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The Effects of *Helicobacter pylori* Eradication Therapy for Chronic Idiopathic Thrombocytopenic Purpura

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See editorial on page 323.

Background/Aims: The aim of this study was to evaluate the ability of *Helicobacter pylori* eradication treatment to increase platelet counts in Korean patients with chronic idiopathic thrombocytopenic purpura (ITP). **Methods:** A total of 102 patients were evaluated against two criteria. First, those diagnosed with *H. pylori* infections in whom eradication was successful were assigned to the *H. pylori*-positive and -eradicated group (n=39), whereas those diagnosed with *H. pylori* infections in whom eradication failed were assigned to the *H. pylori*-positive and -non-eradicated group (n=3), and those without *H. pylori* infections were assigned to the *H. pylori*-negative group (n=60). Second, patients with complete remission in whom the platelet recovery effect was maintained over the average follow-up period of 6 months after eradication therapy were defined as the responder group (n=58), whereas those with partial or no response were defined as the nonresponder group (n=44). **Results:** The platelet counts of the *H. pylori*-positive and -eradicated group were significantly increased 6 months after eradication therapy compared to those of the *H. pylori*-positive and -non-eradicated group and the *H. pylori*-negative group (43.2±29.1 to 155.3±68.7×10^3/μL vs 42.5±28.1 to 79.8±59.7×10^3/μL vs 43.1±28.9 to 81.2±62.2×10^3/μL; p=0.041). The eradication therapy success rate in the responder group was 100.0% (39/39), in contrast to the nonresponder group (0%, 0/3) (p<0.001). **Conclusions:** *H. pylori* eradication therapy was related to increased platelet count, and successful eradication affected the increased platelet count in Korean patients with chronic ITP. **(Gut Liver 2016;10:356-361)**

Key Words: *Helicobacter pylori*; Eradication therapy; Purpura, thrombocytopenic, idiopathic; Platelet count

INTRODUCTION

Helicobacter pylori is a causal factor in gastritis, peptic ulcer, and gastric adenocarcinoma and has a close relationship with the occurrence of mucosal-associated lymphoid tissue lymphoma.[1] In addition to gastric disorders, *H. pylori* is associated with various non-gastrointestinal-related illnesses such as coronary artery disease, autoimmune disorders, and pernicious anemia.[2-4] *H. pylori* was recently demonstrated as an etiological factor in idiopathic thrombocytopenic purpura (ITP) in some prospective studies, with reports of platelet numbers increasing in these patients after *H. pylori* eradication treatment.[5-7] However, other studies have shown a negative result after eradication treatment, with the *H. pylori* infection rate of patients with ITP showing little difference with the infection rate of normal subjects, leading to controversy.[8,9]

ITP is an acquired blood disorder in which autoantibodies or immune complexes destroy platelets, leading to a decreased platelet count to below the lower limit of the normal range (150×10^3/μL) through which mucocutaneous hemorrhage characteristically occurs. In the treatment of ITP, steroids, γ-globulin, anti-RhD, splenectomy, immunosuppressive agents, and other similar therapies have been employed to reduce or block autoantibody production. Among these treatment modalities, steroid therapy is considered the most effective; however, if discontinued, most patients experience relapse, with only 10% to 30% of total patients maintaining sustained remission. When other treatment methods were used, 64% of patients reportedly showed increased platelet counts.[10] If a patient's condition is refractory to conventional treatment methods or treatment side effects such as immunosuppression are observed, keeping the

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patient on long-term therapy may be difficult, which creates a demand for treatment methods with fewer side effects. In the case of *H. pylori* eradication therapy, the advantages offered include fewer side effects and shorter treatment duration than conventional therapy.

In this study, the effectiveness of *H. pylori* eradication therapy in patients with ITP patients was assessed in relation to its ability to increase platelet numbers in patients with chronic ITP in Korea.

MATERIALS AND METHODS

1. Study population

This study was conducted in Seoul National University Bundang Hospital between January 2003 and December 2013. The medical records of patients diagnosed with chronic ITP were retrospectively reviewed. The patients selected for the study met the following inclusion criteria: (1) age >18 years; and (2) diagnosis of ITP according to American Society of Hematology criteria based on an initial platelet count $<100\times10^3/\mu L$. The exclusion criteria were as follows: (1) age <18 years; (2) thrombocytopenia was related to autoimmune disorders, drugs, a family history consistent with inherited thrombocytopenia, human immunodeficiency virus infection, hepatitis, or pseudothrombocytopenia; (3) previous history of *H. pylori* eradication; and (4) history of medication with proton pump inhibitors, H_2 receptor antagonists, or antibiotics in the previous 4 weeks.

