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Research Article

CHANGES OF THE EFFECTIVENESS OF TRIPLE ANTIBIOTICS THERAPY OF HELICOBACTER PYLORI

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ABSTRACT

Background: Triple therapy (Proton Pump Inhibitor+Clarithromycin+Amoxicillin or Metronidazol) is widely used throughout the world against Helicobacter pylori. Eradication rates in due course after use of the triple antibiotics therapy were investigated.

Methods: Data of 1000 patients who received the standard therapy between 2000 and 2010 and after 2010 were selected for the study; they were administered PPI, claritromycin 500 mg BID, Amoxicillin 1 g BID for 14 days and the eradication of Helicobacter pylori has been verified using urea breath test after six weeks starting from the cessation of the therapy. 500 patients have got the therapy before 2010; 500 of them were treated after 2010. The decrease in Helicobacter pylori eradication rate after using the standard triple therapy has been discussed.

Results: Retrospective analysis of data from 1000 patients was made. 608 patients (60.8%) had gastric problems except ulcer and 192 patient (19.2%) had duodenal ulcers. During the period between 2000 and 2010, 412 patients (82.4%) got successful Helicobacter pylori eradication treatment; for the period after 2010, 262 patients (52.4%) were successfully treated. Statistically significant difference was found between the groups in terms of Helicobacter pylori eradication results ($p < 0.001$).

Conclusions: In this study it was stated that the eradication rate has been observed in due course was below 80% which is the recommended treatment goal. Despite differences existing between regions in terms of the response to the therapy quadruple therapy including bismuth should be considered as the first choice.

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INTRODUCTION

Helicobacter pylori (H. pylori) which has been discovered first by Marshall and Warren in 1982 is the most common infection around the world. 20 to 50% of the western world, and 80% of developing countries suffer from H. pylori infection. 30% of children and, 50 to 60% of adults are infected with H. pylori around the world. Approximately one million people a year lose their lives due to H.pylori-borne diseases. An important factor for the development of gastritis, gastric and duodenal ulcers, gastric-mucosa-related lymphoma (MALT lymphoma) and adenocarcinoma of the stomach(1-4). All of those infected with these bacteria suffer from gastritis. The risk of contracting peptic ulcers for those infected with H.pylori is 15%, while the risk for gastric cancer is 0.1-1%, and the risk for gastric lymphoma is 0.01-0.1%.H.pylori is an etiological factor in 95% of duodenal ulcer cases, and 80-85% of gastric ulcer cases(4). The H. pylori prevalence in Turkey is similar

to that in developing countries(4).The most preferred treatment pattern for the first level H. pylori eradication in Turkey and throughout the world is the standard therapy procedure consisting of proton pump inhibitor (PPI), claritromycin (CLA) and amoxicillin (AMO). In recent years due to the increasing resistance to antibiotics eradication rates decreased and search for alternative therapies started. Quadruple therapy consisting of bismuth, PPI, metronidazole, and tetracycline treatment is also suggested as a first-line treatment(2). Thus, there are outcomes of studies in Turkey reflecting regional differences. The success rate is 97% on the eastern part of the country whereas it is 55.7% on other regions. There are local differences in eradication rates. The change in the efficiency of a standard treatment in a crowded city that receives immigration from all parts of the country and how treatment should be done were studied.

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MATERIALS AND METHODS

Data of 14 542 patients who underwent gastroscopy due to various reasons at Uskudar State Hospital (former Istanbul Police Hospital) after the year 2000 were evaluated. Histological analysis of specimen taken from antrum and corpus were done. Data of 1000 patients among them who were treated before and after the year 2010 and received standard PPI, CLA 500 mg BID, AMO 1g BID for 14 days were randomly selected; the eradication of H. pylori was verified by the urea breath test after six weeks starting from the cessation of the therapy. 500 patients were treated before 2010 and 500 were treated after 2010. The decrease in Helicobacter pylori eradication rate using the standard triple therapy has been evaluated. Research inclusion criteria: There should be dyspeptic complaints from patients and no alarm symptoms such as weight loss, dysphagia, vomiting, gastrointestinal bleeding and anemia. In addition, H. pylori with the method of histology in gastric mucosal biopsies during the upper gastrointestinal endoscopy should be detected. Research exclusion criteria: Detection of malign lesion in endoscopy, having gone through upper gastrointestinal system surgery, having used proton-pump-inhibitor (PPI), antibiotics or bismuth composite within the last two weeks, presence of a disease that prohibits the usage of medication within the eradication protocol and pregnancy.

R 3.4.4 programme used for statistical analysis. Descriptive statistics are given with frequency and percent for categorical variables like Helicobacter pylori eradication rates after using the standard triple therapy. Pearson chi-square test used for 2 group comparison. P value below 0.05 assumed as statistically significant.

RESULTS

In our study retrospective analysis of data from 1000 patients has been made. 438 patients (43.8%) were female and 562 patients (56.2%) were male; their mean age was 46.5+-27.54. 608 patients (60.8%) had gastric problems except ulcer and 192 patients (19.2%) had duodenal ulcers. During the period between 2000 and 2010 412 patients (82.4%) got successful Helicobacter pylori eradication treatment; for the period after 2010 262 patients (52.4%) were successfully treated (Table 1). Statistically significant difference was found between the groups in terms of H. pylori eradication results (p <0.001).

