REVIEW ARTICLE

Helicobacter pylori infection eradication: An effective treatment to increase platelet count in patients with chronic immune thrombocytopenic purpura for at least 6 months after treatment

Author

Mohamadreza Amiri, MD

Correspondence
Mohamadreza Amiri, MD
E-mail: drmr.amiri@yahoo.com

Abstract

This before-and-after randomized clinical trial examined the impact of *Helicobacter pylori* elimination on the number of platelets among 23 patients (< 20 years) with chronic immune thrombocytopenic purpura (CITP). In order to detect *H. pylori* infections, urea breath test was performed. Based on the findings, the subjects were divided into 2 groups: uninfected (13 cases) and infected (10 cases). The groups were not significantly different regarding sex, age, anti-D treatment, history of splenectomy, or prednisolone use. None of the patients had a history of fatal diseases. Two out of 10 infected patients did not respond to *H. pylori* eradication treatment (resistant to treatment), while 8 patients responded to the treatment (responder group). The platelet count was assessed at baseline, as well as 3 and 6 months posttreatment. However, a steady increase was reported in the platelet count only in the responder group. A major increase was observed at 6 months after treatment versus the baseline (56.2±22.2 vs. 233±85.6 $\times 10^3$/mcL; $P< 0.01$). Therefore, treatment was successful in CITP patients below 20 years and resulted in increased platelet count for at least 6 months.

Keywords: ^{13}C-urea breath test, Chronic immune thrombocytopenic purpura, Eradication therapy, *Helicobacter pylori* (*H. pylori*), Platelet count

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1. Introduction

Helicobacter pylori organisms are described as a type of Gram-negative microaerophilic bacteria. These bacteria have a characteristic curved to spiral morphology, while some may be short or tapered and rod-shaped. They are characterized by flagellum-dependent motility. These features can be of significance, given the aggregation of these organisms in the gastrointestinal mucus of humans and different animal species (Figure 1).

