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HELICOBACTER PYLORI ERADICATION IMPROVES SPLENECTOMY RESULTS IN REFRACTORY IDIOPATHIC THROMBOCYTOPENIC PURPURA

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ABSTRACT

Background

Management of chronic idiopathic thrombocytopenic purpura (ITP) refractory to medical treatments has been a major challenge. While splenectomy is the most effective treatment for ITP, its success cannot be ensured. Despite the confirmed relationship between Helicobacter pylori infection and chronic ITP, the efficacy of H. pylori eradication in enhancing the response to splenectomy has not been well examined. The present pilot study examined the effects of H. pylori eradication on improving response to splenectomy in patients with ITP.

Methods

In 50 cases who were found to have both chronic ITP unresponsive to medical treatment and H. pylori infection, eradication treatment was given. From March 2007 - 2015 these patients had been followed up precisely by their platelets count. Among them 38 patients who needed splenectomy followed up in a five-year period, and the complete response rate compared with the global one.

Results

Of all the ITP patients who underwent both H. pylori eradication and splenectomy, 36 (94.7%) subjects exhibited a complete response. Two patients (5.3%) also showed a partial response and the overall response rate (ORR) was hence 100%. There was a significant difference between complete response rate to splenectomy in the present research and the previously reported rates throughout the world ($P < 0.0001$).

Conclusion

This research suggested the efficacy of H. pylori eradication in enhancing sustained response to splenectomy in patients with refractory ITP. Considering its accessibility and affordability, H. pylori eradication is strongly recommended as an adjuvant therapy in refractory ITP before splenectomy.

Keywords: Helicobacter Pylori, Idiopathic Thrombocytopenic Purpura (ITP), Splenectomy.

Introduction:

Helicobacter pylori (H. pylori) is a helical-shaped gram-negative bacterium. H. pylori infection is driven by urease, flagella, and adhesions (1-3). The role of various virulence factors such as cytotoxin-associated gene A (CagA) and vacuolating cytotoxin (VacA), in H. pylori colonization and infection has also been confirmed (4-6). Age and geographic location are two main determinants of the prevalence of H. pylori infections. In developing countries, the infection is present in 70% of children over 10 years and almost all adults over 20 years (7-10). H. pylori not only as the most

common microbial cause of chronic gastritis, gastric and duodenal ulcers, and even gastric cancer (1, 7, 11), but has also been found to contribute to the development of several autoimmune disorders such as idiopathic thrombocytopenic purpura (ITP) and iron deficiency and pernicious anemia (1, 12, 13).

ITP is an acquired autoimmune disease in which autoantibodies show antiplatelet activities and reduce platelet counts. Although the condition is commonly asymptomatic, bleeding may develop in severe forms of ITP (12, 14). Despite extensive research, the pathogenesis, epidemiology, diagnosis, and management of ITP are still under debate (14). Nevertheless, the involvement of some infections in the development of ITP has been documented (7, 15, 16). Platelet counts in adult patients with ITP range between 30,000 and 50,000 and most patients do not experience any specific events during their life. However, treatment would be required in severe cases of thrombocytopenia (17, 18). While steroids are accepted as the treatment of choice in adult patients with ITP, splenectomy is recommended as the only potentially curative treatment in adult patients with chronic ITP (17, 19-21). Meanwhile, relapse occurs in about 30% of the patients. Unclear determinants of relapse have turned the management of refractory ITP into a major challenge.

The first report on the role of H. pylori infection in ITP was published in 1998. An Italian group examined 11 patients with both ITP and H. pylori infection. After eradicating the bacteria, the researchers detected a significant increment in platelet counts in eight patients (7, 12, 22). Several mechanisms have been proposed to justify the role of H. pylori in the development of ITP (1, 23, 24). The role of factors such as platelet-associated immunoglobulin G, CagA, and lipopolysaccharide (LPS) in platelet apoptosis has been well established (1, 24, 25). While H. pylori screening and treatment seems to be a simpler and safer therapeutic option, compared to immunosuppression or splenectomy, in particular cases of ITP (29-32), there have been controversial reports about its efficacy. In fact, although H. pylori eradication has been associated with increases in platelet counts in some studies (1, 4, 6, 10), some other studies have not confirmed such an association (33,34). It is hence essential to elucidate the role of H. pylori eradication in ITP management.

