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Effectiveness of ranitidine bismuth citrate and proton pump inhibitor based triple therapies of *Helicobacter pylori* in Turkey

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Background: *Helicobacter pylori* infection is the main cause of gastritis, gastroduodenal ulcer disease, MALT lymphoma, and adenocarcinoma of the stomach. The reported prevalence of *H. pylori* in the adult population in Turkey is 67.6%–81.3%. A national meta-analysis showed that the average *H. pylori* eradication rate with proton pump inhibitor-based triple regimens in Turkey had decreased from 84% in 1997 to 55.3% in 2004, suggesting a need to evaluate alternative regimens.

Materials and methods: The study was a prospective, single-center trial with a parallel group design. After the selection procedure, consecutive out-patients were assigned to one of six study groups using random sampling numbers. All patients received amoxicillin 1,000 mg b.i.d. and clarithromycin 500 mg b.i.d. along with ranitidine bismuth citrate 400 mg b.i.d., or omeprazole 20 mg b.i.d., or lansoprazole 30 mg b.i.d., or rabeprazole 20 mg b.i.d., or pantoprazole 40 mg b.i.d., or esomeprazole 40 mg b.i.d. for 14 days.

Results: When we look at the eradication rates of the treatment groups, only two groups (ranitidine bismuth citrate and rabeprazole groups) had eradication rates greater than 80%, both at intention to treat and per protocol analyses. The other four groups (omeprazole, lansoprazole, pantoprazole, and esomeprazole groups) showed statistically significant lower eradication rates both at intention to treat (between 57.6 and 66.7%) and per protocol (between 60.3 and 72.1%) analyses when compared with ranitidine bismuth citrate and rabeprazole groups ($p < .05$).

Conclusion: Ranitidine bismuth citrate and/or rabeprazole based triple therapies must be preferred for the first-line treatment of *H. pylori* infection.

Keywords: *Helicobacter pylori*; *eradication*; *esomeprazole*; *lansoprazole*; *omeprazole*; *pantoprazole*; *rabeprazole and ranitidine bismuth citrate*

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Helicobacter pylori (*H. pylori*) infection is the main cause of gastritis, gastroduodenal ulcer disease, and mucosa associated lymphoid tissue lymphoma and adenocarcinoma of the stomach. Prevalence of *H. pylori* infection in adults varies in different parts of the world depending on the social and economic standards of the population. While the prevalence among the middle-aged population in developing countries is about 80%, it is only 20%–50% in developed countries (1, 2). The reported prevalence of *H. pylori* in the adult population in Turkey is 67.6%–81.3% (3–5). The treatment of *H. pylori* is still a big challenge in the era of rising antibiotic resistance. The Maastricht III consensus report recommended proton pump inhibitor (PPI) or ranitidine bismuth citrate (RBC) based triple regimen with clarithromycin and amoxicillin or metronidazole as first-line therapy (6). The strong inhibition of gastric acid secretion with PPIs made it the treatment of choice for many clinicians. Therefore, standard triple therapies containing a proton pump inhibitor and two antibiotics are the most commonly used treatments for *H. pylori* eradication in clinical practice. Consensus conferences have recommended therapeutic regimens that achieve *H. pylori* cure rates higher than 80% on an 'intention-to-treat' (ITT) basis (6, 7). However, during the last few years, several studies have reported ITT eradication rates lower than 75% (8–11) and even lower than 50% (12, 13) with PPI-based regimens. A national meta-analysis showed

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that the average *H. pylori* eradication rate with PPI-based triple regimens in Turkey had decreased from 84% in 1997 to 55.3% in 2004 (14), suggesting a need to evaluate alternative regimens.

In this study, we aimed to investigate the current success rate with 2 weeks of RBC-based and PPI-based triple therapy regimens for eradication of *H. pylori*.

Patients and methods

The study was a prospective study including consecutive *H. pylori* positive dyspeptic and peptic ulcer patients referred to our gastroenterology clinic. During endoscopy, two antrum and two corpus biopsies were taken for histological examination and, in addition, two antrum biopsies were taken for rapid urease test. A patient was considered to be infected when both tests (histology and rapid urease test) were found positive. The exclusion criteria were under 18 years of age, pregnancy, presence of clinically significant comorbidities (insulin dependent diabetes mellitus, neoplastic diseases, coagulopathies and severe hepatic, renal or cardiorespiratory diseases), previous gastric surgery, known allergies to any of the drugs used in the study, and previous *H. pylori* eradication therapy. The protocol was approved by the local ethical committee and informed consent was obtained from all of the patients.

