

# A multicenter, randomized, prospective study of 14-day ranitidine bismuth citrate- vs. lansoprazole-based triple therapy for the eradication of *Helicobacter pylori* in dyspeptic patients

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**Background/aims:** Proton-pump inhibitor- and ranitidine bismuth citrate-based triple regimens are the two recommended first-line treatments for the eradication of *Helicobacter pylori*. We aimed to compare the effectiveness and tolerability of these two treatments in a prospective, multi-centric, randomized study. **Materials and Methods:** Patients with dyspeptic complaints were recruited from 15 study centers. Presence of *Helicobacter pylori* was investigated by both histology and rapid urease test. The patients were randomized to either ranitidine bismuth citrate 400 mg bid plus amoxicillin 1 g bid plus clarithromycin 500 mg bid (n=149) or lansoprazole 30 mg bid plus amoxicillin 1 g bid plus clarithromycin 500 mg bid (n=130) treatment arm for 14 days. Adverse events have been recorded during the treatment phase. A <sup>13</sup>C urea breath test was performed 6 weeks after termination of treatment to assess the efficacy of the therapy. Eradication rate was calculated by intention-to-treat and per-protocol analysis. **Results:** Two hundred seventy-nine patients (123 male, 156 female) were eligible for randomization. In per-protocol analysis (n=247), *Helicobacter pylori* was eradicated with ranitidine bismuth citrate- and lansoprazole-based regimens in 74,6% and 69,2% of cases, respectively (p>0,05). Intention-to-treat analysis (n=279) revealed that eradication rates were 65,1% and 63,6% in ranitidine bismuth citrate- and in lansoprazole-based regimens, respectively (p>0,05). Both regimes were well-tolerated, and no serious adverse event was observed during the study. **Conclusion:** Ranitidine bismuth citrate-based regimen is at least as effective and tolerable as the classical proton-pump inhibitor-based regimen, but none of the therapies could achieve the recommendable eradication rate.

**Key words:** Ranitidine bismuth citrate, lansoprazole, *Helicobacter pylori*, eradication

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## Dispeptik hastalarda *Helicobacter pylori* eradikasyonu için 14 günlük ranitidin bizmut sitrat vs lansoprazol tabanlı üçlü tedavi; çok merkezli, randomize, prospektif çalışma

**Giriş ve Amaç:** Proton pompa inhibitörü ve ranitidin bizmut sitrat bazlı üçlü tedavi rejimleri *Helicobacter pylori* eradikasyonunda ilk basamak tedavi olarak önerilir. Çok merkezli prospektif, randomize bir çalışma ile bu iki tedavi rejiminin etkinlik ve tolere edilebilirliğini araştırmayı amaçladık. **Gereç ve Yöntem:** On beş çalışma merkezinden dispeptik yakınmaları olan hastalar seçildi. Hem histolojik hem de hızlı üreaz testi ile *Helicobacter pylori* pozitifliği tanımlanan hastalar belirlendi. Hastalar 14 gün boyunca günde ikişer defa olmak üzere ya ranitidin bizmut sitrat 400 mg + amoksisilin 1 g + klaritromisin 500 mg ya da lansoprazol 30 mg + amoksisilin 1 g + klaritromisin 500 mg kullanacak şekilde randomize edildi. Tedavi süresince yan etkiler kaydedildi. Tedavi bitiminden 6 hafta sonra <sup>13</sup>C üre nefes testi ile *Helicobacterin* eradike olup olmadığına bakıldı. Etkinlik intension to treat ve per protocol analizleri ile değerlendirildi. **Bulgular:** 279 hasta randomizasyona uygundu (123 erkek, 156 kadın). Per protocol analizinde (247 hasta) ranitidin bizmut sitrat bazlı tedavinin ve lansoprazol bazlı tedavinin eradikasyon oranları sırasıyla %74,6 ve %69,2 idi ( $p>0,05$ ). Intension to treat analizinde ise (279 hasta) ranitidin bizmut sitrat bazlı tedavinin ve lansoprazol bazlı tedavinin eradikasyon oranları sırasıyla %65,1 ve %63,6 idi ( $p>0,05$ ). Her iki tedavide iyi tolere edildi ve anlamlı bir yan etki gözlenmedi. **Sonuç:** Ranitidin bizmut sitrat bazlı tedavi klasik proton pompa inhibitörlü tedavi kadar etkin ve tolere edilebilirdir. Ama her iki tedavi de önerilebilir eradikasyon oranlarına ulaşamamıştır.