The prevalence of H. pylori infection ranges between 22% and 90.6% in patients with ITP (1, 8, 9, 23). H.pylori is highly prevalent in developing countries and has been reported in 57%-91% of Iranians (12, 35). The geographical location and ethnicity of different populations may affect the beneficial effects of H. pylori eradication on the management of ITP. Therefore, this preliminary study was aimed to assess the efficacy of H. pylori eradication on relapse-free response rate after splenectomy in adults with chronic ITP refractory to medical treatments. The results were then compared with the global response rate to splenectomy. The short-term restoration of platelet counts after H. pylori eradication was also assessed.

Materials and methods

This prospective study was conducted during an eight-year period (March 2007-March 2015). A total of 100 consecutive Iranian adult patients (age range: 18-70 years) with a confirmed diagnosis of chronic ITP were recruited. The patients were referred to the Infectious and Internal Diseases Clinics of Qaem Hospital (affiliated to Mashhad University of Medical Sciences, Mashhad, Iran) by their hematologist and evaluated for the presence of gastric H. pylori infection. The diagnostic criteria for ITP (e.g. platelet counts < 100,000/L) were extracted from the Autoimmunity Reviews (17). All patients had received a variety of medications without obtaining the favorable results, i.e. their platelet counts mostly stayed below the normal range.

The patients were first asked to provide an informed consent. They then underwent a urea breath test (UBT). Individuals with secondary ITP, i.e. those with drug-induced thrombocytopenia, pseudothrombocytopenia, a family history indicating inherited thrombocytopenia, human immunodeficiency virus (HIV) infection, and other autoimmune disorders, were excluded. A history of H. pylori treatment within the past two years and antibiotics or proton pump inhibitors within the past four weeks was another exclusion criterion in the present research. Moreover, subjects with a history of gastrectomy and those with negative UBT results at the time of study were excluded.

Finally, 50 eligible patients with positive UBT results (i.e. with H. pylori infection) were recruited. Triple therapy (a combination of clarithromycin 500 mg, omeprazole 20 mg, and either amoxicillin 1000 mg or metronidazole 500 mg, twice daily for two weeks) was administered for H. pylori eradication. UBT was repeated two weeks after the completion of triple therapy to ensure H. pylori eradication. Platelet counts were monitored after H. pylori eradication and patients with poor platelet response underwent splenectomy as a last therapeutic choice. The subjects were followed up for a five-year period.

Platelet counts were monitored at 1, 6, 12, 36, and 60 months after splenectomy. In order to determine the efficacy of H. pylori eradication in preventing relapse following splenectomy, the complete response (CR) rate in the last follow-up session after splenectomy was compared with the response rates reported in previous researches. The response rate one month after H. pylori eradication was also calculated. The patients did not receive any ITP treatments from the beginning of the evaluation phase until the end of the study. Splenectomy was performed for all subjects with platelet counts ≤ 30,000/L at any stage after H. pylori eradication.

The definition provided by the International Working Group on ITP was used in the measurement of clinical response to treatment (36). CR was considered as platelet counts ≥ 100,000/L for more than two months with or without maintenance therapy. Platelet counts ≥ 30,000/L, i.e. at least twice the baseline values, over a period of more than two months were regarded as partial response (PR). No response (NR) was defined as platelet counts below 30,000/L or those with less than 50% increments compared to the baseline values with or without maintenance therapy.

Results

Normally distributed quantitative variables were described as mean ± standard deviation (SD). The normality of quantitative variables was tested by Shapiro-Wilks test. A Fisher's exact test was used to compare the rate of CR to splenectomy in our

study with the previously reported rates. The same test was adopted to examine the associations of age, gender, and ITP classification with both initial response (one month after H. pylori eradication) and response after H. pylori eradication plus splenectomy. P values less than 0.05 were considered statistically significant. All analyses were performed using SPSS 11.5 (SPSS Inc., Chicago, IL, USA).

