Poor platelet Count Response to Helicobacter Pylori Eradication in Patients with Severe Idiopathic Thrombocytopenic Purpura

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ABSTRACT

Introduction: ITP is an autoimmune blood disorder in which platelet destruction is mediated by anti-platelet antibodies. The mechanisms of anti-platelet antibodies development are still a little known. The rate of some bacterial or viral agents in cause of ITP is well known. Recently, some study proposed that H pylori infection may be associated with ITP and H pylori eradication can improves platelet counts in infected ITP patients.

Materials and Method: A baseline platelet count <50×10^3 µL for 4 weeks prior to study entry were required. These patients were tested for H. pylori infection by urea breath. All positive H pylori patients received triple therapy for 7 or 14 days to eradicate H pylori infection. These patients followed for six months.

Results: Of 92 patients with ITP, H pylori infection was found in 59.7% (55/92). After excluding patients with confounding factors, 41 patients were remained. After H pylori eradication, CR wasn't obtained in any patients. Partial response were obtained only in 3 (7.3%) of the 41 patients and no response in 38 (92.6%) patients. There is a significant difference between the platelet counts of PR and NR groups (P<0.001).

Conclusion: the results of this study and our previously study showed H pylori eradication therapy has beneficial effect for patients with mild thrombocytopenia but the chance of obtaining a response by H pylori treatment is lower in patients with severe thrombocytopenia.

Key Words: Idiopathic thrombocytopenic purpura, Helicobacter pylori, Platelet counts

INTRODUCTION

Idiopathic thrombocytopenic purpura (ITP) is an autoimmune blood disorder characterized by the production of antibodies against platelets antigens and therefor platelet destruction. The major cause of this disorder is IgG antibodies bind to the platelet surface glycoprotein such as GPIIb-IIIa, GPIb-IX and etc.1 Still, all causes factors for developing ITP aren’t known. However, the association between this disorder with hepatitis C, Cytomegalovirus, HIV, sepsis and other viruses are known to common childhood was confirmed and this issue showed association between ITP and infection agents.2-4 In the late 1990s, Initial case reports described increased platelet counts in patients with ITP following after Helicobacter pylori (H pylori)
eradication. Since then, several studies have investigated that whether H pylori eradication can improves platelet counts in infected ITP patients. 5

H pylori is a gram-negative microaerophilic bacterium that colonizes in over half the human population. Interestingly, the prevalence of H pylori in ITP patients from 22 to 90.6 percent is changing in different parts of the world. 6-11 Since, the role of H pylori in developing ITP isn’t well known. There are several hypotheses as to why H pylori, that predominately inhabits the gastric mucosa, may be associated with developing ITP that improve or resolve after H pylori eradication. 12, 13 One hypothesis proposes that an H pylori surface antigen, such as the anti cytotoxin associated gene A protein (CagA), evokes a host systemic immune response that produces auto-antibodies cross reactive with host platelets. This hypothesis may explain the observed variability in treatment effect by country since CagA-positive strains of H pylori are more prevalent in some countries. Other proposed mechanisms are modulation of host immunity following colonization by H pylori to favor the emergence of autoreactive B-1 cells and the enhancement of phagocytic capacity of monocytes together with low levels of the inhibitory Fcγ receptor IIB following H pylori infection. 15-18 Further, another hypothesis explain eradication therapy may result in the improvement of thrombocytopenia by mechanisms independent of H pylori including the immune modulating effects of the treatment itself or the removal of other commensal bacteria. 19

However, in reject of this hypothesis there are some data showing that a beneficial effect of the H pylori eradication without infection was not observed. 20-21

Our previously study 22 showed revealed eradication therapy of H pylori infection can improve platelet counts in ITP patients with mild thrombocytopenia and it seems this eradication cannot have a major role in the treatment in a little group of severe ITP patients of our study. In this study we investigated the effects of H pylori eradication on platelet counts in a larger group of severe ITP patients in a teaching hospital in Kermanshah, west of Iran.

