

A New Modified Concomitant Therapy for *Helicobacter pylori* Eradication in Turkey

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Keywords

Eradication, *Helicobacter pylori*, metronidazole, resistance.

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Abstract

Background: *Helicobacter pylori* eradication rates have tended to decrease recently, mostly due to antibiotic resistance. In the present study, our aim was to determine Hp eradication rate with the LAC plus tid metronidazole regimen and the secondary objective of this study was to identify an effective regimen for our population.

Methods: Eighty-four Hp-positive patients with non-ulcer dyspepsia were assigned into the same group. Patients were administered the classical LAC protocole (lansoprazole 30 mg bid, amoxicillin 1 g bid and clarithromycin 500 mg bid for 14 days) plus metronidazole 500 mg tid for 14 days. Gastroscopy and histopathological assessment were performed before enrollment and C¹⁴ urea breath test and stool antigen test were performed 6 weeks after treatment.

Results: All 84 patients completed the study. No patient left the study because of drug side effect. Total eradication rate was 75% (63/84).

Conclusion: Although LAC plus tid metronidazole regimen achieved a much better eradication rate compared with the standard LAC regimen; this is the first study that has a relatively low success with a concomitant therapy. So in areas of high resistance like Turkey, one cannot expect a high success with any clarithromycin containing regimen and those should be avoided.

The current standard first-line treatment to eradicate *Helicobacter pylori* is a triple therapy combining a proton-pump inhibitor (PPI, double dose) with two antibiotics, mainly clarithromycin (500 mg b.i.d.) and amoxicillin (1 g b.i.d.) or metronidazole (500 mg b.i.d.; LAC), according to worldwide guidelines, including the Maastricht III Consensus Report [1–3]. Although this combination has been shown to be effective in numerous clinical trials, the success rate varies widely, ranging from 50 to 70% [4–6]. Many studies on the efficacy of triple therapy have reported poor results, especially in some Mediterranean regions [7,8]. In fact, the cure rates for first-line 14-day triple therapy in Turkey barely reach 50–60% [9].

Treatment failure may occur because of inadequate patient compliance or bacterial resistance. The widespread use of macrolide antibiotics for respiratory tract infections and the rise in clarithromycin resistance may play a role. According to the literature, clarithromycin resistance reaches 38.5% in Turkey [10]. A 10-year

epidemiological analysis (1996–2005) in the Turkish population reported a gradual decrease in eradication success from 80% to 60% with a PPI, amoxicillin, and clarithromycin [11].

According to our clinical observations, we think that the eradication rate of *H. pylori* with the standard first-line therapy is much lower in Istanbul, Turkey. Our intention was to overcome this resistance with a modification (Metronidazole three times daily instead of twice daily) of the concomitant therapy (Also called; four drug, three antibiotic, non-bismuth containing therapy). Although the Maastricht III Consensus Report proposed metronidazole as an alternative for amoxicillin and the drug itself has high rates of primary resistance (Up to 40% in some regions); recent clinical experience says the opposite with reported excellent results [12]. These findings encouraged us to plan this study.

In the present study, our aim was to determine *H. pylori* eradication rate with the LAC plus tid metronidazole regimen and the secondary objective of this

study was to identify an effective regimen for our population. The relatively low economic burden of the new regimen is also impressive.

Material and Methods

Patients

Between January and December 2009, consecutive patients, naive to *H. pylori* treatment, aged >18 years with histologically proven *H. pylori* infection were enrolled in this prospective trial in a single center at the Istanbul Education and Research Hospital.

The principal exclusion criteria were a previous attempt of *H. pylori* eradication and administration of PPIs, histamine (H₂)-receptor blockers, NSAIDs, bismuth salts or antibiotics within the previous 6–8 weeks. Pregnant or breastfeeding women, patients with a history of gastric surgery, presence of liver dysfunction or renal failure, alcohol abuse, and known allergy to the prescribed antibiotics were also excluded. Written informed consent was obtained from each patient before enrollment and the study protocol was approved by the local ethics committee of our institute.

Study Design and Treatment

This was a 14-day, open-label, prospective, single center study. After the enrollment procedure, 84 patients were assigned into the same group. Patients were administered the classical LAC protocol (lansoprazole 30 mg b.i.d, amoxicillin 1 g b.i.d and claritromycin 500 mg b.i.d for 14 days) plus metronidazole 500 mg t.i.d for 14 days. Compliance was done by pill count and the patients were actively interviewed about side effects (nausea, vomiting, diarrhea etc.) during the treatment period. No antibiotics, PPI or H₂-receptor blockers were allowed prior to the control eradication test. Successful eradication of bacteria was defined as a negative C¹⁴-UBT (Carbon-14 urea breath test) and a negative *H. pylori* stool antigen test result 6 weeks after the end of treatment.

