Low eradication rate of *Helicobacter pylori* with triple 7-14 days and quadriple therapy in Turkey

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Abstract

AIM: The eradication rate of *Helicobacter pylori* (*H pylori*) shows variation among countries and regimens of treatment. We aimed to study the eradication rates of different regimens in our region and some factors affecting the rate of eradication.

METHODS: One hundred and sixty- four *H pylori* positive patients (68 males, 96 females; mean age: 48±12 years) with duodenal or gastric ulcer without a smoking history were included in the study. The patients were divided into three groups according to the treatment regimens. Omeprazole 20 mg, clarithromycin 500 mg, amoxicillin 1 g were given twice daily for 1 week (Group I) and 2 weeks (Group II). Patients in Group III received bismuth subsitrate 300 mg, tetracyline 500 mg and metronidazole 500 mg four times daily in addition to Omeprazole 20 mg twice daily. Two biopsies each before and after treatment were obtained from antrum and corpus, and histopathologically evaluated. Eradication was assumed to be successful if no *H pylorus was* detected from four biopsy specimens taken after treatment. The effects of factors like age, sex, *H pylori* density on antrum and corpus before treatment, the total *H pylori* density, and the inflammation scores on the rate of *H pylori* eradication were evaluated.

RESULTS: The overall eradication rate was 42%. The rates in groups II and III were statistically higher than that in group I ($P<0.05$). The rates of eradication were 24.5%, 40.7% and 61.5% in groups I, II and III, respectively. The eradication rate was negatively related to either corpus *H pylori* density or total *H pylori* density ($P<0.05$). The median age was older in the group in which the eradication failed in comparison to that with successful eradication (55 yr *vs* 39 yr, $P<0.001$). No correlation between sex and *H pylori* eradication was found.

CONCLUSION: Our rates of eradication were significantly lower when compared to those reported in literature. We

believe that advanced age and high *H pylori* density are negative predictive factors for the rate of *H pylori* eradication.

INTRODUCTION

Eradication treatment for *H pylori* infection has been generally accepted since the relation between *H pylori* and peptic ulcer disease was established[1,2]. Furthermore, this treatment approach has gained importance since the eradication of *H pylori* was found to reduce the recurrence of duodenal and gastric ulcer[3,4]. The eradication rate of *H pylori* has reached high levels with combined use of antibiotics and proton pump inhibitors (PPIs), being 60-90% in Turkey[5]. Different treatment protocols have been used for *H pylori* eradication. The rate of *H pylori* eradication was higher than 85% with the combination of drugs consisting of two antibiotics and a PPI[6]. We aimed to study the rates of *H pylori* eradication in Cukurova region with regard to different treatment regimens and the effects of patient age, sex, and *H pylori* density on *H pylori* eradication rates.

MATERIALS AND METHODS

One hundred and 64 patients (68 males, 96 females; mean age 48±12 yr, range 17-78 yr) with gastric or duodenal ulcer and *H pylori* detected at endoscopy were included in the study. Two biopsies from antrum and two from corpus were taken. *H pylori* density and gastric inflammation in both antrum and corpus were assessed based on Sydney classification (normal=0, mild=1, moderate=2, marked=3)[7]. The patients were randomly divided into three groups and each group was treated with one of the protocols as follows. Group I received Omeprazole (0) 20 mg, Clarithromycin (C) 500 mg, amoxicillin (A) 1 000 mg, twice daily for 7 d. Group II received the same drugs as in group I for 14 d. Group III received Omeprazole 20 mg twice daily, Bismute subsitrate (BS) 300 mg 4 times daily, tetracycline (T) 500 mg 4 times daily, metronidazole (M) 500 mg 4 times daily for 10 d. There were 53, 59 and 52 patients in the 3 groups, respectively. Antibiotics, PPIs, and H_2 receptor blockers were used for at least one month. Smoking, pregnancy and lactation, past history of gastric surgery, renal or liver failure, diabetes mellitus and irregular use of drugs in the eradication regimens were accepted as exclusion criteria. Endoscopy was repeated and two biopsies each from corpus and antrum were obtained after 45-60 d of treatment. Eradication was accepted to be successful if *H pylori* were not found in any of the 4 samples. Total bacterial density was calculated semi quantitatively by addition of antrum and corpus *H pylori* density[8]. None of the patients had atrophy in histologic evaluation. The relations of *H pylori* densities in

different locations before treatment, age, and sex with the rate of *H pylori* eradication were analyzed.

