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Comparison of ranitidine bismuth citrate, tetracycline and metronidazole with ranitidine bismuth citrate and azithromycin for the eradication of *Helicobacter pylori* in patients resistant to PPI based triple therapy

PPİ temelli üçlü tedaviye dirençli hastalarda *Helicobacter pylori* eradikasyonu için ranitidine bismuth citrate, tetracycline ve metronidazole ile ranitidine bismuth citrate ve azithromycin'in karşılaştırılması

Engin ALTINTAŞ[1], Oğuz ULU[2], Orhan SEZGİN[1], Özlem AYDIN[3], Handan ÇAMDEVİREN[4]

Mersin University Medical Faculty Hospital of Department of Gastroenterology[1], Department of Internal Medicine[2], Depatment of Pathology[3], Department of Biostatistics[4], Mersin

Background/aims: *Helicobacter pylori is the most common infectious disease all over the world. Ten to twent parcent of the patients remain infected despite treatment with proton pump inhibitors (PPIs), amoxicillin and clarithromycin. We compared PPI, bismuth, tetracycline and metronidazole with ranitidine bismuth citrate, tetracycline and metronidazole in cases resistant to PPIs-based triple therapies.* ***Methods:*** *The study included 52 patients who underwent a triple therapy with PPI, clarithromycin and amoxicillin for 14 days between September 2001 and December 2002, and were found to be resistant to the therapy. They were randomized to take ranitidine bismuth citrate (Rb) 400 mg twice a day, tetracycline (T) 1 g twice a day and metronidazole (M) 500 mg three times a day for 14 days (RbTM), or ranitidine bismuth citrate (Rb) 400 mg twice a day for 14 days and azithromycin (A) 500 mg once a day for 7 days (RbA). Four weeks after the treatment, endoscopies were repeated, and patients were assessed with respect to changes in symptoms. When H. pylori was negative on histological analysis and urease test, eradication was achieved.* ***Results:*** *A total of 52 patients, 32 females and 20 males with a mean age of 49±12 years, were included in the study. Eradication was achieved in 15 (28%) out of 52 patients in total. There was a significant difference between RbA and RbTM groups (p-0.01). In fact, H. pylori was eradicated in 3 (12%) out of 25 patients in the RbA group, whereas it was eradicated in 12 (44.4%) out of 27 patients in the RbTM group. Symptom scores significantly improved in both groups after the treatment, though there was not a significant difference between the groups (p-0.705).* ***Conclusions:*** *Triple therapy including azithromycin does not seem to be a good choice in cases resistant to the first line therapies; however, a similarly lower rate of eradication was achieved with the quadruple therapy proposed. Therefore, different treatment schemes should be applied in resistant patients, and further studies are needed as well.*

Keywords: *Helicobacter pylori,* eradication, bismuth

Amaç: *Dünyadaki en yaygın infeksiyöz etkendir. Proton pompa inhibitörleri (PPİ), amoxycillin ve clarithromycin ile tedaviye rağmen hastaların %10-20'si infekte kalmaya devam etmektedir. Biz PPİ temelli üçlü tedavilere dirençli olgularda PPİ, bismuth, tetracycline ve metronidozole ile ranitidine bismuth citrate, tetracyclin ve metronidazole'ü karşılaştırdık.* ***Yöntem:*** *Çalışma Eylül 2001 ile Aralık 2002 arasında PPİ, clarithromycin ve amoxycillin'e dirençli 52 hastayı kapsamaktadır. Hastalar ranitidine bismuth citrate (Rb) 400 mg günde iki kez, tetracycline (T) lgr günde iki kez ve metronidazole (M) 500mg günde üç kez 14 gün (RbMT) veya ranitidine bismuth citrate (Rb) 400 mg günde iki kez 14 gün ve azithromycin (A) 500mg günde bir kez 7 gün olacak şekilde randomize edildi. (RbA). Tedavi bitiminden dört hafta sonra, endoskopik inceleme tekrarlandı, ve hastalar semptomlardaki düzelme yönünden değerlendirildi. Histolojik değerlendirmede ve üreaz testinde H. pylori negatif olduğunda, eradikasyon kabul edildi.* ***Bulgular:*** *Elli iki hastanın, 32'si kadın, 20'si erkekti ve ortalama yaş 49±12 yıldı. Eradikasyon 52 hastanın 15'inde (%28) sağlandı. RbA ve RbTM gruplarının rarsında anlamlı bir fark vardı (p-0.01). Gerçekte, H. pylori RbA grubundaki 25 hastanın 3'ünde (%12) eradike olurken, RbTM grubundaki 27 hastanın 12'sinde (%44.4) eradike olmuştu. Semptom skoru her iki grupta anlamlı şekilde düzeldi, ancak gruplar arasında anlamlı bir fark yoktu (p=0.705).* ***Sonuç:*** *Birinci basamak tedavisine dirençli olgularda azithromycin içeren tedaviler iyi bir seçenek değildir. Ancak, benzer şekilde dörtlü tedavi ile de düşük oranlı eradikasyon elde edilmiştir. Bu nedenle, dirençli olgularda farklı tedavi şemaları denemelidir, ve daha fazla çalışmaya gerek vardır.*