Histology

During upper endoscopy, two biopsies were taken from the prepyloric antrum and two from the gastric body. Biopsy specimens were fixed in 4% buffered formalin, embedded in paraffin wax, sectioned, and mounted on slides. Sections were stained with Giemsa and hematoxylin-eosin and examined by a single pathologist who was blinded to the endoscopic findings and C¹⁴-UBT results. The activity of gastritis and density of *H. pylori*

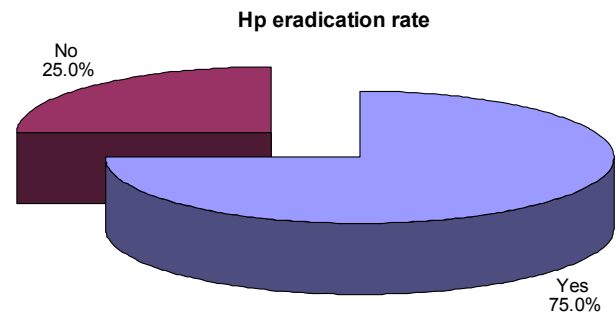


Figure 1 Distribution of *Helicobacter pylori* Eradication Status.

Table 1 Distribution of patient demographics

	Min–Max	Median ± SD
	17–85	44.55 ± 14.26
Age	n	%
Gender		
Male	37	44.0
Female	47	56.0
<i>Helicobacter pylori</i> eradication status		
Eradicated	63	75.0
Not eradicated	21	25.0

colonization were graded according to the updated Sydney System on a scale of 0–3 (0 = none, 1 = mild, 2 = moderate, 3 = severe) [13].

Statistics

All statistical calculations were performed with Number Cruncher Statistical System (NCSS) 2007&PASS 2008 Statistical Software (Utah, USA). Besides standard descriptive statistical calculations (mean, median and standard deviation), Student *t* test was used in the assessment of parameters with normal distribution. Mann–Whitney *U* test was used in the assessment of parameters without normal distribution. Chi square test was used in the evaluation of qualitative data. Spearman's rho correlation analysis was also used in the evaluation of the correlations of parameters. The statistical significance level was established at $p < .05$.

Results

All patients who enrolled in the study had non-ulcer dyspepsia (dyspeptic complaints and gastritis and/or duodenitis at endoscopy) and had positive histology. The age and gender distribution of patients who completed the study is shown in Table 1.

All 84 patients completed the study. The average age of the patients was 44.55 ± 14.26 years (Age interval 17 and 85 years, median 43.5 years). Thirty-seven were male (44%) patients and 47 were female (56%) patients. In 75% of patients (98% CI = 67–82%; $n = 63$), *H. pylori* was eradicated; in 25% of patients *H. pylori* was not eradicated (95% CI = 17–32%; $n = 21$) (Figure 1).

The most frequent side effects were nausea and metallic taste in the mouth. However, these reported side effects were mild and well tolerated. No patient left the study because of drug side effect.

Discussion

Helicobacter pylori is one of the most important clinical causes of gastroduodenal diseases. Eradication criteria were defined in the Maastricht III report, published by the European *H. pylori* Study Group in 2005. Test-and-treat is an accepted approach in high-prevalence locations such as Turkey; however, resistance to antibiotics is an important problem and some have reported that *H. pylori* eradication rate is decreasing worldwide [14].

In our region, results with standard triple therapy are far lower than expected [9]. In fact, it is estimated that *H. pylori* eradication fails in at least 40–50% of patients after standard therapy based on clarithromycin and amoxicillin [9,10]. In a large, randomized-controlled trial performed in Turkey, *H. pylori* eradication rates achieved with an omeprazole + clarithromycin + amoxicillin regimen for 7 and 14 days were 24% and 43%, respectively [15]. A meta-analysis by Aydın et al. [10] documented that the average *H. pylori* eradication rate with PPI-based triple regimens was 93.3% in 1996 and decreased to 47.1% in 2004. Decreases in eradication rates may be attributed to antibiotic resistance, especially clarithromycin resistance.

There are some studies on the use of metronidazole as second-line drug for the treatment of *H. pylori* infection. In a meta-analysis; PPI, bismuth, metronidazole and tetracyclin containing quadruple therapy regimen was found to provide a high eradication rate [16]. Nowadays, for local populations with high resistance rates, it is recommended to use treatments such as; a 14 day concomitant quadruple regimen containing a PPI, amoxicillin, clarithromycin, and a nitroimidazole [17]. On the contrary, this is the first study that has a relatively low success with concomitant therapy. So; in areas of high resistance like Turkey, one cannot expect a high success with any clarithromycin containing regimen and those should be avoided.

This 14-day regimen uses inexpensive and safe drugs. The protocol is also modified by means of using t.i.d metronidazole instead of b.i.d. Adding metronidazole

on the standard triple therapy has not caused a remarkable increase on the well-known side effects [18] of the standard triple therapy, since none of the 84 patients stopped the medications. Adding 500 mg t.i.d metronidazole to the standard therapy and turning it into a quadruple second-line therapy, increases success rates in a statistically proven manner.

Turkey is a difficult region in terms of *H. pylori* eradication therapy and both first and second line therapies have been providing lower success over time. There are data that sequential and concomitant therapy are equal and both are effective in areas where clarithromycin resistance is not very high and dual resistance is also uncommon [19]. In Turkey, both clarithromycin and metronidazole resistance are common and in our study, concomitant therapy gave lower results than has been previously reported. However, the eradication rate was better than most regimens in Turkey although still below what is currently considered 'acceptable'.

Acknowledgements and Disclosures

Competing interests: the authors have no competing interests.

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