2. Diagnosis of *H. pylori* and eradication therapy

All participants were tested for the presence of *H. pylori* with a ^{13}C-urea breath test. If the result was positive, the patient was diagnosed as having *H. pylori* infection. Patients who were diagnosed with *H. pylori* received standard triple therapy (rabeprazole 20 mg twice a day, amoxicillin 1,000 mg twice a day, and clarithromycin 500 mg twice a day) for 1 week to eradicate *H. pylori*. The results of the eradication therapy were assessed by using a ^{13}C-urea breath test 4 weeks after eradication therapy. Patients without *H. pylori* infection received no eradication therapy. None of the patients received additional concurrent immunosuppressive treatment or prednisolone except for previous maintenance treatment over 6 months during the *H. pylori* eradication therapy and follow-up periods.

3. Assessment of treatment efficacy

We evaluated treatment efficacy of the patients with chronic ITP by two criteria. The primary criterion was the increased platelet count according to *H. pylori* infection or eradication success. We divided the patients by three groups. Those diagnosed with *H. pylori* infection who had eradication success after therapy were assigned to the *H. pylori*-positive and -eradicated (HPPE) group; those diagnosed with *H. pylori* infection who had eradication failure after therapy were assigned to the *H. pylori*-positive and -non-eradicated (HPNE) group and those without *H. pylori* infection after initial *H. pylori* assessment were assigned to the *H. pylori*-negative (HPN) group. We evaluated the platelet counts at baseline and 2 and 6 months between the three groups.

The secondary criterion was the increased platelet count according to treatment response. The definition of treatment response was assessed according to the ITP International Working Group guidelines.[11] Complete remission was determined to have occurred if the platelet count increased to at least $100\times10^3/\mu L$ within 2 months of the start of treatment regardless of whether maintenance therapy was ongoing. Partial remission was defined as an increase in platelets to a minimum of $30\times10^3/\mu L$ within 2 months of the start of treatment regardless of whether the patient was on maintenance therapy or an increased platelet count to more than twice the number in the pretreatment period. No response was defined as a platelet count that remained below $30\times10^3/\mu L$, showed an increase of <50% compared with the initial platelet count, or showed no increase. In this study, patients who achieved complete remission and maintained the platelet recovery effect over the average follow-up period evaluated at 6 months after eradication therapy were defined as the

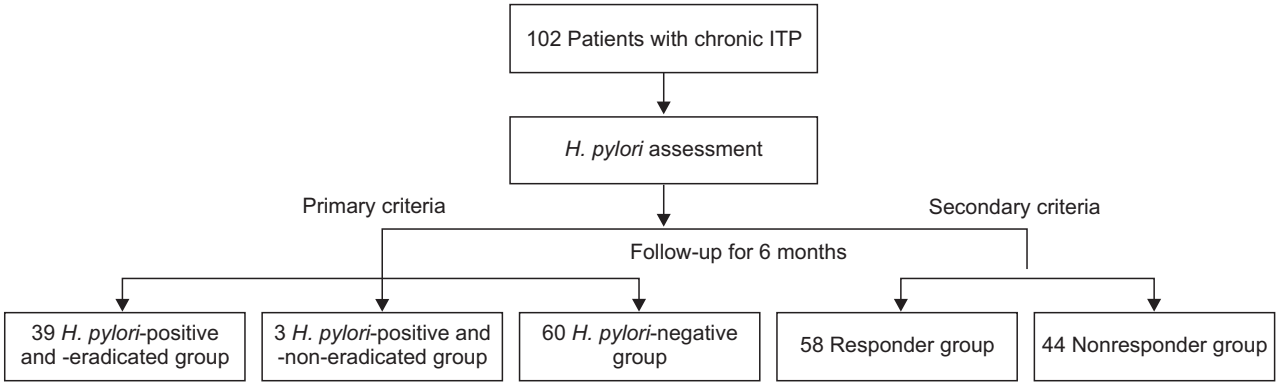

Fig. 1. A schematic diagram of the study.
ITP, idiopathic thrombocytopenic purpura; *H. pylori*, *Helicobacter pylori*.

responder group, while those who achieved partial remission or no response were defined as the nonresponder group. We evaluated the platelet counts at baseline and 2 and 6 months between the two groups. A schematic diagram of the study is provided in Fig. 1. The study protocol was approved by the Ethics Committee at Seoul National University Bundang Hospital.