Anahtar kelimeler: *Helicobacter pylori,* eradikasyon, bizmut

Address for correspondence: Engin ALTINTAŞ
Mersin Üniversitesi Tıp Fakültesi Hastanesi
Zeytinlibahçe Caddesi, Eski Otogar Yanı Mersin, Turkey
E-mail: enginaltintas@mersin.edu.tr

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INTRODUCTION

Helicobacter pylori (H. pylori) is the most common infectious disease throughout the world, and it is associated with peptic ulcer, atrophic gastritis, MALT lymphoma and stomach adenocarcinoma. Although there have been various drugs used for its eradication until now, currently the treatment of choice is a combination of amoxicillin, clarithromycin, and proton pump inhibitors (PPIs) used for 7-10 days (1). It is also suggested that patients resistant to this first line therapy should be given a quadruple therapy including omeprazole, bismuth, tetracycline and metronidazole (OBTM) (1).

The aim of the present study was to compare two eradication regimens including bismuth in patients resistant to triple therapies including PPIs, which are considered as standard treatment modalities at present.

MATERIALS AND METHODS

The study included 52 patients who underwent a triple therapy with PPI, clarithromycin and amoxicillin for 14 days between September 2001 and December 2002, and were found to be resistant to this therapy. Persistence of *H. pylori* in the fast urease test and on histological examination was considered as resistance to *H. pylori* treatment with PPI, amoxicillin and clarithromycin. The study did not include patients who received antibiotics and bismuth in the past month, those who had hepatic, cardio-respiratory or renal diseases, and those who had diabetes, malignancy, coagulopathy or history of gastric surgery. All eligible patients gave their written consent. A total of 52 patients were randomized to take either ranitidine-bismuth citrate (Rb) 400 mg twice a day, tetracycline (T) 1 g twice a day, and metronidazole (M) 500 mg three times a day for 14 days (RbTM), or ranitidine-bismuth citrate (Rb) 1 g twice a day for 14 days and azithromycin (A) 500 mg once a day for 7 days (RbA). The patients were subjected to routine laboratory tests, and their history, physical examination and concomitant treatment regimens were recorded. Their complaints (pain in epigastrium, swelling, nocturnal pain and pyrosis) were graded according to the Licert scale (0=none, l=mild, 2=moderate, 3=severe, 4=very severe). On endoscopy, two biopsies were obtained from the antrum and two biopsies from the corpus for pathological examination and a biopsy from the antrum for urease test. The pathological assessment was based on the Sydney classification for gastritis and Watherspoon-Doglioni classification for gastric maltoma. Four weeks after the treatment, endoscopies were performed and patients were assessed with respect to changes in their symptoms. Absence of *H. pylori* on histological analysis and urease test was considered as eradication of the disease. The patients were asked how many of the prescribed drugs they took to determine whether they complied with the treatment. Compliance was graded as 100% when a patient never forgot to take the drugs, 80-99% when s/he forgot it only for one day, 60-79% for two days and less than 59% for more than two days. The side effects which led to discontinuation of treatment were recorded.

Statistical analysis

The definitive statistics were calculated (mean ± SD, numbers and % values). For age comparison in the groups, simple analysis of variance was used while gender, smoking, NSAID use, alcohol consumption, eradication status and the relationship among the groups were determined by Pearson chi-square test. The differences in the symptom scoring between the eradicated and non-eradicated were investigated by Wilcoxon test separately before and after the eradication. Furthermore, a t-test was applied to compare the improvement rates in the separate symptom scoring between the eradicated and the non-eradicated in relation to the difference between the rates in the groups.

RESULTS

Of 52 patients, 32 were female and 20 male, and the mean age of the patients was 49 ± 12 years. Twenty-seven patients were assigned into the RbTM group and 25 into RbA. Demographic features of the patients in both groups are shown in (Table 1). No significant difference was observed between the two groups in age, gender, smoking and NSAID use. Two patients in RbA group did not receive the drugs for two days due to nausea, swelling and diarrhea, and three patients in the

Table 1. Demographic features of patients

	RbTM	RbA	P
Age	47±9	49±12	NS
Gender (F/M)	16/11	16/9	NS
Smoking	21/6	20/5	NS
Alcohol	23/4	21/4	NS
NSAID	19/8	18/7	NS

RbTM: Ranitidine-bismuth citrate, tetracycline, metronidazole;
RbA: Ranitidine-bismuth citrate and azithromycin

RbTM group did not receive their drugs for two days due to nausea and metallic taste in their mouth. However, they later complied with their regimen. Patient compliance was 100% except for five patients in both groups. A successful eradication was achieved in 3 (12%) of 25 patients in the RbA group and in 12 (44.4%) of 27 patients in the RbTM group (Figure 1). A significant difference was observed in the eradication between the groups (p=0.01). Eradication was achieved in 15 (28%) of 52 patients, in total. There was a significant difference in symptom scores obtained before the treatment and those obtained after the treatment. However, no significant difference was found between the groups (p=0.705). There were significant improvements in the severity of endoscopic gastritis in both groups before and after the treatment (p=0.01); however, no significant difference was found between the groups (p=0.600).

