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Comparison of Hybrid and Sequential Therapies for *Helicobacter pylori* Eradication in Iran: A Prospective Randomized Trial

Hossein Sardarian, Hafez Fakheri, Vahid Hosseini, Tarang Taghvaei, Iradj Maleki and Marjan Mokhtare

Department of Gastroenterology, Mazandaran University of Medical Sciences, Sari, Mazandaran, Iran

Keywords
Helicobacter pylori, clarithromycin, sequential, hybrid, Iran.

Reprint requests to: Hafez Fakheri, MD, Professor of Gastroenterology, Department of Internal Medicine, Imam Hospital, PO Box: 48166-33131, Sari, Iran. E-mail: fakher42@yahoo.com

Abstract

Background: The eradication of *Helicobacter pylori* has been always a concern. In the present study, we aimed to compare two novel treatments in Iran.

Method: Four hundred and twenty patients with peptic ulcer and naïve *H. pylori* infection were randomized in the study. Two hundred and ten patients received hybrid therapy: pantoprazole 40 mg/b.i.d. and amoxicillin 1 g/b.i.d. for 14 days plus 500 mg clarithromycin and 500 mg tinidazole, both twice daily for the last 7 days. The other 210 patients received sequential therapy: 40 mg pantoprazole/b.i.d. for 10 days and 1 g amoxicillin/b.i.d. for the first 5 days, followed by 500 mg clarithromycin/b.i.d. and 500 mg tinidazole/b.i.d. for the last 5 days. C^{1}-urea breath test was performed 8 weeks after the treatment.

Results: Three hundred and ninety-six patients (197 patients in the hybrid group and 199 patients in the sequential group) completed the study. The compliance rates were 96.7 and 98.6% for the two groups, respectively. The intention-to-treat eradication rate was 89.5% (95% CI = 85.4–93.6) for the hybrid group and 76.7% (95% CI = 71–82.4) for the sequential group ($p = .001$), and the per-protocol eradication rates were 92.9% (95% CI = 89.2–96.5) and 79.9% (95% CI = 74.1–85.4) for the hybrid and sequential groups ($p = .001$), respectively. Severe adverse effects were observed in 2.4% of patients in the hybrid group and 3.8% of those in the sequential group.

Conclusion: According to our results, sequential regimen does not seem to be an appropriate therapy for *H. pylori* eradication in the Iranian population, whereas hybrid therapy showed to be more effective. However, considering the high cost of clarithromycin in Iran, we recommend further studies to compare hybrid therapy with bismuth-containing regimens or to assess the effects of hybrid therapies with periods shorter than 14 days.

About 50% of the adult population is infected with *Helicobacter pylori* and it is the major risk factor for gastritis, peptic ulcer, gastric adenocarcinoma, and mucosa-associated tissue lymphoma [1].

Until recently, the gold standard regimen for *H. pylori* eradication consisted of triple therapy with a proton-pump inhibitor (PPI) plus clarithromycin and amoxicillin or metronidazole, administered for 7–14 days [2,3]. However, the increasing bacterial resistance has lowered the average eradication rate with PPI-based triple regimens to below 80% [4,5] which is unacceptable. Thus, ethical issues have been raised regarding the continued prescription of standard triple therapy, and new strategies have been proposed to replace it as the first line of treatment.

One novel therapy is sequential therapy, starting with a simple double regimen of a PPI plus amoxicillin for 5 days, followed by a triple regimen of a PPI, clarithromycin, and tinidazole for the next 5 days [6]. Several randomized studies (including pooled data and

meta-analysis) indicated the sequential regimen to be more efficient compared with the standard triple therapy [7–11].

If we consider *H. pylori* infection as an infectious disease, an ideal treatment should be able to eradicate the infection in more than 95% of cases. Graham classified the efficacy of *H. pylori* eradication regimens based on per-protocol (PP) success as follows: (A) excellent (>95%); (B) good (90–95%); (C) fair (85–89%); (D) bad (81–84%); and (F) unacceptable (<80%) [12]. Sequential therapy, however, was not demonstrated reliably to achieve 95% PP eradication rate.

A recent report from Taiwan used a hybrid protocol, starting with a double regimen or a PPI and amoxicillin for 7 days, and followed by quadruple regimen of a PPI, amoxicillin, clarithromycin, and metronidazole for the next 7 days. The PP and intention-to-treat (ITT) eradication rates were 99 and 97%, respectively [13]. In this study, we compared the sequential and hybrid regimens for *H. pylori* eradication in a region of Iran with high resistance to metronidazole and clarithromycin.