A total of 50 patients with complete H. pylori eradication were recruited. However, data from 38 cases who needed splenectomy during the follow-up visits were included in the statistical analyses. The mean age of these patients was 34.82 ± 15.66 years and 22 of them (57.9%) were female. Mild, moderate, and severe ITP were observed in six (15.8%), four (10.5%), and 28 (73.7%) patients, respectively. Age, gender, and ITP classification were not significantly related with either initial response or response after splenectomy.

After splenectomy, CR and PR were seen in 36 (94.7%) and two (5.3%) patients, respectively. The overall response rate (ORR) was 100%. According to previous research, the average sustained CR to splenectomy is 65% around the world (37). Apparently, the CR rate obtained in the current research (94.7%) significantly higher than the mentioned rate ($P < 0.0001$; Table 1).

Table1. Complete response rate in the present research and previous studies (around the world)

Treatment/Response	No. of complete responses	No. of patients	Percentage
Splenectomy after H. pylori eradiation	36	38	0.947368
Standard success rate of splenectomy	65	100	0.650000

Notes: Difference = p (1) - p (2), Estimate for difference: 0.297368, 95% confidence interval for difference: (0.179981, 0.414756), Test for difference = 0 (vs. ≠ 0), Z = 4.97

In addition, our results showed that after H. pylori eradication alone, CR, PR, and NR were detected in only one (2.6%), four (10.5%), and 33 (86.8%) patients, respectively.

Discussion

Splenectomy has long been employed as the treatment primary option in ITP patients who require additional treatment after a course of medical treatment (38). Although splenectomy leads to a rapid rise in platelet counts in 85% of patients, only 60%-65% of patients remain in clinical remission after splenectomy (20, 21, 38). Over the years, attempts have been made to identify the determinants a satisfactory sustained response to splenectomy.

Although the role of H. pylori infection in ITP and the need for H. pylori monitoring and treatment in such patients have been frequently investigated, the subject is still under debate due to the controversial results of research in various populations. Interestingly, different studies on ITP patients have reported a very wide range of response rates to H. pylori eradication, i.e. from 0% to 100% (4, 22, 26, 29-31).

Based on our findings, H. pylori eradication was of long-term benefit in 36 of 38 (94.7%) patients with ITP who were H. pylori positive. In fact, the treatment led to a sustained CR after splenectomy. The statistically significant difference between the sustained CR rate in our study and the global rate indicated that the rate of response to splenectomy was increased by early treatment of patients for H. pylori infection. Indeed, H. pylori eradication before splenectomy is a valuable predictor of increased response to splenectomy in patients with chronic ITP. To the best of our knowledge, this was the first research to evaluate H. pylori eradication therapy as a possible predictive factor for the long-term, relapse-free response rate to splenectomy in ITP patients. What makes our study distinctive is the long-term (five-year) follow-up of ITP patients who underwent splenectomy.

While only five out of our 38 patients (13.1%) showed response to H. pylori eradication one month after the treatment, the overall response rate after H. pylori eradication and splenectomy was 100%. In fact, there was no significant association between overall response rate and H. pylori eradication in a short-term period. Similar findings were reported by Ahn et al., Micheal et al., Suvajdzic et al., and Stasi et al. (29, 30, 31, 39). Even though the pathogenic mechanism of H. pylori-induced thrombocytopenia remains obscure, the results of this prospective study supported the use of H. pylori eradication as an effective non- immunosuppressive treatment to increase response rates after splenectomy in patients with chronic ITP. These results need to be confirmed in a study with a larger sample size and inclusion of non-endemic areas.

In conclusion, although H. pylori eradication has been accepted as an alternative ITP treatment in mild to moderate cases, this research suggested the efficacy of this treatment in enhancing sustained response to splenectomy in refractory ITP. Considering its accessibility and affordability, H. pylori eradication is strongly recommended as an adjuvant therapy in refractory ITP before splenectomy at least in endemic areas for this infection.

Compliance with Ethical Standards

Funding: There is no funding for this study because the mentioned intervention is considered as part of routine approach to patients who have ITP and H.pylori infection.

Conflict of interest: The authors declare that they have no conflict of interest.

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