MATERIALS AND METHODS

Patients

The medical records of 92 (50 male and 42 female) adult with severe chronic ITP that refer to us between June 2008 and November 2012 were retrospectively examined for the presence of gastric H pylori infection. The diagnosis of ITP was confirmed by a hematologist according to standard criteria. 21 A baseline platelet count <50×10³ μL for 4 weeks prior to study entry were required. Cases of thrombocytopenia caused by drugs, pseudo thrombocytopenia, family history consistent with inherited thrombocytopenia, human immunodeficiency virus infection, hepatitis, and autoimmune disorders were excluded. Patients were excluded if they had been treated for H pylori within 2 years of recruitment or if they had been treated with an antibiotic or proton pump inhibitor within the previous 4 weeks. 13 According to declaration of Helsinki; we took consent from all patients before H pylori eradication for remedy of their ITP disorders.

Diagnosis and Treatment

All 92 Patients were screened for H pylori infection using H pylori urea breath test (UBT) and serum H pylori antibody. H pylori infection was treated with standard eradication therapy: amoxicillin 1000 mg twice daily, clarithromcin 500 mg twice daily, and a proton pump inhibitor 40 mg twice daily for 2 weeks. Platelet counts were obtained at baseline and then every 2 weeks until month 6.

Response Criteria

Complete response (CR) was defined as a platelet count >150×10³ μL at month 6. Partial response (PR) was defined by a platelet increase of >30×10³ μL at month 6. Relapse was defined as any platelet count below either of these values after month 6. No response (NR) was defined as any platelet count below either of these values after month 6.

Statistical Analysis

Differences of platelet count are expressed as the mean (SD) as appropriate. A Mann-Whitney-u test was used for analysis of platelet differences in 3
groups (CR, PR and NR). A P-value of less than 0.05 was considered statistically significant. All statistical analysis was performed by using SPSS software version 21.0.

RESULTS

Of 92 patients with ITP, H pylori infection was found in 59.7% (55/92) of patients. Five patients with autoimmune disorders, two patients with HBV infection and one patient with HCV infection were excluded. Thus 47 patients were considered whom 41 (21 males, 20 females) achieved H pylori eradication (87.2%). Median disease duration before H pylori eradication was 2.2 month (1- 4.5 months). There is no significant different between platelet response and disease duration (P>0.08). We followed up patients 6 mount. Outcomes after H pylori eradication of the patients with ITP are indicated in Table 1. After H pylori eradication, CR wasn’t obtained in any patients. Partial response were obtained only in 3 (7.3%) of the 41 patients and no response in 38 (92.6%) patients (Figure 1). There is a significant difference between the platelet counts of PR and NR groups (P<0.001).

Table 1: Clinical and Platelet Response Characteristics by Patient

| No | Patient | Sex | Age | Baseline platelet count×10^3 | Mount 6 platelet count×10^3 | Response status |
|----|---------|-----|-----|-----------------------------|-----------------------------|----------------|
| 1  | F       | 27  | 26  | 39                          | NR                          |
| 2  | M       | 19  | 38  | 52                          | NR                          |
| 3  | F       | 54  | 47  | 72                          | NR                          |
| 4  | M       | 37  | 31  | 51                          | NR                          |
| 5  | M       | 63  | 35  | 59                          | NR                          |
| 6  | M       | 29  | 41  | 69                          | NR                          |
| 7  | F       | 61  | 29  | 37                          | NR                          |
| 8  | F       | 35  | 21  | 32                          | NR                          |
| 9  | F       | 39  | 23  | 35                          | NR                          |
| 10 | F       | 22  | 44  | 86                          | PR                          |
| 11 | M       | 46  | 43  | 71                          | NR                          |
| 12 | M       | 31  | 36  | 59                          | NR                          |
| 13 | M       | 44  | 37  | 65                          | NR                          |
| 14 | F       | 28  | 48  | 79                          | PR                          |
| 15 | M       | 51  | 33  | 49                          | NR                          |
| 16 | F       | 39  | 28  | 32                          | NR                          |
| 17 | F       | 48  | 24  | 38                          | NR                          |
| 18 | M       | 33  | 35  | 58                          | NR                          |
| 19 | M       | 67  | 22  | 35                          | NR                          |
| 20 | F       | 31  | 47  | 86                          | PR                          |
| 21 | F       | 25  | 26  | 42                          | NR                          |
| 22 | F       | 20  | 31  | 47                          | PR                          |
| 23 | F       | 38  | 38  | 52                          | NR                          |
| 24 | M       | 48  | 29  | 41                          | NR                          |
| 25 | M       | 58  | 27  | 49                          | NR                          |
| 26 | F       | 30  | 31  | 59                          | NR                          |
| 27 | M       | 48  | 47  | 75                          | NR                          |

