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The Early Results of Helicobacter Pylori Eradication Therapy for Patients with Chronic Immune Thrombocytopenic Purpura

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Abstract

Background: Immune thrombocytopenic purpura is an autoimmune disease caused by excessive destruction of circulating platelets and characterized by temporary or permanent low platelet count and increased risk of bleeding. Helicobacter pylori can result in various clinical manifestations such as chronic atrophic gastritis, peptic ulcer, gastric cancer, and primary gastric B cell lymphoma. Helicobacter pylori infection has been associated with immune thrombocytopenic purpura, and potential mechanisms have been suggested to increase platelet count after bacterial eradication. We aimed to investigate the association between immune thrombocytopenic purpura and Helicobacter pylori. In addition to reveal improvement platelet count after eradication therapy.

Methods: A total of 85 patients with a diagnosis of immune thrombocytopenic purpura were included in the study. A Urea breath test was conducted. The patients with positive test results underwent standard primary eradication therapy. Two months after eradication therapy, patients were evaluated for Helicobacter pylori infection status and platelet response using the control urea breath test.

Results: The urea breath test was positive in 63.5 % of patients. In 21 of 35 patients with eradication there was a significant increase in platelet count after therapy and the rate platelet response was 60%.

Conclusion: Although Helicobacter Pylori eradication therapy is not currently a primary care option for the treatment of immune thrombocytopenic purpura, it may be considered as an alternative treatment option in unresponsive patients.

Keywords: Immune Thrombocytopenic Purpura; *Helicobacter Pylori*; Platelet Recovery; Eradication Therapy

Introduction

Immune thrombocytopenic purpura (ITP) is an autoimmune disease caused by excessive destruction of circulating platelets and characterized by temporary or permanent low platelet count and increased risk of bleeding. ITP is diagnosed by thrombocytopenia, shortening of the platelet life span, presence of anti-platelet factors in the plasma, and normal or elevated megakaryocyte counts in the bone marrow [1-3]. The annual incidence of ITP is estimated to be 3.3/100,000 [4]. Bleeding findings in ITP are usually mucocutaneous types such as petechia and purpura. Gingival and nasal bleedings are common. The most serious and frightening complication of ITP is intracranial hemorrhage. Various hereditary and congenital diseases, drug interactions, autoimmune diseases, and infections are among the causes of ITP [5,6]. *Helicobacter Pylori (H. pylori)* can result in various clinical manifestations such as chronic atrophic gastritis, peptic ulcer, gastric cancer, and primary gastric B cell lymphoma [7].

More than half of the world's population, particularly in developing countries, is infected with *H. pylori* [8]. *H. pylori* infection is associated with extraintestinal autoimmune diseases such as pernicious anemia, immune thrombocytopenic purpura, rheumatoid arthritis, autoimmune thyroiditis, and Sjögren's syndrome [9,10]. In recent years there has been a growing appreciation for the association between ITP and *H. pylori* infection. *H. pylori* several potential mechanisms have been proposed. The prevalence of the HLA-DRB1*11 and DQB1*03 alleles is reduced among ITP patients relative to healthy controls, suggesting a genetic

component to disease pathogenesis [11]. However, the absence of this allele is more common among *H. pylori* negative patients, which suggests that there may be multiple subgroups of ITP with distinct pathologies.

It has been previously reported that bacterial eradication and platelet elevation are accompanied by a reduction in autoantibodies in most cases. These results may indicate the presence of cross-mimicry between *H. pylori* and platelet antigens and a possible autoimmune pathogenesis [12-15]. The *H. pylori* protein CagA was bound by platelet associated IgG antibody in chronic ITP patients, and antibody levels due to cross-reaction decreased after eradication therapy. CagA antigen may stimulate Th4 cells, resulting in proliferation and maturation of B cells. Antibodies against CagA may also disrupt platelet function [16,17]. The aim if this study is to investigate *H. pylori* incidence and difference in platelet count after bacterial eradication in patients with ITP diagnosis.

Materials and Methods

A total of 85 patients with a definitive diagnosis of ITP and older than 18 years who were treated and followed up in Uludağ University Medical Faculty Department of Internal Diseases, were included in the study. The study was approved by the local ethics committee. The exclusion criteria were as follows:

a) Age < 18 years,

b) Patients with gastrectomy history,

c) Patients with positive viral markers,

d) Previous history of *H. pylori* eradication therapy,

e) History of medication with proton pump inhibitors, anti-acids, H2 receptor antagonists or antibiotics in the previous 4 weeks.

Demographic characteristics of the patients such as age, gender, duration of primary disease, previous treatments and responses to these treatments, and gastric symptoms and findings were recorded. All participants were tested for the presence of *H. pylori* with a 13C-urea breath test (UBT). Patients with positive test results underwent eradication therapy. The eradication therapy was amoxicillin 1,000mg twice a day, clarithromycin 500mg twice a day and lansoprazole 30mg twice a day for 14 days. Two months after eradication therapy, patients were evaluated for *H. pylori* infection status and platelet response using a urea breath test. None of the patients received additional treatment except for previous maintenance treatment over two months during the *H. pylori* eradication therapy and follow-up periods. At the same time, the effect of eradication therapy on other peripheral blood values was investigated.

Statistical Analysis

Statistical analyses were conducted using the SPSS 13.0 statistical software package. Descriptive (mean, median, standard deviation) statistics and frequency distributions were calculated. Normality of continuous variables was analyzed using the Shapiro-Wilk and Kolmogorov-Smirnov tests. The Mann-Whitney U test, a non-parametric test, was used in comparisons among groups for continuous variables. Pearson (Yates corrected) chi-square and Fisher's exact chi-square tests were used in the comparison of categorical variables. The results were interpreted at 95% confidence level. $P<0.05$ was used as the threshold for determining statistical significance.