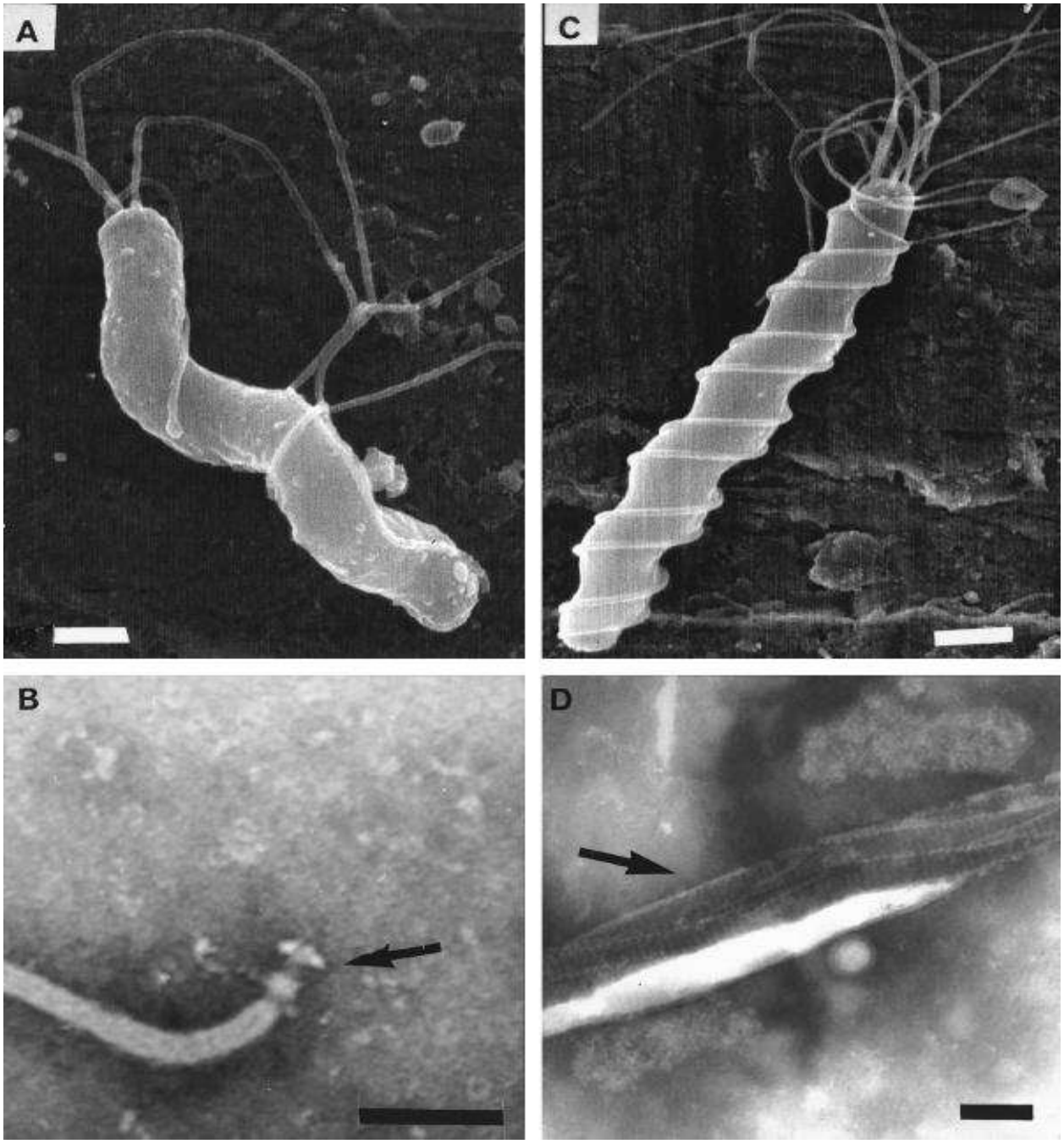

Figure 1: *H. pylori* morphology. (a) *H. pylori* (S-shaped) with 5 to 7 sheathed polar flagella (SEM; bar, 0.5 μm); (b) The flagellar hook (negative staining; bar, 0.05 μm); (c) *H. felis* (helical) with bipolar tufts of sheathed flagella and paired periplasmic fibers (field emission SEM; bar, 0.5 μm); (d) periplasmic fibers with a striated appearance (negative staining; bar, 0.05 μm) (*Helicobacter pylori*: Physiology and Genetics, Mobley HLT, Mendz GL, Hazell SL, Editors. Washington (DC): ASM Press; 2001)

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H. pylori is a causative agent of gastric adenocarcinoma, peptic ulcer, and gastritis (3, 14). It is also strongly linked to mucosa-associated lymphoid tissue lymphoma, gastric diseases, and several nongastrointestinal disorders, including autoimmune diseases, cardiovascular disorders, and pernicious anemia (14, 24).

Immune thrombocytopenic purpura (ITP), as an acquired disorder, results from the interaction between autoantibodies and platelets, which ultimately leads to their destruction and reduced platelet count below the normal range (< 150 $\times 10^3$/mcL). The classic presentation of ITP was reported in an otherwise healthy patient (1–4 years old) with a sudden presentation of generalized petechiae and purpura. Bleeding from the mucous membranes and gums was reported, especially in association with profound thrombocytopenia (platelet count < 10×109/L) (11, 14).

Nearly 20% of acute ITP patients show persistent thrombocytopenia for more than 1 year (CITP). In these conditions, monitoring of relevant diseases (eg, systemic lupus erythematosus and HIV) is necessary. Moreover, nonimmune causes of chronic thrombocytopenia (eg, platelet-type von Willebrand disease, autoimmune lymphoproliferative syndrome, X-linked thrombocytopenia, autosomal macrothrombocytopenia, and Wiskott-Aldrich syndrome) were identified (14). CITP treatment includes steroids, intravenous immunoglobulin (IVIG), anti-RhD, splenectomy, rituximab, and immune-suppressive drugs. In case of resistance to conventional treatments or experience of side effects (including immunosuppression), long-term treatment may be difficult; therefore, other treatments with fewer side effects may be required (11).