4. Statistical analysis

All statistical analysis was performed using Predictive Analytics Software for Windows version 20.0 (SPSS Inc., IBM, Chicago, IL, USA). After eradication therapy, to assess the association with the increase platelet count, age, gender, initial platelet count, white blood cell (WBC) count, hemoglobin, absolute neutrophil count (ANC), total follow-up period length, and various other factors such as previous treatment (steroids, immunosuppressive agents, splenectomy, and so forth) were analyzed. Student t-test and analysis of variance test were used to evaluate continuous variables, while Pearson chi-square test and Fisher exact test were used to assess noncontinuous variables. p-values <0.05 were defined as statistically significant.

RESULTS

1. Patient characteristics

The patients' baseline characteristics by HPPE, HPNE, and HPN group are shown in Table 1. Between 2003 and 2013, a total of 102 patients (HPPE group, n=39; HPNE group, n=3; HPN group, n=60) were diagnosed with chronic ITP. The prevalence of *H. pylori* infection was 41.1% (42/102) in the study population. The average period from the diagnosis of ITP to the date of the last follow-up was 31.5±29.6 months in the HPPE group, 31.0±28.3 months in the HPNE group and 31.6±29.0 months in the HPN group (p=0.468). There were no statistical differences in age, gender distribution, baseline platelet count, WBC count, hemoglobin, ANC, or previous ITP treatment between three groups (Table 1).

2. Relationship between treatment response and *H. pylori* eradication

Table 2 compares platelet counts at baseline and 2 and 6 months between the HPPE, HPNE, and HPN groups. Although the baseline platelet count did not differ significantly between the three groups (p=0.487), at 2 months after eradication therapy, the platelet count significantly increased from 43.2±29.1 to 104.1±47.4×10^3/μL in the HPPE group, from 42.5±28.1 to 59.2±46.1×10^3/μL in the HPNE group and from 43.1±28.9 to 63.7±47.3×10^3/μL in the HPN group (p=0.041) (Table 2). The platelet count 6 months after eradication therapy was 155.3±68.7×10^3/μL in the HPPE group, 79.8±59.7×10^3/μL in the HPNE group and 81.2±62.2×10^3/μL in the HPN group (p=0.036) (Table 2). The platelet count significantly increased in the HPPE group compared to those in the HPNE and HPN groups. The recovery effect of the platelets was maintained over the average follow-up period.

Table 1. Baseline Characteristics of the Study Population between the *H. pylori*-Positive and -Eradicated (HPPE) group, the *H. pylori*-Positive and -Non-Eradicated (HPNE) Group and the *H. pylori*-Negative (HPN) Group

Characteristic	HPPE group (n=39)	HPNE group (n=3)	HPN group (n=60)	p-value*
Age, yr	52.9±19.3	53.5±12.3	53.0±11.1	0.318
Gender				0.392
Male	14/39 (35.9)	1/3 (33.3)	27/60 (45.0)	
Female	25/39 (64.1)	2/3 (66.7)	33/60 (55.0)	
Baseline platelets, ×10^3/μL	43.2±29.1	42.5±28.1	43.1±28.9	0.487
WBC, ×10^3/μL	5.4±2.7	5.9±1.6	5.6±1.1	0.695
Hb, g/dL	13.5±1.4	13.6±2.1	13.3±1.7	0.917
ANC, ×10^3/μL	3.1±2.1	3.6±1.8	3.2±1.1	0.358
Previous treatment of ITP				0.972
None	31/39 (79.5)	2/3 (66.7)	48/60 (80.0)	
Drugs	8/39 (20.5)	1/3 (33.3)	6/60 (10.0)	
Splenectomy	0/39	0/3	3/60 (5.0)	
Drugs+splenectomy	0/39	0/3	3/60 (5.0)	
Follow-up periods, mo	31.5±29.6	31.0±28.3	31.6±29.0	0.468

Data are presented as mean±SD or number (%).
WBC, white blood cell; Hb, hemoglobin; ANC, absolute neutrophil count; ITP, idiopathic thrombocytopenic purpura; ITP drug, prednisolone or immunosuppressive agents.
*ANOVA test.