The study was a single-center trial with a parallel group design. After the selection procedure, consecutive outpatients were assigned to one of six study groups using random sampling numbers. We put six cards with numbers between one and six on them in a pocket, then the patient picked one of them. When all of the cards were picked, we put them back into the pocket and started the picking again. All patients received amoxicillin 1,000 mg b.i.d. and clarithromycin 500 mg b.i.d. along with RBC 400 mg b.i.d. (RBC-AC group), or omeprazole 20 mg b.i.d. (OAC group), or lansoprazole 30 mg b.i.d. (LAC group), or rabeprazole 20 mg b.i.d. (RAC group), or pantoprazole 40 mg b.i.d. (PAC group), or esomeprazole 40 mg b.i.d. (EsAC group) for 14 days. Patients were advised of the possibility of having a metallic taste, nausea, and diarrhea during the treatment period. Compliance was evaluated at the end of the treatment by pill count and was considered good if more than 90% of medication had been taken. *H. pylori* eradication was defined as a negative ^{13}C-urea breath test (UBT) performed 6–8 weeks after completion of the eradication therapy. The UBT was carried out by operators unaware of therapy and patients' past *H. pylori* status.

Statistical analysis

The Chi-square test was used to determine the difference in eradication between the groups. Both ITT and per protocol (PP) analyses were performed. Independent *t*-test was used for determination of difference in age and two proportions test for the difference in gender, smoking, and the use of aspirin and NSAIDs. A *p*-value less than 0.05 was considered significant. All statistical analyses were performed using the SPSS 13 software.

Results

There were 396 patients randomized for the study (66 patients for each of the six study groups). Seventeen patients were dropped from the study (Table 1). Five patients were stopped taking drugs because of side effects (two allergies, two diarrhea, and one numbness). Five patients were excluded from the study because of poor compliance and seven patients lost to follow-up. When we look at the characteristics (sex, age, smoking status, and aspirin or NSAID usage) of the groups, we cannot detect any statistical difference between the groups. Also, there is no difference between the groups according to the etiology, nearly one-fourth of the patients of all of the groups had peptic ulcer disease and the rest had *H. pylori* gastritis.

When we look at the eradication rates of the treatment groups (Table 1), only two groups had eradication rates greater than 80%, both at ITT and PP analyses. These are the RBC-AC and RAC groups. The other four groups (OAC, LAC, PAC, and EsAC groups) showed statistically significant lower eradication rates both at ITT (between 57.6 and 66.7%) and PP (between 60.3 and 72.1%) analyses when compared with the RBC-AC and RAC group ($p < 0.05$).

Table 2 shows eradication rates of the different subgroups. We cannot detect any difference between males and females, smokers or non-smokers, aspirin users or non-users, NSAID users and non-users, and lastly the peptic ulcer group and *H. pylori* gastritis group.

Discussion

The Maastricht III consensus report recommended PPI- or RBC-based triple regimen with clarithromycin and amoxicillin or metronidazole as first-line therapy (6). Consensus conferences have recommended therapeutic regimens that achieve *H. pylori* cure rates higher than 80% on an ITT basis (6, 7). However, recent studies from many countries have reported the failure of these regimens (8–13). A national meta-analysis showed that the average *H. pylori* eradication rate with PPI-based triple regimens in Turkey had decreased from 84% in 1997 to 55.3% in 2004 (14).