H. pylori has been recently described as an etiological cause of CITP, and in some retrospective studies, its eradication has been linked to the increased number of platelets in CITP patients (1, 5, 10, 11, 14, 18, 21). However, some studies have reported conflicting results and found no improvement in the platelet count following effective bacteria eradication (23, 25).

Given the scarcity of relevant studies on Iranian children and adolescents, we investigated the changes in platelet count in a group of 23 patients (age, < 20 years), who were admitted to a clinic, affiliated to Zahedan University of Medical Sciences during 2010-2011. The impact of *H. pylori* elimination on the number of platelets was examined during 6 months.

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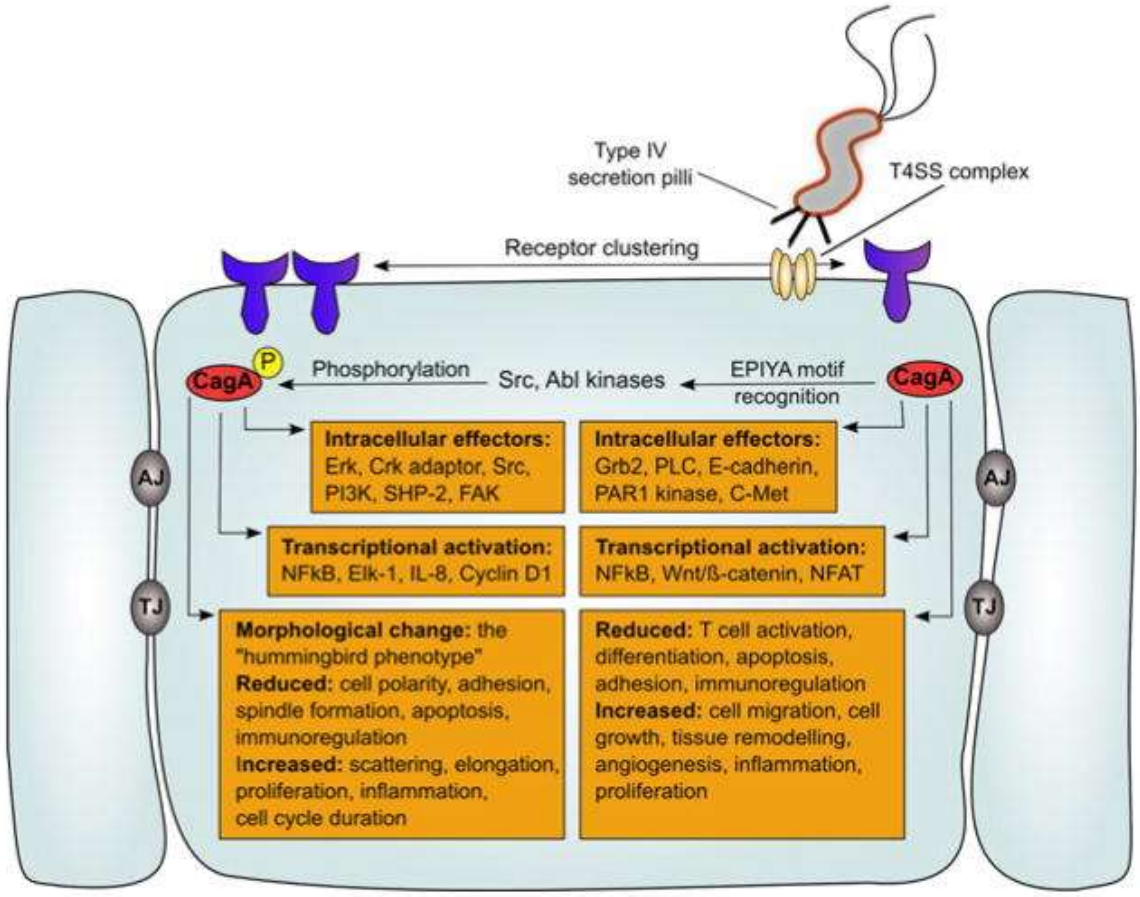