Statistical analysis

Data were expressed as medians with interquartiles. Mann-Whitney-*U* test or χ^2 test was used to assess significant differences between values in various groups of patients. $P<0.05$ was considered statistically significant. Data were analyzed using the SPSS for Windows (version 9.05; SPSS, Inc., Chicago, Illinois, USA).

RESULTS

Out of 164 patients who completed the study, 69 (42%) had eradication of *H pylori* infection, and 151 (91.4%) showed ulcer healing. Eradication could not be achieved in 10 of 13 patients without ulcer healing. The eradication rate in group I, II, and III was 24.5%(13/53), 40.6%(24/59), and 61.5%(32/52), respectively. The rate of eradication in group III was higher than group I and II ($P<0.03$). There was a difference between groups I and II, which did not reach statistical significance ($P=0.07$). The ulcer cure was 45/53, 55/59, and 51/52, respectively in the 3 groups. *H pylori* density in antrum before treatment or severity of inflammation was not statistically related to its eradication. Corpus and total *H pylori* densities were higher in patients who failed the eradication treatment when compared to those who showed successful eradication ($P<0.01$ and $P<0.05$, respectively for corpus and total densities) (Table1). The median patient age was higher in the group in which eradication failed. (55 *vs* 39 yrs, $P<0.001$). The distribution of age, sex and *H pylori* density of corpus in the patient groups were summarized in Table 2.

Table 1 Rates of *H pylori* eradication and ulcer healing in various treatment regimens

Group	n	Age	F/M	Eradication (%)	Ülcer healing[d] (%)
I	53	49±12	30/23	13 (24.5)[a,b]	45 (84.9)
II	59	48±11	35/24	24 (40.7)[c]	55 (93.2)
III	52	45±12	31/21	32 (61.5)	51 (98)
Total	164	48±12	96/68	69 (42)	151(92.1)

[a]$P=0.07$ *vs* Group II; [b]$P<0.01$ *vs* Group III; [c]$P<0.03$ *vs* Group III; [d]$P=$N.S. among the three groups.

DISCUSSION

The discovery of *H pylori* by Marshall and Warren has been considered as a revolution[9]. As the role of this microorganism in gastric pathologies is fully understood, the treatment principles of some of the gastro-duodenal lesions have been changed[10].

Nowadays, *H pylori*-positive peptic ulcer disease is accepted as an infectious process, and combination of drugs, including the same antibiotics were used in all of the treatment protocols[11-13]. No standard therapy for *H pylori* eradication has been underlined. An ideal *H pylori* treatment must be safe, cheap, easy and tolerable with more than an 80% eradication rate and must have a low rate of antibiotic resistance[14,15].

PPIs are commonly used in the combined regimens as a result of significant *in vivo* and *in vitro* effects on *H pylori*. Many treatment regimens including PPls were still hard to eradicate *H pylori*[16-19].

In Europe and in the USA despite resistance to metronidazole, clarithromycin, and tetracycline was 30-40%, 2-10% and <1%, respectively, the eradication rate of the combined treatment with clarithromycin, PPl and amoxicillin or metronidazole for 7-14 d was 87-100% in metronidazole sensitive group and 57-88% in metronidazole resistant group. In 10-12 d of PPl-A-C regimens, 88-96% eradication rate was maintained in clarithromycin sensitive group and 50% in the resistant group. These findings showed the importance of antibiotic resistance in unsuccessful eradication trials[20]. Several studies, in which the antibiotic resistance was analyzed as one of the independent parameters that can be predictors of eradication failure, supported the same suggestion[21-23]. In Turkey, Boyanova *et al* found the resistance to M 37.9%, to C 9.5%, and to A 0.9%, respectively. The double drug resistance (M+C) was 6.1%[24]. In a former study we found C and M resistance rates were 5.2% (1/19) and 36.8% (7/19) in a group of 19 patients (data unpublished). These observations suggested that antibiotic resistance could not explain completely the low eradication rate as we observed in the present study. The resistance in our patients was similar to that detected in the Western world whereas the rate of eradication was markedly lower when compared to Western population.

