Efficacy of helicobacter pylori eradication as an upfront treatment of secondary immune thrombocytopenia: an experience from Pakistan

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ABSTRACT

Background: The effect of *Helicobacter-pylori* eradication therapy on the platelet counts in patients with immune thrombocytopenia is still debatable. The aim of this study was to assess the response rates of standard triple eradication therapy in secondary immune thrombocytopenia with *Helicobacter pylori* infection.

Methods: From January 2012 to December 2013, 197 patients were diagnosed to have immune thrombocytopenia, out of which 22(11.1%) patients infected with *Helicobacter-Pylorus* were enrolled in this study. *Helicobacter-Pylori* infection was documented by *Helicobacter-pylori* stool antigen enzyme immunoassay method. All positive patients were put on triple eradication therapy. The responses rates to treatment were defined as per International Working Group on ITP.

Results: Mean age of patients was 43.18±12.5 years. There were 10(45.5%) males and 12 (54.5%) females. Of the 22 patients, 7(31.8%) exhibited a complete response (CR) to *H-pylori* eradication therapy; 10(45.4%) attained a response; and 5(22.7%) had no response. Mean base line platelet counts were 53.36±24.5x10^9/l, while platelet counts at 4 week following eradication was 80.86±51.0x10^9/l (P=0.003). The predictive factor of response following eradication therapy was baseline platelet counts. Virtually all responders had baseline platelet counts >30x10^9/l and all non-responders had <30x10^9/l of platelet counts.

Conclusions: Though the prevalence of *H-pylori* is low, this study confirmed the efficacy of eradication in increasing the platelet counts in *H-pylori* positive patients with ITP. It is an important measure in short time, safe and very cost effective to achieve platelets increment. We endorse the routine detection and eradication treatment of *H-pylori* infective ITP patients.

KEY WORDS:
Helicobactor Pylori, Immune thrombocytopenia, Eradication, Platelet counts

INTRODUCTION

Immune Thrombocytopenic Purpura (ITP) is an acquired immune mediated thrombocytopenia defined by a low platelet count secondary to rapid platelet destruction and impaired production by auto-antibodies against the platelet.[1,2] The incidence of adult ITP range 1.6-3.9 per 100,000 peoples per year with female to male ratio of 1.9.[2] ITP is more commonly seen in older people being twofold greater in people older than 60 years.[3] Gender variance disappears with the progression of age.[3]

ITP may follow secondarily in certain infectious diseases, lymphoproliferative neoplasm, autoimmune disorders and drugs.[4] Amongst the infections, *Helicobacter Pylori* is an important etiological factor as its existence can cause the persistence of disease. [5] *Helicobacter pylorus* is a spiral shaped microaerophilic gram negative bacterium which has been implicated in the aetiology of many gastrointestinal disorders. Recently, *H. pylorus* has been linked with various extra-intestinal and immune mediated diseases including pernicious anaemia, idiopathic thrombocytopenic purpura, rheumatoid arthritis and auto immune thyroiditis.[6]

The prevalence of *Helicobacter pylori* infection in ITP patients varies to a great extent according to the geographical distribution.[7] Several studies have demonstrated significant improvement in the platelet count after *H. pylori* eradication therapy in ITP patients.[6-8] Initial reports from Japanese and Italian studies showed the significant recovery in platelet counts following eradication in secondary ITP. On the contrary, some investigators have reported that there was no notable increment in the platelet counts following eradication treatment.[9,10] A large systemic review of 25 western studies by Stasi *et al*, found a complete response rate of 42.7%.[11] However, data from South Asian countries is limited on this aspect of ITP.

Previously no studies have been reported from Pakistan regarding the efficacy of eradication treatment of H. pylori in ITP patients. Hence, this study has been done to evaluate the role of H. pylori infection in ITP and to determine the effect of its eradication on platelets recovery.

MATERIALS AND METHODS

Patients:

This prospective cross-sectional study was conducted in Hematology Unit, Liaquat National Hospital, Karachi from January 2012 to December 2013. Patients were diagnosed as

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ITP on the basis of careful history, physical examination, complete blood count and peripheral smear examination. An informed consent was obtained from all the participating patients.