Results

A total of 85 patients were evaluated. The average age was 42.6±15.3 (18-76) years. There were 25 male (29.5%) and 60 female (70.5%) patients (Table 1). Gastric symptoms included bloating (43.7%), epigastric burning (37.9%), epigastric pain (25.2%), belching (25.2%), pyrosis (20.4%), nausea (20.4%), early satiety (17.5%), and vomiting (8.7%). The most common gastric symptom was bloating (46.1%) in females and belching (40.7%) in males. The patients included in this study underwent UBT at the beginning of the study. The UBT was positive in 54 patients (63.5%) and negative in 31 patients (36.5%). The patients with positive UBT tests were given *H. pylori* eradication therapy. Two months after eradication therapy, patients were evaluated for *H. pylori* infection status and platelet response using a urea breath test. Among the UBT positive patients, 35 were UBT negative at the second test, indicating eradication of *H. pylori*.

Table 1: Baseline Characteristics of the Study Population.

Total Patients (n:85)	
Age	42,6±15,3 (18-76)
Gender	
Male	25/85 (29,5%)
Female	60/85 (70,5%)
Baseline platelets, x10^3µL	43,1±28,9 (1,6-98,2)
WBC (white blood cell), x10^3µL	10,5±4,5 (3,8-24,3)
Hemoglobin, g/dL	13,41±1,42 (9-16)
Splenectomy	38/85 (44,7%)

Table 2: The classification of patients according to the results of UBT and eradication therapy.

Total Patients (n:85)	Eradicated (n)	Non-Eradicated (n)	Unknown
UBT positive (n:54)	35	2	17
UBT negative (n:31)	-	-	-

Eradication therapy was unsuccessful in 2 patients. The results of eradication therapy could not be obtained in 17 patients because they did not complete the study (Table 2). The patients with *H. pylori* eradication were divided into two groups, platelet responsive and unresponsive, according to the change in the platelet count. Patients who had an increase in platelet count of 30000-50000K/µL after eradication were partially responsive, and patients who had an increase in platelet count of more than 50000K/µL were completely responsive. Furthermore, patients who had a decrease in platelet count or an increase of less than 30000K/µL after eradication therapy were considered unresponsive. Accordingly, 15 patients (43%) were completely responsive, 6 patients (17%) were partially responsive, and 14 (40%) were unresponsive. The

total response rate was 60% (Table 3). There was no difference between platelet responsive and platelet unresponsive groups in terms of age and gender. The incidence of gastric complaints was similar both groups. s

Table 3: Platelet responses of eradicated patients.

Platelet Responses	Number of Patients n (%)
Complete Response	15 (43%)
Partial Response	6 (17%)
Unresponsive	14 (40%)
Total responsive patients /Total eradicated patients	21/35: 60%

Discussion

There are several options for the treatment of ITP. The current standard of care generally results in a high rate of success. However, some problems remain with regards to ITP treatment. There pathogenesis of ITP remains poorly understood and it is unclear why some patients are resistant to treatment. Several recent studies have suggested as association between ITP and *H. pylori* infection. The incidence of *H. pylori* in patients with ITP has been reported in various studies. The prevalence of *H. pylori* is 50-85% in Asian and Middle East countries, and 20-30% in Western countries [18-20]. This prevalence of *H. pylori* was 63.5% in our study population. Several researchers have examined platelet count after *H. pylori* eradication in patients with ITP. Emilia et al [21]. reported an *H. pylori* incidence of 51%; platelet response after eradication therapy was 68%. Ando et al [22]. reported a platelet response in 67% of patients in their study. In the study conducted by Kodama et al. 67 (62%) of 116 patients were *H. pylori* positive and infection was successfully eradicated in 85% of patients [13].

Moreover, a platelet response was observed in 62% of *H. pylori* eradicated patients. Several studies have reported similar results [21,23-31]. In our study, there was a significant increase in platelet count in 21 of 35 *H. pylori* eradicated patients after therapy, and the platelet response was 60%. Other studies have reported different results. In a study including 142 patients, 79 patients (61%) were *H. pylori* positive, and infection was eradicated in 62. The platelet response after eradication was 48% [32]. In another study, 64 (47%) of 137 patients were *H. pylori* positive and *H. pylori* was successfully eradicated in 52 patients. Moreover, platelet response was observed in only 17 (33%) of eradicated patients [33]. Some researchers have suggested based on the results of these studies that *H. pylori* incidence in ITP patients is not higher than among the normal population, and eradication therapy is not an efficient method of increasing platelet count [33,34].

In a meta-analysis evaluating 25 studies and including total of 1555 patients, complete remission occurred in 42.7% of patients and total remission occurred in 50.3% [35]. *H. pylori* eradication therapy seems to be more advantageous to long-term immunosuppressive therapy in ITP patients due to the reduced side effect risk. In addition, platelet response after *H. pylori* eradication is an important aspect of recovery. Although there is evidence of an association between *H. pylori* and ITP, the mechanism remains unclear. Some researchers have suggested that eradication therapy can be conducted in cases of *H. pylori* infection in patients who are unresponsive to steroid and immunoglobulin therapy or who develop rapid relapses after treatment. This approach avoids the long-term effects of steroid treatments [16]. The limitation of our study is that it is single-centered, and the number of patients is not much.

Conclusion

The relationship between ITP and *H. pylori* remains uncertain. The general view is that *H. pylori* eradication therapy increases platelet count in a subgroup of patients. Although *H. pylori* eradication therapy is not typically considered as a primary care option for ITP, it may be considered as an alternative treatment option in unresponsive patients.

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