The effect of combination therapies on *H pylori* eradication rates varied according to the differences in treatment duration. Some studies which showed that 14 d trials were more successful than 7 d trials, whereas other studies showed no difference. In our study the rate of *H pylori* eradication was higher in prolonged treatment but did not reach any statistical significance[25].

The reported higher rates of *H pylori* eradication with either OCA or OCM combination in early studies in our country as compared to recent ones suggested the development of resistance was due to irregular and unsubscribed use of antibiotics in our population[17]. The possible differences in the production process of drugs by various manufacturers may play a role in the bioavailability of active compounds. We could not find any study regarding to this issue. However, Kim *et al.* from South Korea have found similar benefits in *H pylori* eradication rate of three drug combinations with two different Omeprazole preparations[26]. If similar studies can be made for antibiotics, questions on this matter can be answered.

Patient incompliance to treatment is another factor contributing to eradication failure. Graham *et al* have found that the eradication rate was about 96% in patients who used

Table 2 The distribution of age, sex and *H pylori* density of corpus in the patient groups

Group	Eradicated				Non-eradicated			
	n	Age[a]	F/M	Density	n	Age[a]	F/M	Density
I	13	35.3 ±11.7[a]	9/4	1.31±0.95[b]	40	54.0±9.1[a]	21/19	2.17±0.87[b]
II	24	40.04±9.3[a]	13/11	1.92±0.8[b]	35	54.94±8.8[a]	21/14	2.37±0.77[b]
III	32	40.03±11.6[a]	20/12	1.91±0.69[b]	20	55.15±9.0[a]	12/8	2.35±0.75[b]
Total	69	39.14±10.9[a]	42/27	1.8±0.83[b]	95	54.61±8.9[a]	54/41	2.28±0.79[b]

[a]$P<0.001$, *vs* noneradicated in each group for age, [b]$P<0.05$, *vs* noneradicated in each group for *H pylori* corpus density.

60% or more of their drugs and 69% in those who used less than 60% of drugs[27]. We tried to eliminate this factor via good questioning and follow-up throughout the study. Patient incompliance did not seem to be a determinant factor for H pylori eradication failure in our study.

The response to combination of four drugs was around 87-100% in several studies. Nelson *et al.* found that the ulcer cure and eradication rate of H pylori with BSOMT in a 2 d and 7 d regimen were 95.7% and 76.1%, and 98% and 100%, respectively[11]. In studies using BSTMO combination, the eradication rate of H pylori was 96% in the metronidazole sensitive group and 82% in the metronidazole resistant group[28]. The rate of H pylori eradication with the same protocol in our study was much lower compared to previous trials, but significantly higher than two other protocols we used. This shows the necessity for studying some geographic factors.

Smoking; one of the parameters of antibiotic resistance in literature, was restrained during the inclusion phase of this study. We studied two other factors associated with H pylori eradication failure, namely the grade of H pylori density and gastritis. Our findings suggested that the eradication was more difficult in patients who had high total or corpus H pylori density. Georgopoulos *et al* found no relation between eradication and H pylori density or the severity of gastritis[21]. Yang *et al* reported a lower total bacterial density in the eradicated group[8]. In our study corpus and total (sum of H pylori density in antrum and corpus) H pylori densities were higher in patients with eradication failure compared to the successfully eradicated group. Consequently, the factors affecting H pylori density can be expected to affect the eradication rate. Some studies on this issue showed that some factors related with host or bacteria could affect H pylori density in gastric mucosa[21,29-31].

The patients' lifetime exposure to several kinds of antibiotics could cause resistance and this might partly explain the difference noted in the age groups with respect to H pylori eradication rate[32].

Another factor that can contribute to the resistance to antibiotic treatment is intracellular settling of bacteria. The examples of this fact were some chronic infections such as tuberculosis and brucellosis for which a long term use of antibiotics was required[33,34]. The difficulty in eradication treatment of H pylori may in part be due to intracellular location of these bacteria since H pylori has been shown to penetrate into cells in cell cultures[35]. This suggestion was firmly supported when 14 d regimens were shown to be more effective than 7 d regiments as reported in this and previous studies.

The rate of eradication we encountered was significantly lower than those in literature, which suggests further studies concerning the mechanisms underlying the eradication failure in our community should be designed.

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