Methods

Four hundred and twenty *H. pylori*-positive patients with endoscopically confirmed peptic ulcer or gastric/duodenal erosions were enrolled in the study. *H. pylori* infection was documented by antral biopsy (Giemsa staining) and/or rapid urease test (RUT, Shim-anzym, Tehran, Iran). Upper endoscopy and antral biopsies were performed using Pentax upper endoscopes (Video gasteroscope HD EG-2990i with Video processor HD EPK-i, Tokyo, Japan, 2010 and Video gasteroscope EG-2985K with Video processor EPK-1000, Tokyo, Japan, 2011). All patients were naïve to *H. pylori* treatment, and written informed consent was obtained from all patients. Our study was approved in the ethic committee of Mazandaran University of Medical Sciences (MAZUMS number: 90–107, 1375), and the proposal was also registered in Iranian Registry of Clinical Trials (IRCT: 201110312499N2).

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

Demographic information, history of nonsteroidal anti-inflammatory drugs (NSAIDs) consumption, smoking, previous upper gastrointestinal bleeding (GIB), and some endoscopic findings including ulcers (duodenal or gastric), erosions (duodenal or gastric), 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 [14].

The patients were randomly enrolled to either of the two groups using a computer-generated randomization: 210 patients received (PA_{14}–CT_7): Pantoprazole (40 mg/b.i.d.) and amoxicillin (1000 mg/b.i.d.) for 2 weeks and tinidazole and clarithromycin (each 500 mg/b.i.d.) just during the second week in the hybrid group. The other 210 patients received ($P_{10}A_5$–CT_5): Pantoprazole (40 mg/b.i.d.) for 10 days, amoxicillin (1000 mg/b.i.d.) for the first 5 days, and tinidazole plus clarithromycin (each 500 mg/b.i.d.) just during the second 5 days in the sequential group. The patients were given both verbal and written instructions about the importance of taking the medications regularly and were recommended not to stop medication in the event of mild to moderate side effects. Patients recorded side effects of medications on a daily basis and were advised to call the doctors if side effects were severe.

Hybrid and sequential groups were visited after 14 and 10 days, respectively. They were also asked about their compliance to treatment, number of remaining drugs (if any), and side effects. The severity of side effects was classified as 0 = no side effect; 1 = mild side effects (no limitation in daily activities); 2 = moderate (partial limitation in daily activities); and 3 = severe (profound limitation in daily activities). The compliance to treatment was considered to be excellent if the patient had consumed more than 80% of prescribed medications, good for 60–80% medication consumption, and poor for <60%. Ten weeks after starting the treatment, *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 composition (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 Analyser, 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

We assumed to have about 13% difference between the two regimens in their ability to eradicate *H. pylori*

infection and we considered $\alpha = 0.05$ and $\beta = 0.80$. Therefore, 123 patients were needed for each group. We also assumed a 20% withdrawal rate; therefore, the sample size was calculated to be at least 148 for each group. This study was performed for first time in our country. So to improve the accuracy of the study, we considered a larger sample size. Therefore, the study was designed for 420 patients.

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 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 final results was blind to the assignment of patients.

Results

Four hundred and twenty patients were enrolled in the study. Demographic characteristics, history of GIB or NSAIDs intake, smoking and endoscopic findings were not statistically different between the two groups (Table 1).

Table 1 Demographic, clinical characteristics, and endoscopic findings of the patients[a]

Variable	Hybrid therapy	Sequential therapy
Male/Female	106/104	97/113
Age (mean ± SD; years)	43.43 ± 12.87	41.93 ± 13.44
Smokers, n (%)	8 (3.5)	8 (3.5)
History of GIB, n (%)	17 (8.1)	20 (9.5)
History of NSAID consumption, n (%)	6 (2.9)	14 (6.7)
Duodenal ulcer, n (%)	114 (54)	90 (43)
Gastric ulcer, n (%)	30 (14)	43 (20)
Duodenal ulcer + Gastric ulcer, n (%)	4 (0.2)	7 (1.4)
Erosive duodenitis, n (%)	27 (12)	26 (12)
Erosive gastritis, n (%)	42 (20)	56 (26)
Bulb deformity, n (%)	32 (15.2)	21 (10)

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

[a]*p*-Values < .05 were considered significant, and there were not any statistically significant differences between the two groups in any of the above characteristics.