Figure 2: The impact of *H. pylori* virulence factor, CagA, on the host cell. *H. pylori* inserts CagA (red) in a host epithelial cell with a secretion system (type IV; T4SS, tan). Primary receptor dimerization is promoted by the T4SS core complex ($\alpha_5\beta_1$ integrin and receptor tyrosine kinase; purple). In endothelial cells, the main host kinases (ie, Src and Abl) identify CagA EPIYA motif, causing tyrosine phosphorylation (yellow). CagA which is phosphorylated (red & yellow) stimulates the pathology of the host cell. Intracellular and phosphorylated CagAs exert significant effects on the signalling of host cells, causing changes in cell morphology, proinflammatory cytokine transcription, and regulation of the cell cycle (intercellular junctions, gray; TJ, tight junctions; AJ, adherens junctions) (Helicobacter. 2015 Aug; 20(4): 239–251.Published online 2015 Mar 1. doi: 10.1111/hel.12200)**.**

2. Materials and Methods

2.1. Subjects

In this before-and-after randomized clinical trial, patients, who were treated for CITP in a pediatric hematology clinic, were recruited in 2010-2011. The exclusion criteria were: 1) history of *H. pylori* eradication treatment; 2) serious disorders including renal or liver diseases, malignant tumors, and cardiovascular disorders; 3) prednisolone treatment (> 0.5 mg/kg/day) 1 month before the study; 4) necessity of platelet injection or need for drugs increasing platelet content; and 5) unwillingness to cooperate.

For diagnosis, bone marrow aspiration (BMA) was performed in all the patients. Overall, 24 subjects were first analyzed; one patient died because of brain hemorrhage and was eliminated. Extreme bleeding was reported in none of the patients at 1 year before or after the study.

2.2. *H. pylori* Infection Diagnosis

Infection with *H. pylori* was examined with ^{13}C-urea breath test (^{13}C-UBT). No antibiotics or proton pump inhibitors (PPIs) were used 1 month before the administration of UBT. Following overnight fasting, ^{13}C-UBT was carried out. The samples were acquired before and 30 minutes after ^{13}C-urea ingestion (Simac Diagnostica, Netherlands) and were dissolved in water (100 mL).

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The concentration of ^{13}C-urea was 50 and 75 mg among children < 6 years and > 6 years, respectively. Using an isotope ratio mass spectrometer (HeliView; MediChems, Korea), 13C of exhaled carbon dioxide was calculated; values > 4% were regarded as positive (13). The positive findings of stool antigen test for *H. pylori* using HP Ag T Kit (Genesis Diagnosis, UK) confirmed the results (sensitivity, 92%; specificity, 96%) (8).

2.3. *H. pylori* Elimination

Subjects with *H. pylori* infection received a triple treatment using metronidazole (20 mg/kg/day) and clarithromycin (15 mg/kg/day) over 14 days, as well as omeprazole (PPI; 1 mg/kg/day) over 30 days (14). After 4 to 6 weeks, ^{13}C-UBT was carried out again in order to confirm the success of the procedure. Two resistant patients received quadruple treatment during 2 weeks, using omeprazole (1 mg/kg bid), bismuth subcitrate (2 q8h tablets; 250 mg), clarithromycin (15 mg/kg bid), and metro-nidazole (20 mg/kg bid) (17). However, *H. pylori* infection remained positive, and the patients were described as nonresponsive to treatment.

