings

Variables	PACT-10 group	PACT-14 group
Patients in each group (%)	134 (49.6)	136 (50.4)
Male/Female ratio	54/80	64/70
Age (mean $\pm$ SD; years)	46/42 $\pm$ 13/59	45/43 $\pm$ 12/88
Smoker, n (%)	10 (7.5)	12 (8.8)
History of GIB, n (%)	8 (6)	2 (1.5)
History of NSAID consumption, n (%)	10 (7.5)	7 (5.1)
Duodenal ulcer, n (%)	61 (45.5)	46 (33.8)
Gastric ulcer, n (%)	23 (17.2)	23 (17.2)
Duodenal ulcer + Gastric ulcer, n (%)	4 (3.0)	7 (5.1)
Erosive duodenitis, n (%)	22 (16.4)	19 (14)
Erosive gastritis, n (%)	46 (34.3)	51 (37.5)
Bulb deformity, n (%)	20 (14.9)	20 (14.7)

GIB, gastrointestinal bleeding; NASID, nonsteroidal anti-inflammatory drug.

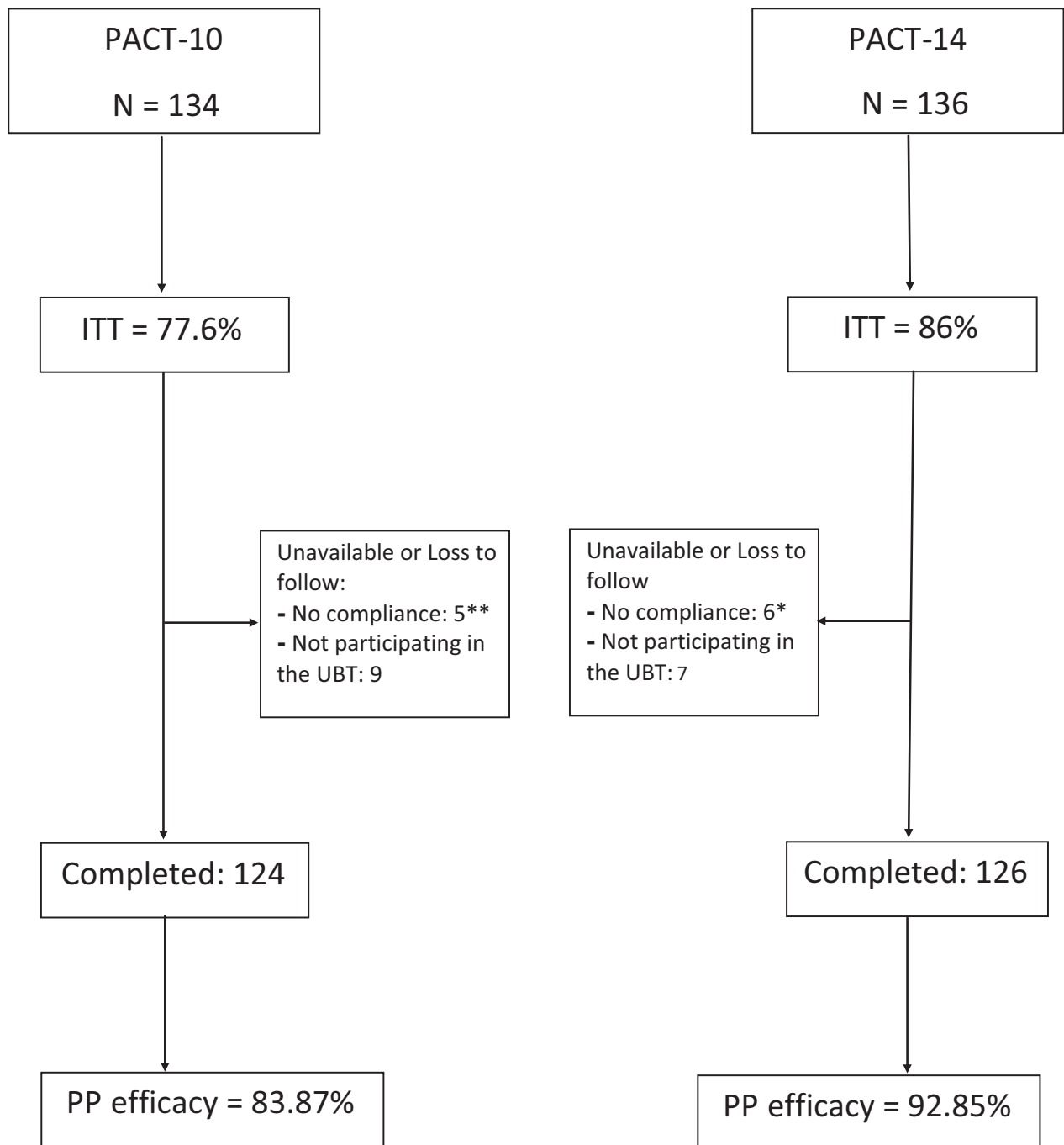


Figure 1 Flowchart of method of follow-up and treatment efficacy. ITT, intention-to-treat; PP, per-protocol. *Three patients in 14 days hybrid group were both noncompliant and unavailable for UBT. **Four patients in 10 days hybrid group were both noncompliant and unavailable for UBT.