Three hundred and ninety-six patients completed the study: 197 patients in the hybrid and 199 in the sequential groups. Thirteen (3%) patients had missed follow-up and not returned for UBT (5 in hybrid and 8 in sequential groups). Five (1.2%) patients had drug withdrawal due to severe side effects (3 in hybrid and 2 in sequential). Among the patients, 5 (1.2%) had <80% compliance (4 patients in hybrid and 1 in sequential groups) and therefore were not included in PP analysis. Compliance rates were 96.7% in the hybrid and 98.6% in the sequential groups.

The ITT eradication rates were 89.5% (95% CI = 85.4–93.6) in the hybrid group and 76.7% (95% CI = 71–82.4) in the sequential group ($p = .001$). PP eradication rates were 92.9% (95% CI = 89.2–96.5) and 79.9% (95% CI = 74.1–85.4; $p = .001$), respectively (Fig. 1; Table 2).

Also, 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 effects of therapy are shown in Table 3. The most common side effects were bitter taste in both groups: 38 patients (18.2%) in the hybrid and 25 patients (12%) in the sequential group. But the severity of total side effects did not significantly differ between the two groups. Severe side effects were rare: five patients (2.4%) by hybrid therapy and eight patients (3.8%) by sequential therapy. Three patients discontinued treatment owing to severe adverse events in the hybrid group (epigastric pain: 2 patients; epigastric pain, nausea, vomiting, and bitter taste: 1 patient). Only one patient discontinued therapy because of severe vomiting and bitter taste in the sequential group. Most of adverse reactions occurred in the second half of therapy.

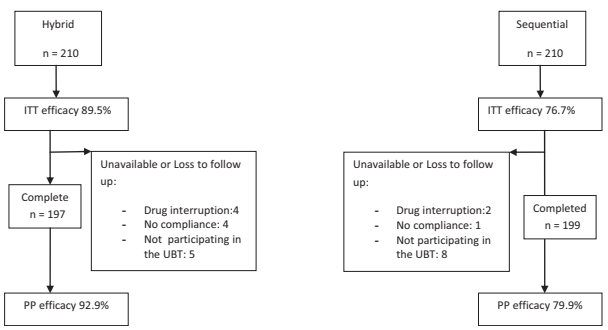

Figure 1 Flow chart of method of follow up and treatment efficacy. ITT, intention-to-treat; PP, per-protocol.

Table 2 Efficacies of hybrid and sequential therapy in *Helicobacter pylori* eradication

	Hybrid therapy		Sequential therapy			
Variable	Patients	Eradication rate, %	Patients	Eradication rate, %	95% Confidence interval	*p*-Value
Intention-to-treat analysis	188	89.5	161	76.7	85.4–93.6	.001
Per-protocol analysis	183	92.5	159	79.9	89.2–96.5	.001

Table 3 Adverse effects reported by the patients during treatment

Adverse effect	Hybrid therapy (n = 210)	Sequential therapy (n = 210)	Total (n = 420)
Bitter taste	38	25	63
Epigastric pain	3	11	14
Nausea and vomiting	4	7	11
Burning tongue	5	0	5
Dizziness	4	3	7
Flatus	3	2	5
Diarrhea or constipation	2	2	4
Pruritus	2	0	2
Fever	1	0	1
Rash	2	0	2
Miscellaneous	8	8	16
Severity of side	n (%)		
None	151 (71.9)	158 (75.2)	309 (73.6)
Mild	46 (21.9)	41 (19.6)	87 (20.7)
Moderate	8 (3.8)	3 (1.4)	11 (2.6)
Severe	5 (2.4)	8 (3.8)	13 (3.1)

Discussion

The eradication rate of *H. pylori* has been declining with triple drug regimens, leading to the introduction of new treatment protocols [4,5]. In this study, we compared the efficacy of two novel therapies, namely sequential and hybrid therapies, for *H. pylori* eradication. With hybrid therapy, we found the eradication rates of 92.9% for PP and 89.5% for ITT analyses, while with sequential therapy, the PP and ITT eradication rates were 79.9 and 76.7%, respectively.