2.4. Platelet Monitoring

Venous blood samples (2 cc) were obtained at baseline, as well as 3 and 6 months after treatment. Automated platelet counting was used for determining the platelet count.

2.5. Statistical Analysis

All data were analyzed with SPSS 20.0 software (SPSS, Inc., Chicago, IL, USA). According to the sample size, The results computed based on 1000 bootstrap samples.Chi-Square tests, Mann-Whitney U, Wilcoxon W , Monte Carlo Sig. (2-tailed) ,Monte Carlo Sig. (1-tailed) , Asymp. Sig. (2-tailed) , Exact Sig. , were performed for statistical analysis. The significance level was 0.01.

3. Results

A total of 24 participants were recruited in the study. However, one patient died because of cerebral hemorrhage. Among the remaining patients (n, 23), 10 (43.5%) were *H. pylori* positive, while 13 (56.5%) were negative. Infection was reported in 43.4% of the study population, similar to other Asian countries. For 6 months, the patients were followed-up. The groups were not significantly different regarding sex, age, initial platelet count, history of splenectomy, anti-D treatment, or corticosteroid treatment (Tables 1, 2, & 3).

Table 1: The patients' characteristics according to H. pylori infection status

Groups	No.	Age (years) mean±SD	Sex (male/female)	History of splenectomy (No.)	Corticosteroid treatment (No.)
Infected	10	9.50±4.73	6/4	1	5
Uninfected	13	10.30±5.05	7/6	1	6
P-value		0.840 [c]	1.000 [d]	1.000 [d]	1.000 [d]

c : The result computed based on 1000 bootstrap samples**.**
d: The result computed based on Fisher's Exact Test

Table 2: Comparison of initial platelet count between treatment responder and uninfected groups

Groups	Initial platelet count (×10^3/mcL)
Treatment responders (n=8)	56.19±22.15
Uninfected (n=13)	56.06±32.26
P-value	0.902

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Table 3: Comparison of initial platelet count between the treatment non-responder and uninfected groups

Groups	Initial platelet count ($\times 10^3$/mcL)
Treatment non-responders (n=2)	50.00±49.50
Uninfected (n=13)	56.06±32.26
P-value	1.000

The result computed based on 1000 bootstrap samples.

Table 5 shows the patients' data. BMA was carried out and diagnosis of ITP was confirmed in the patients. Among 10 *H. pylori*-positive cases, 8 responded positively to treatment (negative ^{13}C-BUT findings after treatment; 80% success in eradication therapy). Two patients were resistant to the initial triple eradication treatment (positive ^{13}C-BUT findings after 4 weeks of treatment). These patients remained positive even after 4 weeks of quadruple treatment and were considered resistant to treatment. The subjects were classified as:

Group A: CITP cases with *H. pylori* (HP+) and successful treatment (8 cases),

Group B: CITP cases with *H. pylori* (HP+) and unsuccessful treatment (2 cases), and

Group C: CITP cases without *H. pylori* (HP-) or any treatment (13 cases).

After eradication therapy, platelet counting was performed after 3 and 6 months. After 6 months, a significant increase were observed in group A from 56.2±22.2 to 233.0±85.6$\times 10^3$/mcL; $P<$ 0.01); nevertheless, no significant increase was observed in platelet count in group B or C (from 50.0±49.5 to 52.5±50.9$\times 10^3$/mcL and 56.0±32.2 to 56.1±27.8$\times 10^3$/mcL; $P=$ 0.28 and 0.98, respectively) (Table 4).