Table 2. Comparison of Platelet Counts at 2 and 6 Months Follow-Up between the *H. pylori*-Positive and -Eradicated (HPPE) Group, the *H. pylori*-Positive and -Non-Eradicated (HPNE) Group and the *H. pylori*-Negative (HPN) Group

Platelet count, $\times10^3/\mu L$	HPPE group (n=39)	HPNE group (n=3)	HPN group (n=60)	p-value*
Baseline	43.2±29.1	42.5±28.1	43.1±28.9	0.487
At 2 months	104.1±47.4	59.2±46.1	63.7±47.3	0.041
At 6 months	155.3±68.7	79.8±59.7	81.2±62.2	0.036

Data are presented as mean±SD.
*ANOVA test.

Table 3. Characteristics of the Study Population between the Responder Group and the Nonresponder Group

Characteristic	Responder (n=58)	Nonresponder (n=44)	p-value*
Age, yr	52.9±17.4	53.0±17.1	0.593
Male sex	24/58 (41.3)	18/44 (40.9)	0.797
Baseline platelet, $\times10^3/\mu L$	40.3±31.2	40.7±29.5	0.257
WBC, $\times10^3/\mu L$	5.3±2.7	6.2±1.5	0.151
Hb, g/dL	13.4±1.7	13.7±1.8	0.647
ANC, $\times10^3/\mu L$	3.3±2.3	3.5±1.3	0.779
Previous treatment of ITP	6/58 (10.3)	7/44 (15.9)	0.148
Drugs	6/58 (10.3)	4/44 (9.0)	0.234
Splenectomy	0/58	2/44 (4.5)	0.348
Drugs+splenectomy	0/58	1/44 (2.2)	0.465
HP infection (positive)	39/58 (67.2)	3/44 (6.8)	0.356
HP eradication success	39/39 (100.0)	0/3	<0.001
Follow-up periods, mo	25.3±28.4	26.5±27.1	0.881

Data are presented as mean±SD or number (%).
WBC, white blood cell; Hb, hemoglobin; ANC, absolute neutrophil count; ITP, idiopathic thrombocytopenic purpura; ITP drug, prednisolone or immunosuppressive agents; HP, *Helicobacter pylori*.
*Student t-test, Pearson chi-square test, and Fisher exact test.

3. Comparison of the treatment responder and nonresponder groups

A total of 58 patients had maintained platelet counts $\geq100\times10^3/\mu L$ during the follow-up period of up to 2 months and were categorized into the responder group, while the other 44 patients were categorized into the nonresponder group (Table 3). *H. pylori* infection was confirmed in 39 patients in the responder group (39/58, 67.2%) and three in the nonresponder group (3/44, 6.8%). The success rate of eradication therapy in the responder group was 100.0% (39/39), which was significantly higher than that of the nonresponder group (0%, 0/3) (p<0.001) (Table 3). Table 4 compares the platelet counts at 2 and 6 months between the responder group and the nonresponder group with the baseline platelet count. Although the baseline platelet count was not significantly different between groups (p=0.257), it increased from $40.3\pm31.2\times10^3/\mu L$ to $104.3\pm38.7\times10^3/\mu L$ at 2 months after eradication therapy in the responder group and from $40.7\pm29.5\times10^3/\mu L$ to $43.1\pm24.9\times10^3/\mu L$ in the nonresponder group (p=0.037) (Table 4). The platelet count 6 months after eradication therapy was $152.1\pm49.8\times10^3/\mu L$ in the responder group and $51.0\pm26.6\times10^3/\mu L$ in the nonresponder group (p=0.045) (Table 4).

Table 4. Comparison of Platelet Counts at 2 and 6 Months Follow-Up between the Responder Group and the Nonresponder Group

Platelet count, $\times10^3/\mu L$	Responder (n=58)	Nonresponder (n=44)	p-value*
Baseline	40.3±31.2	40.7±29.5	0.257
At 2 months	104.3±38.7	43.1±24.9	0.037
At 6 months	152.1±49.8	51.0±26.6	0.045

Data are presented as mean±SD.
*Student t-test.