Table 1 Helicobacter pylori eradication rates

Group	Patient number (n)	Treatment Regimen	Treatment Duration (week)	Eradication Rate n (%)
1	500	PPI b.i.d, Clarithromycine 500 mg b.i.d, Amoxicilline 1000 mg b.i.d	2 weeks	412(82.4%)
2	500	PPI b.i.d, Clarithromycine 500 mg b.i.d, Amoxicilline 1000 mg b.i.d	2 weeks	262(52.4%)

Table 2 Helicobacter pylori eradication rates were different between the groups

Group	Eradication(+)	Eradication(-)	p
Between 2000 and 2010	412 (82.4%)	88 (17.6%)	<0.001
After 2010	262 (52.4%)	238 (47.6%)	

Pearson chi-square test

DISCUSSION

In our study we observed that there was difference between two groups and the eradication rate decreased after a certain period, It was in accordance with the literature data from the country and all over the world. It was below 80% which is regarded as the recommended value. In a study conducted by Kadayifci *et al*(5). it was shown that H. pylori eradication rates with triple treatment have decreased over time in Turkey especially after the 2000's, from 79.4% to 68.8%, suggesting the bismuth-based treatments as first-line treatment. Recently, H. pylori eradication rates in Turkey were found to be 50-57% with clarithromycin-based triple treatment (6-8) and 89-90% with bismuth-based quadruple treatment(9,10). In a meta-analysis report on studies throughout Turkey it has been reported that after PPI-based triple therapy the Hp eradication rate decreased from 84% in 1997 to 55.3% in 2004 and ranitidin bismuth citrate or rabeprazol-based triple therapies could be preferred in first level therapy(11). it has been observed that the triple therapy lose its effectiveness in due course in the literature too . As South Korean researchers Na *et al.* have reached an eradication rate of 84.3% by using the triple therapy in 2007 Chang *et al.* found a success rate of 67.6% in 2012. The 90.7% eradication rate achieved by Asaka could not be observed in studies of Fujioka in 2012, Nishizawa in 2012 and Nishida in 2014 for which eradication rates were 80.7%, 80.4%, and 76.9% respectively. In 2000 Sheu reported an eradication rate of 87.8% in Taiwan and in 2014 Chen has found an eradication rate of 61.8%. In 1999 Catalano found an eradication rate of 94.0% in Italy; Paoluzi found 75.0 % in 2014; Özçay *et al.* found 75.7% in 2004; Kutluk *et al.* found a rate of 55.7% in 2014(12,13).

Reasons for the failure in H. pylori eradication are the resistance to antibiotics and the CYP2C19 genetic pleiomorphism(4). In many European countries resistance rates against metronidazol and claritromycin were found between 20 - 40% and 2 - 15% respectively (13). In Turkey resistance rate against claritromycin is over 27% (14,15).

In our research, H.pylori eradication rate was found as 52.4% after 2010. Meanwhile, different outcomes from region to region were observed in Turkey. For example, it has been found that in Eastern Anatolia high success rates were reached up to 97% using standard triple therapy(16). We consider that the local clarithromycin resistance difference between the different geographical regions of the country might play a role in the different results of two studies. Successful eradication rate makes us consider that the clarithromycin resistance in the studied region is low. It was reported that the information related to local resistance rates are crucial for an effective treatment(17). It's possible to observe different medication resistance in different parts of the country. There are studies with similar results in the literature. For instance; a research in Italy indicates that the primary clarithromycin resistance shows

a significant difference in different regions(18).Point mutations are crucial in clarithromycin resistance. A2143G point mutation is the most frequent. We could also observe the same in various Western countries(18).Another reason may be pseudo-eradication. Early H. pylori treatment control as like after 2 - 4 weeks may cause higher pseudoeradication rates. Therefore it is recommended to make treatment controls in the seventh month after the medical therapy. Controls after 1 - 2 years would be a better choice, if possible(15). This may result obtaining different eradication rates. Another important factor for the response to the therapy is smoking .in literature. Smoking decreases eradication rates especially in treatment plans which include amoxicillin(19,20).On the contrary,Savaş *et al* demonstrated that factors such as age, smoking and alcohol usage did not affect eradication(21).Another cause for the differences in the study could be CYP2C19 genetic pleomorphism. PPI is metabolized by CYP2C19 in the liver. This enzyme has three genotypes that metabolize slowly, medium and rapidly. Serum PPI levels, gastric pH values, H.pylori eradication rates of people with rapidly metabolizing genotypes are lower compared to other peoples' with different genotypes. It has been observed that keeping the PPI and antibiotic doses high in the rapidly metabolizing ones affected the treatment results positively(22).

The weak points of the study are; not making the seventh month and first year H.pylori eradication checks of the patients within our study, not knowing the antibiotic resistance statuses and CYP2C19 genotypes, and the strong points are the high number of patients, them being able to complete the treatment, usage of the urea breath test in eradication controls which does not rely on biopsy.

CONCLUSION

According to the Maastricht V Florence Declaration of the European Study Committee (gut October 5, 2016 online) the first choice in order to eradicate Helicobacter pylori should be the quadruple therapy including bismuth if there exists a resistance against claritromycin over 15% in the region where the treatment is planned. This quadruple therapy including bismuth may be considered instead of the standard triple therapy even for regions where the resistance rate against claritromycin is below 15%. Besides, different clarithromycin resistance in different regions of a country also significantly affects the response to treatment. Despite differences of the response to the therapy between regions in a country are observed and the success rate of the therapy has been found up to 97% in studies the quadruple therapy including bismuth could be the first choice as we consider the high rate of resistance against claritromycin as mentioned in some studies. Knowing the CYP2C19 genotype to achieve H.pylori eradication will ensure that the correct medication with correct dosage is given to the patient. Thus, it will be possible to see an increase in the success rate of treatment.

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