Table 4: Comparison of baseline and final (after 6 months) platelet counts in the groups

	Uninfected (n=13)	**Treatment responders (n=8)**	**Treatment non-responders (n=2)**
Initial platelet count$\times 10^3$/mcL	56.06±32.26	56.19±22.15	50.00±49.50
Final (after 6 months) platelet count$\times 10^3$/mcL	56.06±27.79	233.12±85.61	52.5±50.9
P-value	1.000	.025	.002

The result computed based on 1000 bootstrap samples**.**

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Table 5- Patients' records

Patients	Age (year)	Sex	Months after CITP diagnosis before the study	Previous treatment	Eradication	Platelet count ($\times 10^3$/mcL)		
						Baseline	After 3 months	After 6 months
Pos1	20	Male	7	P,IVIG	Yes (PR)	39,500	79,800	93,800
Pos2	3.5	Male	3	P,IVIG	Yes(CR)	27,000	121,800	263,800
Pos3	5.5	Female	10	P,IVIG,S	NR	15,000	17,000	16,100
Pos4	7.5	Male	5	P,IVIG	Yes(CR)	68,000	218,000	211,800
Pos5	5	Male	5	P,IVIG	Yes(CR)	81,800	122,200	306,900
Pos6	12	Male	6	P,IVIG	Yes(CR)	52,000	285,000	278,700
Pos7	9.5	Female	7	P,IVIG	Yes (PR)	66,700	135,100	121,200
Pos8	9	Male	11	P,IVIG	NR	85,000	86,000	88,000
Pos9	11	Female	6	P,IVIG	Yes(CR)	31,000	214,800	256,000
Pos10	12	Female	3	P,IVIG	Yes(CR)	83,500	238,200	332,800
Neg1	5	Female	10	P,IVIG	----	79,800	81,500	80,000
Neg2	7	Female	12	P,S,IVIG	----	58,700	58,000	55,800
Neg3	8	Female	20	P,IVIG	----	45,000	41,000	41,000
Neg4	4.5	Female	16	P, IVIG	----	93,400	85,000	83,600
Neg5	5.5	Female	6	P, IVIG	----	39,000	47,000	53,000
Neg6	12	Female	9	P, IVIG	----	15,000	21,000	22,000
Neg7	18	Male	8	P, IVIG	----	99,000	89,100	85,000
Neg8	17	Male	10	P, IVIG	----	84,900	80,000	78,000
Neg9	16	Male	14	P, IVIG	----	45,000	38,000	35,000
Neg10	15	Male	14	P, IVIG	----	54,000	70,000	71,000
Neg11	13.5	Male	11	P, IVIG	----	1,000	2,500	3,400
Neg12	6	Male	12	P, IVIG	----	93,000	86,500	90,000
Neg13	6/5	Male	8	P, IVIG	----	21,000	32,000	31,000

CITP: chronic immune thrombocytopenic purpura; IVIG: intravenous immunoglobulin; Pos: *H. pylori*-positive; Neg: *H. pylori*-negative; CR: complete response; PR: partial response; NR: non-response; P: prednisolone; S: splenectomy

In group A, 6 cases exhibited complete response (CR), while 2 showed partial response (PR) to treatment.

CR refers to increased platelet count to > 100×10^3/mcL or the normal range (> 150×10^3/mcL), while PR is described as the increased number of platelets to > 50 up to 100×10^3/mcL. Cases with no response (NR) were described as those with no rise in platelets or platelet count of < 50×10^3/mcL (22). Therefore, the results showed a significant association between increased platelet count and bacteria eradication.

4. Discussion

In different articles, the influence of *H. pylori* elimination on increased platelet count has been evaluated (4, 6, 7, 20). In this regard, Suzuki and colleagues examined 36 patients with CITP in Japan and reported 25 cases of *H. pylori*. Treatment was effective in 84.6% of cases, and a major difference was found between the eradicated and non-eradicated groups regarding platelet count. Furthermore, anti-CagA level was majorly higher in the responder group, compared to the nonresponder group (21).

Furthermore, Azarm and Khami identified 69 cases of *H. pylori* among 95 CITP patients. Thirty cases with a history of treatment showed a significantly increased platelet count (1). Similarly, a study by Rostami et al. assessed 142 patients with CITP. *H. pylori* eradication treatment in 30 out of 71 HP-positive patients, who completed the treatment, resulted in increased platelet count (16).