DISCUSSION

In this study, the platelet count significantly increased 2 and 6 months after eradication therapy in the *H. pylori*-positive and -eradicated group than those in the *H. pylori*-positive and -non-eradicated group and *H. pylori*-negative groups. Moreover, the success rate of eradication therapy was significantly higher in the responder group than in the nonresponder group. Accordingly, this suggests a relationship between the success of eradication therapy and increase in platelet count. Studies have shown that other factors that affected the response after eradication therapy included the length of time after the ITP diagnosis before eradication therapy was administered and the platelet count before treatment.[12,13] In this study, the success rate of *H. pylori* eradication therapy was associated only with the increase in platelet count; in particular, in cases of successful *H. pylori* eradication therapy, patients were more likely to show an effective response to treatment than patients without *H. pylori* infection or *H. pylori* eradication therapy failure.

Some studies on the prevalence of *H. pylori* in patients with ITP and the effect of *H. pylori* eradication on disease progress have recently been published. In 1998, Gasbarrini *et al*.[5] reported improved platelet counts in eight of 11 patients with autoimmune thrombocytopenia who had *H. pylori* eradication; among them, platelet autoantibodies disappeared from six, in-

dicating the possibility of a relationship between ITP and *H. pylori*. Emilia *et al*.[14] subsequently showed positive findings in 13 of 30 patients (43.3%) with ITP; among the 12 cases in which eradication therapy was successful, six (50%) showed an increased platelet count, suggesting the existence of a relationship between ITP and *H. pylori*. In the present study, the prevalence of *H. pylori* infection was 41.1% (42/102) in the study population; among the 42 *H. pylori*-positive patients, 39 showed a significant increase in platelet count (39/42, 92.9%), a finding that is consistent with the report of Emilia *et al*.[14]

Moreover, in a systemic review of clinical trials of *H. pylori* eradication performed not only in patients with ITP and *H. pylori* but also patients with ITP but not *H. pylori* infection, a greater number of *H. pylori*-positive patients showed an increased platelet count compared to those without *H. pylori*.15 Specifically, *H. pylori*-negative patients showed an increased platelet count in only 8.8% of patients, while *H. pylori*-positive patients demonstrated an increase in 51.2%, a difference with an odds ratio of 14.5 (95% confidence interval [CI], 4.2 to 83.2).[15] Additionally, in another meta-analysis of prospective trials, platelet count increases were more common in the *H. pylori*-eradicated group compared to the group in which *H. pylori* eradication failed or was not attempted.[16] The weighted mean difference (WMD) between the successful and failed eradication groups was 52.2 (95% CI, 34.3 to 70.1; p<0.0001), and the WMD between the successful eradication group and that in which eradication was not attempted was 40.8 (95% CI, 20.9 to 60.3; p<0.0001), which shows that the differences were significant.

A large-scale study in Japan involving 207 *H. pylori*-positive patients with ITP reported that platelet counts recovered in 63% after eradication therapy.[17] However, other studies showed no platelet recovery in any patient with ITP after successful *H. pylori* eradication therapy.[9,18] Among the many studies conducted in Japan, Italy, and Spain, 48% to 73% of patients with ITP showed an increase in platelet count.[5,6,19-22] Based on these results, several treatment guidelines recommend *H. pylori* eradication for *H. pylori*-positive patients with ITP.[23-26]

To our knowledge, this is the first study to evaluate the effectiveness of *H. pylori* eradication treatment for increasing platelet counts in patients with chronic ITP in a Korean population. Our study showed that *H. pylori* eradication therapy was related to increasing platelet count and that eradication success affected the increase in platelet counts in patients in Korea with chronic ITP.

In conclusion, to date, *H. pylori* has been believed to be one of the etiological factors of ITP, and eradication therapy is a therapeutic method for managing patients with ITP and coexisting *H. pylori* infection. In particular, in the case of patients with steroid-refractory ITP or who experience relapse and require secondary treatment, the administration of immunosuppressive agents may cause side effects and infection. However, in the case of *H. pylori* eradication therapy, side effects are almost absent, the treatment period is short, and the cost of treatment is low. Accordingly, for patients who require secondary treatment and are *H. pylori*-positive, eradication therapy is thought to be suitable second-line treatment and splenectomy or immunosuppressive agents are considered alternative therapeutic options. In addition, the response is faster when eradication therapy is administered compared to when immunosuppressive agents are administered, and the response is maintained for a relatively long time. In the future, large-scale prospective studies are needed that investigate the exact mechanisms of *H. pylori* in the pathogenesis of ITP and the effectiveness of *H. pylori* eradication therapy in patients with ITP.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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