Discussion

The success rate of *H. pylori* eradication regimens mainly depends on the patient's compliance, the pattern of *H. pylori* antibiotic resistance, and duration of

therapy [19]. If we consider *H. pylori* infection as an infectious disease, the ideal regimen is the one that can eradicate *H. pylori* infection in more than 95% of cases. Graham classified the efficacy of HP treatment according to per-protocol success rates as A: excellent

Table 2 Efficacies of two hybrid (PACT-10- and PACT-14) regimens in *Helicobacter pylori* eradication

Variables	PACT-10 group		PACT-14 group		p-value
	Patient	Eradication rate (%)	Patient	Eradication rate (%)	
ITT analysis	134	104 (77.6)	136	117 (86)	.17
PP analysis	124	104 (83.8)	126	117 (92.85)	<.01

p-values <0.05 were considered statistically significant.

Table 3 Adverse drug effects reported by the patients during treatment

Adverts effect ^a	PACT-10 N = 134	PACT-14 N = 136
Metallic taste (%)	31 (23.1)	38 (27.9)
Epigastric pain (%)	5 (3.7)	2 (1.4)
Black tongue (%)	0	1 (0.7)
Dizziness (%)	1 (0.7)	3 (2.2)
Flatus (%)	1 (0.7)	0
Nausea and vomiting	5 (3.7)	8 (5.8)
Diarrhea (%)	5 (3.7)	5 (3.6)
Constipation (%)	0	1 (0.7)
Dizziness (%)	3 (2.2)	3 (2.2)
Headache (%)	2 (1.4)	1 (0.7)
Pruritus (%)	1 (0.7)	3 (2.2)
Abdominal pain (%)	2 (1.4)	2 (1.4)
Malaise (%)	8 (5.9)	3 (2.2)
Anxiety (%)	0	2 (1.4)
Severity of side effect (%)		
None	83 (61.9)	84 (61.8)
Mild	38 (26.9)	35 (25.7)
Moderate	9 (6.7)	12 (8.8)
Severe	4 (2.9)	5 (3.7)
Overall side effect (%)	51 (38)	52 (38.2)

^aThe frequencies of drug side effects were not statistically different between the two groups.

(>95% eradication rate), B: good (90–95%), C: fair (85–89%), D: poor (81–84%), and F: unacceptable (≤80%) [20].

Some studies have shown good to excellent eradication rates by hybrid therapy [12,13,18]. On the other hand, there are studies in which the eradication rates were suboptimal [15–17]. In our study, the PP eradication rate by PACT-14 hybrid regimen was 92.8%. But when duration of therapy decreased to 10 days, the eradication rate also decreased to 83%, being considered as a poor result ($p < .05$).

In Taiwan, where resistance rates to clarithromycin and metronidazole are low, Wu et al. [12] reported good to excellent eradication rates by 10-, 12-, and 14-

day hybrid therapies (95, 95.1 and 93.4%, respectively). In that study, lowering the duration of therapy did not lead to decrease in eradication rates. Also, Hsu et al. [13] reported 99.1% per-protocol (PP) eradication rate by 14-day hybrid therapy in Taiwan.

In Iran, the only study evaluating the effects of hybrid therapy had reported 92.9% eradication rate by 14-day regimen, which is considered “good” according to Graham’s classification [18]. In the present study, although the eradication rate by 14-day hybrid regimen was good (92.8%), lowering the duration of therapy from 14 to 10 days resulted in significant decrease in eradication rate.

The difference in the eradication rates by 10-day hybrid therapy in Taiwan and Iran might have been related to the differences in the pattern of antibiotic resistance. Contrary to Taiwan, Iran is a country with high clarithromycin and metronidazole resistance rates [21–24]. On the other hand, in the study by Wu et al., the duration of quadruple therapy in the second phase was 7 days, but in our study was 5 days. This is another possible explanation for the discrepancies in the results of the two studies.

According to a systematic review by Francesco et al. in 2010, the overall *H. pylori* antibiotic resistance rates varied from 1.4% for tetracycline up to 26.7% for metronidazole. Prevalence rates of clarithromycin, metronidazole, and levofloxacin resistance significantly increased from Europe to Asia, America, and Africa, respectively [25]. According to Graham’s papers, no clarithromycin-containing quadruple therapy should be used if dual resistance is >15%. However, although the rate of clarithromycin and metronidazole resistance is high in Iran, we designed the present study due to the acceptable eradication rate achieved by hybrid regimen in the previous study performed in this country.

Similar to the results of the previous study performed in Iran, the most common side effect was metallic taste, without significant difference between the two groups [18]. Compliance to treatment was excellent in both groups. Four patients in 10-day regimen and five patients in 14-day regimen had severe adverse effects leading to discontinuation of therapy. The rates of side effects were similar to the previous study performed in Iran [18].

The present study had a number of limitations. As antibiotic resistance is the most important cause of treatment failure, the major weakness of the present study was the lack of antimicrobial susceptibility pattern of *H. pylori*. However, the latest study in the same geographic region has reported 73.4% resistance to metronidazole, 30% to clarithromycin, and 21.2% resistance to both metronidazole and clarithromycin [22]. The

next limitation was diagnosing *H. pylori* infection by just one method (RUT or pathology). It was better to confirm the diagnosis by another method. Another issue is the exclusion of nonulcer dyspepsia patients from the study. According to Iranian Gastroenterology Association, eradication therapy is not recommended in this subset of patients because of the high prevalence rate of *H. pylori* infection and high rates of antibiotic resistance. Consequently, alternative regimens without clarithromycin, such as the bismuth quadruple therapy, merit further investigation in our geographical area.

In conclusion, it seems that 14-day hybrid therapy is an acceptable regimen for *H. pylori* eradication in Iran, but shorter duration therapy cannot be an alternative option. On the other hand, due to the high cost of clarithromycin, we recommend further studies to compare the 14-day hybrid regimen with a nonclarithromycin-containing quadruple therapy in Iran.

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