Bismuth exerts a direct bactericidal effect on *H. pylori*. To date, no resistance to bismuth has been reported. The RBC has been developed as a unique novel compound that presents, on one hand, the antisecretory activity of ranitidine and, on the other, the mucosal protective and anti-*H. pylori* effects of certain other bismuth salts (15, 16). Furthermore, the frequency or the severity of adverse

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Table 1. Characteristics of the patients and eradication rates in the six groups

Characteristics	RBC-AC	OAC	LAC	RAC	PAC	EsAC
Number of patients (ITT)	66	66	66	66	66	66
Reason for drop out						
Side effects	1	1	2	1	0	1
Poor compliance	1	1	1	0	1	1
Lost to follow-up	1	0	2	1	1	1
Number of patients (PP)	63	64	61	64	64	63
Age (mean ± SD)	36.2 ± 10.4	39.6 ± 12.6	38.9 ± 11.6	35.3 ± 7.7	37.6 ± 10.2	36.4 ± 8.4
Male/female	37/26	35/29	35/26	37/27	33/31	37/26
Smoker number (%)	26 (41.3%)	26 (40.6%)	23 (37.7%)	24 (37.5%)	25 (39.1%)	23 (36.5%)
Aspirin user number (%)	8 (12.7%)	9 (14.1%)	7 (11.5%)	10 (15.6%)	10 (15.6%)	9 (14.3%)
NSAID user (%)	10 (15.9%)	15 (23.4%)	12 (19.7%)	14 (21.9%)	12 (18.8%)	12 (19.1%)
Peptic ulcer number (%)	14 (22.2%)	14 (21.9%)	16 (26.2%)	16 (25%)	17 (26.6%)	16 (25.4%)
Eradication number (%)	54/66 (81.8%)*	42/66 (63.6%)	44/66 (66.7%)	54/66 (81.8%)*	40/66 (60.6%)	38/65 (57.6%)
Intention to treat Per protocol	54/63 (85.7%)*	42/64 (65.6%)	44/61 (72.1%)	54/64 (84.4%)*	40/64 (62.5%)	38/63 (60.3%)

*$p < 0.05$ according to other groups.

Abbreviations: RBC: ranitidine bismuth citrate, A: amoxicillin, C: clarithromycin, O: omeprazole, L: lansoprazole, R: rabeprazole, P: pantoprazole, Es: esomeprazole, NSAID: non-steroid anti-inflammatory drugs.

Table 2. Eradication rates in different subgroups

Characteristic	Group	Total number	Eradicated number (%)
Completion of study	All patients	396	272 (68.7%)
	Completed study	379	272 (71.8%)
Gender	Male	214	147 (68.7%)
	Female	165	125 (75.8%)
Smoking	Yes	147	103 (70.1%)
	No	232	169 (72.8%)
Aspirin use	Yes	53	40 (75.5%)
	No	326	232 (71%)
NSAID use	Yes	75	50 (73.3%)
	No	304	217 (71.4%)
Peptic ulcer *H. pylori* gastritis	—	94	68 (72.3%)
	—	285	204 (71.6%)

Note: Statistically significant difference was not present between the groups.

effects reported with PPI- and RBC-based regimens has been similar. A meta-analysis showed that the efficacy of RBC-based triple regimens was similar or even higher than that based on PPIs, perhaps due to a synergistic interaction of RBC with some antibiotics (17).

One recently published trial compared a 10-day bismuth-based regime containing metronidazole, tetracycline, and omeprazole (OBMT) against a 7-day course of triple therapy with OAC. Eradication rates were 93.3% with OBMT and 69.6% with OAC in the PP population ($p < 0.001$) and 79.8 and 55.4%, respectively, in the ITT population (18). An older study that looked at a 14-day OBMT regime had showed an eradication rate of 95% by ITT analysis (19). An *in vitro* synergy between RBC and clarithromycin or tetracycline against resistant *H. pylori* strains makes the combination of these drugs more logical than PPI-based *H. pylori* eradication therapies as first-line treatment (20). Also, bismuth-based therapies have an efficacy of 76% in second-line therapy on the basis of pooled analysis (21). In Turkey, clarithromycin resistance has reached to 50% (22). The eradication rate of RBC-based triple regimens reported from Turkey varies between 74.6 and 95.9%. In one of these studies, an 80% eradication rate was reported in clarithromycin-resistant cases with RBC, amoxicillin, and clarithromycin (22). So our RBC-based triple therapy success rate was consistent with the international and national results.