**Anahtar kelimeler:** Ranitidin bizmut sitrat, lansoprazol, *Helicobacter pylori*, eradikasyon

### INTRODUCTION

It is now very well known that *Helicobacter pylori* (*H. pylori*) infection plays an important role in the pathogenesis of peptic ulcer disease, chronic gastritis, maltoma and adenocarcinoma of the stomach (1), and the eradication of this bacteria significantly reduces the relapse of peptic ulcers (2-5). Recently, it has been shown that *H. pylori* eradication may alleviate dyspeptic symptoms in 20-35% of patients who have functional dyspepsia (6). Currently, drug combinations with 80% eradication rate on intent-to-treat (ITT) analysis or with 90% eradication rate on per-protocol (PP) analysis are approved as effective to treat *H. pylori* (7, 8). Reported *H. pylori* eradication rate of ranitidine bismuth citrate (RBC)-based triple therapy varies between 77 and 98%, by PP analysis (9-10). Proton-pump inhibitors (PPI)-based regimens are effective in 68-95% of cases, by the same analysis (10-11). In our region, the reported efficacy for RBC-based triple therapy is between 58.9 up to 76.7% (12-14). This figures are somehow below the accepted eradication rate. Nevertheless, the power of the aforementioned studies is not enough to conclude that RBC-based therapies are not effective in our country.

In this prospective, multi-centric, randomized study, we aimed to compare the effectiveness and tolerability of two different triple therapies, either using PPI or RBC, in a bigger population that allows concluding whether RBC-based eradication regimen is valuable in Turkey.

### MATERIALS and METHODS

#### Patient Population

From 15 study centers across Turkey, a total of 300 patients (132 male, 168 female) with *H. pylori* infection diagnosed by both invasive test (e.g. rapid urease test) and pathology were assessed for recruitment. All patients had dyspepsia defined as persistent or recurrent upper abdominal pain or discomfort over the preceding 3-month period in accordance with the Rome III criteria. Patients were excluded if they were under 18 years of age, were pregnant, or had been taking aspirin, other non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics, H<sub>2</sub>-receptor blockers, bismuth or PPIs in the preceding 4 weeks. Patients with a history of *H. pylori* eradication or gastric surgery were also excluded. Any patient with current serious medical condition such as severe pulmonary or liver diseases, active malignancy, renal insufficiency with serum creatinine >2.0 mg/dL, gastrointestinal bleeding in the previous 12 weeks was excluded as well. After the exclusion of 21 patients, 279 patients were eligible for randomization. The study protocol was approved by the Institutional Review Board of the Marmara University Medical School. Written informed consent was obtained from all patients who participated in the trial.

#### Diagnosis of *H. pylori* Infection

*H. pylori* infection was diagnosed by both rapid urease test and histopathological examination of biopsy samples. All patients had undergone upper

gastrointestinal (GI) endoscopy and biopsy. One antrum and one corpus biopsy samples were used for rapid urease test, 2 antral and 1 corporal biopsy samples were paraffin embedded, fixed, and stained with both H&E and Giemsa. An experienced pathologist who was blind to all clinical information, including the rapid urease test results, examined the slices. Only patients who had *H. pylori* in both diagnostic modality had been accepted as *H. pylori* positive and were enrolled in the study.