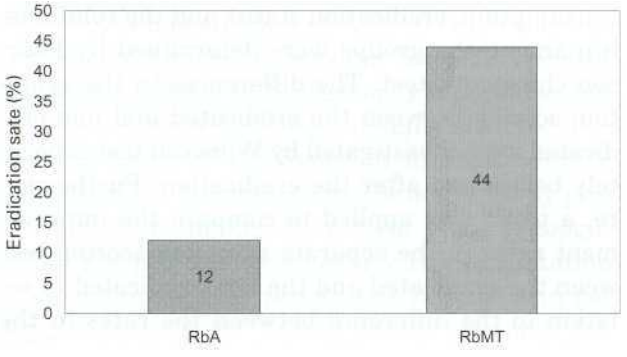

Figure 1. Eradication rates in groups

DISCUSSION

Although recent antibiotic regimens provide higher eradication rates of H. pylori, 10-20% of the patients remain infected (2). Those patients have a high risk for the recurrence of ulcer and its complications. It is still argued whether or not an antibiotics sensitivity test should be performed in resistant cases after the first line therapy (3). It is suggested that it is convenient if the antibiotics given in first line therapy are not repeated, or the treatment period is extended by the addition of bismuth in cases where samples for culture are not available. And if the second line therapy fails, samples should be taken and the treatment should be planned accordingly (3).

A variety of choices are available for cases in which the most common treatment regimen consisting of PPI, amoxicillin and clarithromycin fails, and many of those choices have been already assessed. However, at present what is suggested is treatment with OBTM for a period of 14 days in cases resistant to the first line therapy (4). Eradication rates are reported to range from 63% to 93% with the quadruple therapy proposed (5-11). In Mersin and its environs, the eradication rates with triple therapies including PPIs are low (12-14). Information about treatment possibilities for resistant patients is very restricted in our region and in our country as well. In the present study, we compared the proposed quadruple therapy regimen with the triple therapy including azithromycin.

Use of ranitidine or omeprazole in quadruple therapy as an antisecretory agent in resistant patients did not result in any difference in eradication rates (9). Therefore, we employed a preparation consisting of ranitidine and bismuth salt in combination, which increased compliance. In a study comparing OBTM with RbTM, ranitidine bismuth citrate in combination provided significantly higher rates of eradication than omeprazole alone (3). Therefore, we administered raniditine bismuth citrate to the patients resistant to the first line therapy. An eradication rate of 44% was achieved in the RbTM group. The rate of eradication was low, although drug-compliance was over 95%. To our knowledge, there has been no study on resistance to metronidazole. Host related factors, differences in *H. pylori* strains or resistance to antibiotics might have lowered eradication.

Azithromycin is an antibiotic of the azalid family like clarithromycin. It has an excellent in vitro efficacy in *H. pylori,* and its concentration in gastric mucosa is much higher than it was in the plasma (15). Its single dose per day is also valuable in compliance with the treatment. For this reason, it replaced clarithromycin in several other studies, most of which lasted shorter periods of time (2-7 days) like in our study. Eradication rates were reported to range from 44% to 93% with azithromycin (16-20). There have been few studies in the literature on *H. Pylori* treatment with ranitidine bismuth citrate and azithromycin. The sample size of the studies on azithromycin in resistant patients has been rather small. Eradication rates were reported to range from 40% to 70% in studies on omeprazole and azithromycin in the first line therapy (21-23). In these studies, eradication rates seemed to increase with azithromycin 1 g used for 10 days; however, there was a rise in side effects

correspondingly. We gave azithromycin 500 mg daily for 6 days. A small number of patients experienced mild side effects. The eradication rate was 12%, which was very low. This lower rate of eradication might be associated with the cross resistance against clarithromycin administered during the first line therapy. We obtained a lower eradication rate of 45% in our previous study, and then proposed that clarithromycin might have played a role in the outcome. However, we have not conducted a resistance study to verify our proposition.

In conclusion, triple therapy including azithromycin does not seem to be a good choice in cases resistant to the first line therapy, and yet quadruple therapy also resulted in lower eradication rates. Therefore, it is necessary to evaluate the efficacy of different treatment schemes in resistant patients.

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