Our PPI-based triple therapy results were as expected with the exception of rabeprazole-based triple therapy. Rabeprazole can achieve optimal acid suppression since the first administration and can maintain this advantage in the following days of therapy. Moreover, rabeprazole has the highest pKa ($\sim$5.0, the pH at which a drug becomes 50% protonated); hence, the molecule can be activated at higher pH levels much faster than other PPIs. Due to its peculiar catabolic pathway, i.e. a prevalent metabolism through a non-enzymatic pathway, rabeprazole is less susceptible to the influence of genetic polymorphisms for *CYP2C19* (which encodes a member of the cytochrome P450 superfamily), resulting in minor influences on its pharmacokinetics and pharmacodynamics (23). A recently done meta-analysis concluded that the efficacy of first-line triple therapies based on omeprazole and lansoprazole at the standard doses is dependent on *CYP2C19* genotype status, which appears not to affect the efficacy of the regimens including rabeprazole (24).

Antibiotics have varying stability at acid pH. Amoxicillin is unstable at low pH, but its half-life is still 15 hours at a pH of 2. In contrast, clarithromycin is particularly sensitive to degradation with acid and has a half-life of less than 1 hour at pH 2 (25). Rabeprazole, as we mentioned, provides reliable control of gastric acid secretion, with more potent antisecretory activity than that in other PPIs such as omeprazole and lansoprazole, a more rapid rise in intragastric pH, and less effect of *CYP2C19* on its metabolism (23–26). So, the use of PPIs, especially rabeprazole, in antimicrobial regimens that contain clarithromycin is particularly important in preventing degradation of clarithromycin by acid.

The *H. pylori* eradication rate by triple therapy based on a PPI, amoxicillin, and clarithromycin is thought to be affected by age, smoking habits, drug compliance, polymorphisms of the CYP2C19 gene, drug susceptibility, and clarithromycin resistance (27). In particular, clarithromycin resistance is viewed to have a large effect on

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the eradication rate. That arises from the big deterioration in eradication rate from about 80.6 to 98.3% for clarithromycin susceptible bacteria to 0%–33.3% for clarithromycin resistant bacteria (28). On the other hand, the eradication rate for triple therapies is reported to depend on the degree of acid secretion suppression, in addition to clarithromycin resistance, and the importance of acid secretion suppression has also drawn attention (29). It is thought that the PPIs ability to suppress acid secretion affects the eradication more for clarithromycin-resistant *H. pylori*. While the eradication rates in omeprazole and lansoprazole groups decreased significantly over time, no apparent decline in eradication rate was seen for the rabeprazole group (27). Also, rabeprazole itself is indicated to possess antibiotic effects against *H. pylori* and it might have helped as well.

In the current situation where prevalence of primary resistance to clarithromycin increased, it was difficult to ascertain the reasons why differences arose in the effectiveness of *H. pylori* eradication by acid secretion-suppressing agents and triple therapy based on a PPI. However, the eradication rate for large-scale triple therapy using rabeprazole is reported to be good and to be $\geq$90% in spite of an increase in the clarithromycin resistance in recent years (30). But most of the studies reported in the literature were from Japan and China. There are two studies from Turkey reporting rabeprazole-based treatment success. The first one was a national report that detected 90% eradication rate with 14 days rabeprazole, amoxicillin, and clarithromycin therapy in 10 patients (31). The second one was a modified sequential therapy (rabeprazole and amoxicillin 7 days followed by rabeprazole, metronidazole, and levofloxacin for 7 days) that reported 82.5% ITT and 86.7% PP eradication rates in the treatment of naive patients (32). So together with these results we can suggest that when using PPI-based triple therapy, it is more logical to prefer rabeprazole. But before recommending routine use of rabeprazole we have to test this on a larger scale, and also in patients with documented clarithromycin resistant *H. pylori*. The selection of a PPI should also be important in first-line eradication today and we need to make it clearer thereafter.

Ranitidine bismuth citrate emerged in 1991 as a highly effective drug, but the lack of worldwide availability and a fall in the product's promotion have led to a limited use of this valuable compound. Rabeprazole is the last developed and probably most potent PPI that have different features (has the highest pKa between the PPIs, more potent and rapid rise in intragastric pH, and less effect of *CYP2C19* polymorphism on its metabolism). In conclusion, according to our results, RBC and/or rabeprazole-based triple therapies must be preferred for the first-line treatment of *H. pylori* infection.

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