**Treatment Design (Figure 1)**

Patients were randomized to receive one of the following eradication therapies for 14 day: RbAC–triple therapy regimen consisting of RBC 400 mg twice daily + amoxicillin 1000 mg twice daily + clarithromycin 500 mg twice daily or LAC–triple therapy regimen consisting of lansoprazole 30 mg twice daily + amoxicillin 1000 mg twice daily + clarithromycin 500 mg twice daily. Randomization scheme was created by a computer, and all participants were assigned to one of the treatment arms accordingly. During the treatment period, the patients were allowed to take only antacid medication if they had symptoms; side effects and symptoms were recorded in a diary by the patients. At the end of the treatment period, an evaluation visit was performed. Patient compliance was assessed by counting remaining drug tablets. Adverse events were questioned, the obtained verbal complaints were compared with the patient diaries, and evaluation-visit cards were filled in. Six weeks after completion of the assigned triple therapy, presence of *H. pylori* was tested by urea breath test using Helicobacter Test

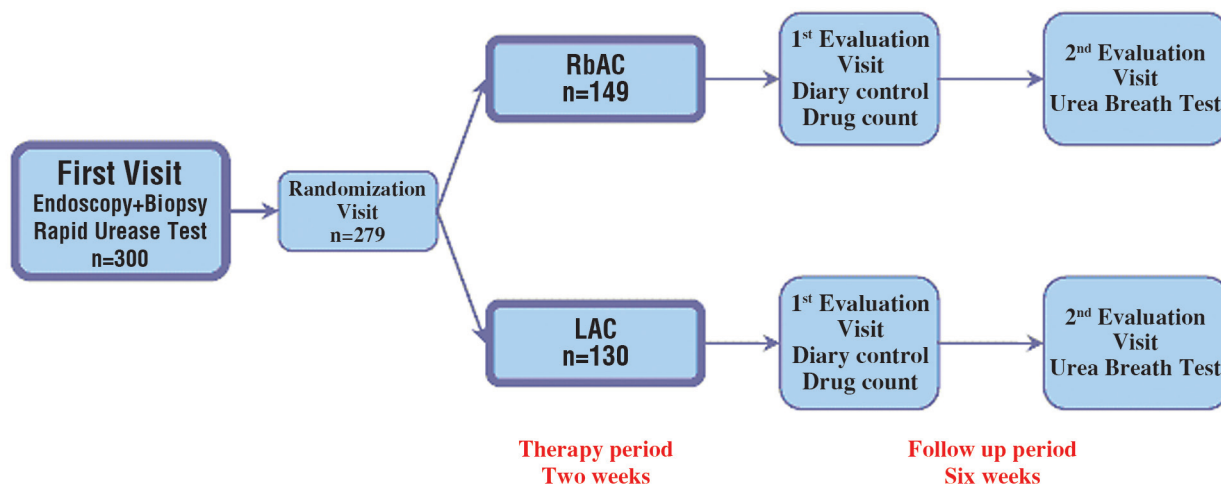
INFAI® kit (INFAI Institute for Biomedical Analytics und NMR Imaging GmbH Universitäts Str, 142, D-44799 Bochum, Germany).

**Statistical Analysis Methods**

Data were presented as median (range). Continuous parameters were compared by student's t-test and the Mann-Whitney U test, as appropriate. Categorical variables were compared with  $\chi^2$ -test, Fisher's exact test between treatment arms. A p-value of <0.05 was considered statistically significant. The ITT analysis included all patients who had taken at least one tablet of drugs. However, in the PP analysis, patients with poor drug compliance (<75% intake of any study drugs) and defaulters were excluded. To establish the sample size, it was assumed that the eradication rate of the most effective treatment was 95% and the least effective was 80%. A two-sided test at the 5% significance level indicated that at least 100 patients in each treatment group would be needed to reach a test power of 90%.

**RESULTS**

Between June and November 2003, 300 patients from 15 study centers across Turkey were recruited, and after exclusion of 21 (8 had antibiotics, 3 pregnant or lactating women, 3 had previous eradication history, 1 had gastric surgery, and 6 did not consent), a total of 279 patients (123 male, 156 female) with an average age of 41,7 (range: 18-65) years were enrolled to the study. 149 (68 male, 81 female) of them were randomized to RbAC group and the remaining 130 (55 male, 75 female) received the LAC treatment. Baseline demographic



**Figure 1.** Study algorithm (RbAC: Ranitidine bismuth citrate, amoxicillin and clarithromycin. LAC: Lansoprazole, amoxicillin and clarithromycin)

**Table 1.** Baseline demographic data and endoscopic findings in the two study groups

	RbAC	LAC
No. of patients	149	130
Mean age: years (range)	40,9 (18-62)	42,6 (19-64)
Male/Female	68/81	55/75
Presence of ulcer	52 (34,9%)	41 (31,5%)

RbAC: Ranitidine bismuth citrate, amoxicillin and clarithromycin.  
LAC: Lansoprazole, amoxicillin and clarithromycin.