Following enrolment, all the 197 patients had baseline platelet counts, complete blood count, HbsAg, Anti HCV, ANA and stool for Helicobacter pylori. Out of 197 patients, 22 patients were selected who had positivity for stool for *H pylori.* The diagnosis of ITP was made according to the criteria set by American Society of Hematology guidelines based on baseline platelets counts <100 x 10^9/l[12].

Patients with other causes of thrombocytopenia such as Hepatitis C virus, Hepatitis B virus infections and ANA positivity were excluded. The patients also were excluded if they had received eradication therapy for *H. pylori* infection within the previous two years of enrolment or an antibiotic/proton pump inhibitors within the previous one month. Those patients who had active life threatening bleeding at the time of enrolment were also excluded.

Ethical approval was obtained from the institutional ethical and research committee prior to the study.

Diagnosis and Treatment:
H. pylori infection was detected by using *Helicobacter pylori* stool antigen (HpSA) enzyme immunoassay method (EIA). The specificity and sensitivity of the test are 96% and 83% respectively, results were reported as positive or negative.[13]

All selected patients were treated with standard triple eradication therapy: amoxicillin 1000 mg twice daily, clarithromcin 500 mg twice daily and a proton pump inhibitor 40 mg twice daily for two weeks.

Response Criteria:
The clinical response to treatment was defined as by International Working Group on ITP.[12] Complete response (CR) was defined as a platelet count ≥100×10^9/L and the absence of bleeding. Response (R) was defined a platelet count ≥30×10^9/L or greater than 2-fold increase in platelet count from baseline and the absence of bleeding.No response (NR) was defined a platelet count <30×10^9/L or less than doubling of the baseline count and the presence of bleeding.

Data analysis:
Data was compiled and analysed on Statistical Package of Social Sciences (SPSS) version 21. Mean±SD was calculated for the quantitative variables, i.e. age, platelet count, haemoglobin, MCV and WBC count. Frequency and percentages were calculated for qualitative variables i.e. gender and outcome. Chi-square test was used to determine significant difference in qualitative variables. P-value <0.05 was considered as significant.

RESULTS

Of 197 patients with ITP, *H. pylori* infection found in 22 (11.1%) patients were enrolled. There were ten (45.5%) males and 12 (54.5%) females. The mean age of patients was 43.18±12.5 years.

In the present study, ten (45.4%) patients were symptomatic and remaining 12 (54.5%) were asymptomatic. Symptomatic patients had mucosal bleeds and none had visceral, intracranial or life threatening bleeds. The most common symptom was epistaxis in five (22.7%) followed by gum bleeding in three (13.6%) and menorrhagia in two (9.0%).

The mean haemoglobin levels at presentation were 12.35±1.44 g/dl, while mean corpuscular volume was 84.9±7.5fl. The total leukocyte count and platelets count were 6.8±2.0x10^9/l and 53.3±24.5x10^9/l respectively.

Successful complete eradication (CR) effects were achieved in 7/22 patients (31.8%). The response rate (R) of platelets recovery was 45.4% (10/22 patients) and 22.7% (5/22) patients were non responder (NR). The mean base line platelets counts were 53.36±24.5x10^9/l, while platelet counts at four week following eradication therapy was 80.86±51.0x10^9/l (P=0.003).

The predictive factor of response following eradication therapy was baseline platelets counts. There is a significant difference between the baseline platelet counts of responders (CR & R) and non-responders (NR) groups. Virtually all responders had baseline platelets counts >30 x 10^9/l and all non-responders had <30 x 10^9/l of platelets counts. None of the patients showed any serious drugs side effects during and after the eradication treatment.