In Iran, according to a study published in 2006, the resistance rates for clarithromycin and metronidazole were 2.4 and 35%, respectively [15] rising to 9.4 and 72.6% in 2007 [16]. In 2011, another report from Iran indicated 30% resistance to clarithromycin, 73.4% resistance to metronidazole, 6.8% resistance to amoxicillin, 21.2% double resistance to clarithromycin and metronidazole, and 12.1% resistance to clarithromycin, metronidazole, and amoxicillin in the region where the present study was conducted [17]. Although we did not conduct susceptibility tests prior to our study to determine antibiotic resistance (which is the main limitation of our study), it is established that double resistance to metronidazole and clarithromycin is highly found in *H. pylori* infection in Iran. A study by Hsu et al. [13] in Taiwan reported 7% resistance to clarithromycin, 2% resistance to amoxicillin, and 56% resistance to metronidazole. In the latter study, PP analyses found 99.1% eradication rate [13]. Also, in the study performed by Hsu et al. [13], only five patients in the hybrid group had strains of *H. pylori* with dual resistance to clarithromycin and metronidazole, but the eradication rate of hybrid therapy for those strains with dual resistance was 100%. In fact, Taiwan has low rates of resistance to antibiotics, which makes excellent (grade A) results expectable [18]. On the other hand, in our region, where a different resistance pattern exists, our therapy yielded grade B results, indicating that hybrid therapy may be acceptably implemented even in areas with high resistance to clarithromycin, metronidazole, and double resistance.

Several large, multicenter studies have reported high eradication rates with sequential therapy [19–22]. Some Asian studies, however, could not indicate sequential therapy to be the superior option [23–26]. Similarly, some Italian studies indicated acceptable eradication rates with sequential therapy, not ideal efficacy [27,28].

A number of factors may play a role in determining the geographic and regional differences in *H. pylori* eradication rates, including more triple and quadruple drug therapies than dual therapy, longer duration of treatment, genetic differences in the PPIs metabolism, regional differences in antimicrobial resistance, degree of gastritis, and the nature of the underlying disease [29].

In a study by Wu et al. [21], patients with double resistance to clarithromycin and imidazole were indicated to have significantly poorer eradication rates following sequential therapy (32.3 vs 95.1%). Provided that the prevalence of double resistance to clarithromycin and metronidazole is on the rise, the efficacy of

sequential regimens will diminish [30,31], and this may account for the unacceptable eradication rates found with sequential therapy in our study that was conducted in a region with high rates of double resistance. On the other hand, because we did not have direct data about the pattern of resistance in our patients, the difference between the eradication rates by the two regimens might have also been influenced by the different therapy duration (14 vs 10 days).

According to our results, it seems that hybrid therapy is more effective than sequential therapy in treating those strains of *H. pylori* with dual resistance to clarithromycin and metronidazole. This theoretical superiority may be the result of lower resistance with concurrent administration of three drugs or the longer period of treatment with each drug (14 days for amoxicillin and 7 days for clarithromycin and tinidazole).

In our study, adverse reactions occurred in 28.1% of patients treated with hybrid therapy, whereas Hsu reported 14.5% adverse events [13]. Severe adverse reactions were found in 2.4% of our patients in the hybrid group and only three patients discontinued therapy due to complications: two patients for epigastric pain and one patient for epigastric pain, nausea, vomiting, and bitter taste. Although the compliance rates did not statistically differ between the two groups, a threefold increased risk of incomplete therapy following hybrid therapy was observed during our study (3.8 and 1.4% in hybrid and sequential therapy, respectively). This might have been due to the longer duration of therapy in the hybrid regimen.

We found the most common side effect to be bitter taste, although it resulted in therapy discontinuation for only one patient. The pattern of severe adverse events in our study is similar to that of Hsu et al. [13].

The major limitation in the present study was the lack of susceptibility tests prior to therapy. Moreover, proper compliance with hybrid therapy may be an issue as one of the patients started taking all the drugs simultaneously despite our written recommendation. On the other hand, in Iran, the prices of clarithromycin-containing regimens are significantly high. The prices of the whole course of therapy with the mentioned hybrid and sequential therapies are 30.37 and 20.55 US dollars, respectively, and the prices of clarithromycin for a complete 7-day (as in hybrid therapy) and 5-day regimen (as in sequential therapy) are 21.69 and 15.49 US dollars, respectively.

In conclusion, a hybrid therapy spanning 14 days accomplished a grade B (>90%) eradication rate for *H. pylori* in a region with high rates of double resistance to clarithromycin and metronidazole. Nevertheless, considering the high cost of clarithromycin in Iran, we recommend further studies to compare the current hybrid therapy with cheaper bismuth-containing regimens or to evaluate the effects of hybrid therapies with shorter periods of treatment.

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Competing interests: the authors have no competing interests.

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