**Table 2.** Reasons for exclusion from per protocol population

	RbAC	LAC
Lost the follow-up	10	7
Discontinuation of drugs	3	3
Pregnancy	0	1
Protocol violation	6	2
Total	19	13

RbAC: Ranitidine bismuth citrate, amoxicillin and clarithromycin.  
LAC: Lansoprazole, amoxicillin and clarithromycin.

and endoscopic characteristics of the two groups were comparable as shown in Table 1. A total of 32 patients were excluded after randomization, of whom 19 treated with RbAC and 13 with LAC because of various reasons (Table 2).

### Endoscopic Findings

Ninty three out of the 279 patients were found to have peptic ulcer on upper GI endoscopy. The rest of the patients had either normal endoscopic finding or gastritis of any type. After randomization, 52 of ulcer patients were placed in the RbAC and 41 of ulcer patients were placed in the LAC group.

### Eradication rates

ITT analysis (n=279) showed that *H. pylori* was eradicated in 65,1% of patients in the RbAC group and in 63,6% of those in the LAC group ( $p>0,05$ ) (Figure 2). Eradication rates were 74,6% and 69,2% in the RbAC and LAC groups, respectively ( $p>0,05$ ), in PP analysis (n=247) (Figure 2). Despite the fact the eradication rate seems numerically higher in the RbAC group than in the LAC group, the difference between eradication rates achieved by the two treatment regimens was not statistically significant in either analysis.

### Compliance and Side Effects

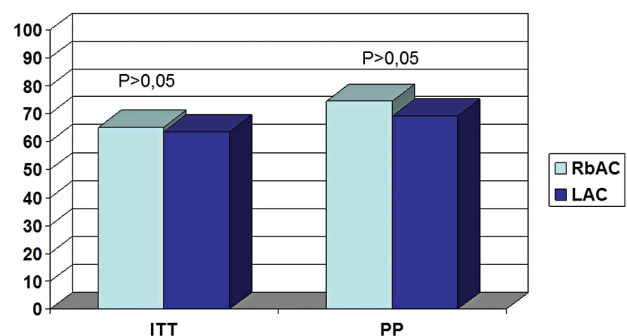
Patient compliance was evaluated at the first visit. All of the participants complied with the suggested treatment, except three patients in each treatment arm who did not take their antibiotics

at the prescribed dose. Similar number of patients reported side effects in both treatment groups (Table 3). The most common side effects were taste disturbance, loose stool/diarrhea, malaise, and dark stools. There were no morbidity that require hospitalization or mortality related to the treatment.

## DISCUSSION

Triple therapy with a PPI or a RBC combined with two antibiotics for more than one week is the most widely accepted choice of various *H. pylori* eradication regimes (7). RBC possesses both the anti-secretory activity of ranitidine and mucosal protective and anti-*H. pylori* effect of bismuth salts (15-17). Combination of RBC and one antibiotic is found to be very effective in *H. pylori* eradication, even though antibiotic therapy should last for 2 weeks (18). Laine et al. reported that a 14-day regimen of RBC, clarithromycin and amoxicillin achieved eradication of *H. pylori* in over 90% of their patients (19). The effectiveness of RBC and clarithromycin combination has been investigated by several other authors and reviews reveal a very encouraging mean eradication rate of 76% (ITT analysis) (18). One head-to-head comparative study has demonstrated that RBC is better than PPI when co-prescribed with clarithromycin (20).