DISCUSSION

Helicobacter pylori is a gram-negative microaerophilic bacterium that inhabits the human stomach of more than 50% of the world population.[14] Several studies have proposed that *H. pylori* infection may be associated with haematological disorders including iron deficiency anaemia and immune thrombocytopenic purpura.[15]

Helicobacter pylorus bacterium association with ITP was initially reported in 1998 by Gasbirrini *et al.* from Italy, in which increment in platelet count were seen in 8/11 ITP patients following eradication.[5] Subsequently many Italian and Japanese studies reported the causative role of *H. pylori* in immune thrombocytopenia and platelet response were seen after eradication therapy in these studies.[5,16-19] Clinical reports have depicted a spontaneous resolution of ITP in about 50% of ITP patients following empirical treatment of *H. pylori* infection, but response rate are variable depending upon geographical distribution.[20]

Noonavath *et al.*, from India reported a complete response and partial response in 13 and three patients respectively, in a series of 16 patients, none was none responder (NR).[15] Recently another regional study from Iran disclosed 57.7% of patients exhibited a complete response following eradication.[21]

A study reported by Inaba *et al.* of 35 ITP patients, in which 25 were *H-Pylori* positive and ten were negative for *H-Pylori.*[22] A platelet response was seen in 11 (44%) of the 25 patients who were *H-Pylori* positive, and in none of the *H pylori*-negative patients (P=0.01).22 Fujimara et al from Japan

reported that after successful eradication therapy platelet increment was seen in 63% of the chronic ITP patients.[23] Another Japanese study in which 37 known ITP patients of both *H-Pylori* positive and negative were revealed 62% patients were responders who were *H pylori* positive, while in the H pylori negative patients none was responder.[24]

Tsutsumi *et al.* matched the treatment effectiveness and advantage of *H pylori* ordinary eradication treatment with PPI single therapy.[25] 4/9 patients in the triple remedy group attained a complete remission (CR) and two attained a partial remission (PR); in the single remedy group three attained a CR and two attained a PR out of 8 patients.[25] The longstanding outcomes of *H pylori* eradication have been described freshly by an Italian researcher.[26] The subsequent follow-up of 60 months, obstinate platelet response was detected in 23/34 (68%) patients with eradicated infection; just one relapse ensued.[26]

In our study the pre-treatment indicator that was more reliably related with a platelet response to *H pylori* eradication was a baseline platelets counts. Those patients who had extremely low platelet counts ($<30 \times 10^9$/L) seemed to have little likelihoods of response, while this matter has not been thoroughly addressed in most of the studies. Stasi *et al* reported that platelet responses were perceived in 17/52 patients, but in severe thrombocytopenic patients, merely one response was perceived.[27] Additional features, such as age, gender, and prior treatments were not valuable to expect the platelet response.

In disparity, the effects of eradication therapy had no favourable effect on platelet recovery in other series. Ahn *et al.* from the USA reported increased platelet count only in 6.7% of treated patients.[9] Similarly mild platelet response were observed in ITP patients after eradication therapy of *H. pylori* infection in studies done by Stasi et al and Micheal *et al.*[27,28] Lastly, a recent report from Malaysia by Gan *et al.* also showed that eradicating the infection did not have any sustained effect in the platelet recovery.[29]

There is a major inconsistency in the platelet response to eradication treatment between different nations. Studies conducted in Japan and Italy reporting the response rates of 39% to 100% in *H pylori* positive patients with ITP.[30] Though, *H-Pylori* positive patients from Spain and the United States with ITP when eradicated by triple regime therapy giving minor or no platelet response.[28,31] Furthermore, comparatively intermediate response rates were perceived from present study (31.8%) and current studies from Serbia and Turkey (26% and 40%, respectively).[10,32]

Lastly results of this study also strengthens to eradicate *H pylori* infection in secondary ITP; as this is simple, short term, cost effective, safe, non-invasive with favourable outcomes and no toxicity of drugs.

CONCLUSION

Although the prevalence is low (11.1%) in our step up, *H. pylori* positive Pakistani patients with ITP definitely benefit from eradication therapy. Results of this study revealed eradication therapy of *H. pylori* infection can restore platelet counts in ITP patients particularly if baseline platelets are >30 x10^9/l. Also, that *H. pylori* eradication cannot have a major role in the management of severe ITP patients. Thus, this study supports routine detection and eradication of *H. pylori* infection in ITP patients in Pakistani population.

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