DISCUSSION

ITP is an autoimmune blood disorder in which platelet destruction is mediated by anti-platelet antibodies. The mechanisms of anti-platelet antibodies development are still a little known. The rate of some bacterial or viral agents in cause of ITP is well known. It has been demonstrated that the mimicry of human antigens by infection agents represents the mechanism underlying this phenomenon. Many studies have shown an association between H pylori infection and ITP, and substantial evidence has indicated that achieving H pylori eradication can lead to a significant improvement in platelet counts in these H pylori -positive ITP patients. Gasbarrini et al., First reported that 61% of 18 ITP cases with H pylori were eradicated, showed significant increases in mean platelet count after 2 and 4 months with disappearance of anti-platelet antibody. In recent
years, many studies have demonstrated improvement of platelet counts in ITP patients after treatment of H pylori infection.\textsuperscript{13-18}  
Several studies have treated both H pylori positive and H pylori negative patients with H pylori eradication therapy with no responses in the H pylori negative group.\textsuperscript{6, 14, 24, 25} Further, Arnold et al., concluded that treatment of thrombocytopenia in adults with ITP using H pylori eradication therapy should be reserved for patients with active H pylori infection.\textsuperscript{21} A beneficial effect of the treatment for H pylori-negative patients was not observed. So, we excluded H pylori-negative patients from our study. Also, we excluded patients with confounding factors to avoid bias in our results.  
In present study, the prevalence of H pylori infection in severe ITP patients was 59.7%. In our previous study,\textsuperscript{22} the prevalence of H pylori infection in ITP patients was 69.3%. This difference indicate that the prevalence of H pylori infection in severe ITP patients is lower than mild ITP patients and it suggest this hypothesis H pylori infection in severe ITP patients is less important as the major cause of this disorder. Nevertheless, this prevalence is high and this rate almost similar to prevalence of H pylori infection in the general population in Iran.\textsuperscript{26} These results also were comparable to those of previous studies which were done in Asian countries such as Japan and South Korea but this rate is in contrast studies were conducted in Western countries.\textsuperscript{27} In general, the prevalence of H pylori infection varies according to geographic location and in Asian countries such as Iran is too high.  
In this study all patients with H pylori infection was treated with triple therapy regime and eradication rate was 87.2%. This finding is in agreement to other studies which they have showed successful eradication greater than 70% using triple therapy.\textsuperscript{28, 29}  
The platelet recovery rate after H pylori eradication therapy appears to be as heterogeneous between studies as the response rates. In most studies, a shorter ITP duration is correlated with better chance of response.\textsuperscript{12, 29} In present study, median disease duration before H pylori eradication was 2.2 month and there is no significant different between platelet response and disease duration.  
There are conflicting reports about the predictive value of baseline platelet count.\textsuperscript{24, 28} In our previous study,\textsuperscript{22} we had 65.6% of patients that have response to eradication and all responders had platelet count $\geq50 \times 10^3 \mu\text{L}$. Also, we observed poor response to treatment in ITP patients with severe thrombocytopenia. So, we concluded H pylori eradication can improve platelet counts in ITP patients with mild thrombocytopenia but not in severe ITP patients. But, because of a few number of severe ITP patients (11/26 patients) we couldn’t conclude exactly.  
In our present study, we saw poor response to treatment in patients with severe thrombocytopenia, again. In this study all of patients had baseline platelet count $<50 \times 10^3 \mu\text{L}$. Of 41 patients that achieved H pylori eradication just 3 (7.3%) patients had partial response and other patients had no response. Also, there were no patients with complete response. These results suggest that probably, patients with severe thrombocytopenia ($<50 \times 10^3 \mu\text{L}$) appear to have fewer chances of response, although this issue has not been systematically addressed in most published reports. In confirm, an Italian/UK study Indicated that 33% (17 of 52) patients had platelet responses, but only 1 response was observed among patients with severe thrombocytopenia.\textsuperscript{30}  
In conclusion, the results of this study and our previously study showed H pylori eradication therapy has beneficial effect for patients with mild thrombocytopenia but the chance of obtaining a response by H pylori treatment is lower in patients with severe thrombocytopenia. Further studies are required to clarify causative factors involved in platelet recovery, monitor the duration of response, and understand the mechanism underlying the response to eradication therapy.  

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