In our trial, *H. pylori* eradication rate was 65,1% in the RbAC group and 63,6% in the LAC group ( $p>0,05$ ) in ITT analysis. This figures were 74,6% and 69,2% for RBC- and lansoprazole-based regimens, respectively ( $p>0,05$ ) in PP analysis. Even though RBC seems to be a little more effective, difference obtained by any of the analysis methods did not reach statistical significance. Keeping in mind that the generally accepted minimum suc-

**Figure 2.** Rates of *H. pylori* eradication in two treatment groups by intention-to-treat (n=279) and per protocol analysis (n=247).

RbAC: Ranitidine bismuth citrate, amoxicillin and clarithromycin.  
LAC: Lansoprazole, amoxicillin and clarithromycin.

**Table 3.** Reported side effects during treatment

	RbAC	Mean duration (days)	LAC	Mean duration (days)
Total number of patients	149		130	
No. of patients reported side effects (%)	81 (54,4)		74 (56,9)	
Taste disturbance (%)	44 (29,5)	2,8	42 (32,3)	3,1
Loose stool / Diarrhea (%)	28 (18,8)	5,3	31 (23,8)	4,9
Malaise (%)	12 (8,1)	4,8	10 (7,7)	4,7
Dark stool (%)	27 (18,1)	6,0	14 (10,8)	4,4
Nausea (%)	11 (7,4)	5,1	10 (7,7)	5,0
Others (%)	13 (8,7)	5,1	6 (4,6)	4,5
Total number of episodes	216		187	

RbAC: Ranitidine bismuth citrate, amoxicillin and clarithromycin. LAC: Lansoprazole, amoxicillin and clarithromycin.

cess rate of treatment regimens to cure *H. pylori* infection is 80%, neither RbAC nor LAC group reached an acceptable rate to eradicate *H. pylori* in our study.

The success rates of the same regimens vary widely between different parts of the world. For instance, the ITT rates achieved in Hong Kong by Sung *et al.* were 94% and 88% for RBC- and omeprazole-based triple therapy regimens, respectively (10), while Spinizi *et al.* reported their eradication rates as 61% and 77%, respectively in Northern Italy (9). From USA, Laine *et al.* reported their eradication rate with RbAC as 92% and 96% by ITT and PP analysis, respectively (19). The diversity between communities and geographical areas due to host and environmental factors requires this combination to be tested in different communities. In our region, the efficacy rates of RBC-based triple therapies are reported between 58.9 up to 76.7% (12-14). The compliance of the patients and the methods chosen to determine eradication are also important factors. The eradication rates we achieved in both groups are lower than those reported in other parts of the world, but our results are similar to our regional reports. We did not analyze *H. pylori* resistance and antibiotic sensitivity in this study. Thus, we can only speculate that lower eradication rates that we achieved reflect emerging antibiotic resistance (especially resistance to clarithromycin) in Turkey (21).

Patient compliance was good since only 6 of 279 patients discontinued the treatment in this study.

Adverse reactions, detected by face-to-face interview at the first evaluation visit and by checking patient diaries filled out during the treatment phase, were all mild and were similar to previously reported ones (23). Taste disturbance, the most frequently encountered complaint, was probably related to clarithromycin, and the two groups had similar rates of taste disturbance. Dark stool, a well-documented side-effect of bismuth subcitrate, was reported more frequently in the RbAC group. In general, both regimens are well-tolerated by most of the patients.

Reported efficacy of PPI plus amoxicillin plus clarithromycin therapies are around 60% (13,22), and this figure corroborates well our results.

The major weakness of the current study is that it evaluates patients with peptic ulcer and non-ulcer dyspepsia together since it is well known that eradication success is somehow lower in patients who have functional dyspepsia. Although the percentage of the patients who had peptic ulcer was similar in both treatment arms, still non-homogeneous patient population may limit extrapolation of our results.

In conclusion, two weeks of RBC- or lansoprazole-based triple therapies have similar efficacy to eradicate *H. pylori* infection and have similar tolerability albeit none of them could achieve acceptable eradication rate. Further studies searching for antibiotic resistance and alternative therapies based on those studies are needed.

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