However, some studies have shown conflicting results (9, 19, 25). Jarque et al. studied 56 cases of CITP and reported 40 cases of infection with *H. pylori*. Eradication therapy performed on 32 infected cases was successful in 23 cases. The

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patients received follow-up treatment, but their platelet count did not increase significantly. The researchers concluded that routine *H. pylori* screening is not required for CITP patients (9).

The results of the present study are in contrast with those reported by Takahashi et al., who concluded that direct pharmacological effects of medications leads to improved platelet count in CITP and HP- patients (22). However, despite receiving eradication therapy drugs, platelet count did not significantly increase in group B after 6 months in our study.

Some pathogenic organisms express antigens with molecular mimicry, which are involved in the pathogenesis of autoimmune disorders (26). There are several assumptions regarding the mechanism through which *H. pylori* leads to CITP. One of these mechanisms is molecular mimicry, which exists in some microbial antigens and platelet glycoproteins. It is a way to disrupt immune tolerance and trigger the formation of autoantibodies. Generally, autoantibodies are not produced by autoreactive B cells, as they are not supported by autoreactive CD^{4+} T cells (functionally removed). Nevertheless, B cells can provide peptides for CD^{4+} T cells (non-self reactive) when facing a cross-reactive non-self antigen, thus promoting the production of autoantibodies (16).

The autoantibodies act against platelet glycoprotein complexes (b-B3 and GPIb). After binding of antibodies to the surface of platelets, Fc receptors on splenic macrophages identify circulating antibody-coated platelets, which are then ingested and destroyed. Synthesis of antiplatelet antibodies and platelet destruction in ITP majorly occur in the spleen. Overall, complete remission is achieved in 64% to 88% of children with CITP via splenectomy (14).

The role of some types of *H. pylori* bacteria with CagA+ or positive Lewis antigens has been also described in the literature (19). *H. pylori* virulence factor, CagA, is characterized as cross-reactive. Autoreactive B cells (anti-platelet) identify CagA and deliver it to reactive CD^{4+} T cells in *H. pylori* in case of continuous infection. According to a previous study, B cells can develop antiplatelet autoantibodies in CITP patients, without autoreactive CD^{4+} T cell involvement (23).

However, some *H. pylori* strains may lack CagA antigen. The presence of CagA+ varies according to geographical region (15). In previous research, the majority of *H. pylori* strains had CagA antigens in Japan (12). This may explain why successful eradication treatment leads to increased platelet count in CITP patients. The number of patients might have been too small (preventing statistically significant results) in studies which indicated the ineffectiveness of *H. pylori* elimination in improving the platelet count. The prevalence of *H. pylori* might have been also low in cases with CagA+ in their study population.

Despite the unknown mechanism of thrombocytopenia in CITP, the current results suggested that *H. pylori* therapy could improve platelet count among patients for at least 6 months. Compared to corticosteroid and immunosuppressive therapies, which are used to improve the number of platelets in CITP patients, *H. pylori* eradication treatment had no adverse effects in this study. After eradication treatment, the platelet count gradually increased in Group A for a relatively long duration (6 months) and remained high in a significant number of patients. Finally, compared to treatment with immunosuppressive agents, eradication therapy had a shorter duration and was more affordable.

5. Conclusion

H. pylori screening is necessary in patients with CITP, and infected cases should undergo eradication treatment. However, further investigation is necessary to identify platelet antigens sharing an epitope with CagA and to determine host susceptibility factors inducing autoimmunity.

6. Research limitations

The limited duration of the study was a major limitation (6 months). A longer study duration would have allowed us to determine the duration platelet count remained high after eradication treatment. Considering the economic and cultural situations in the study location and communication problems among patients and provincial capital, only 23 patients agreed to participate and remain in the study. Therefore, longer study duration could have resulted in increased patient dropout.

Conflicts of Interest

None.

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