

Helicobacter pylori eradication in patients with chronic immune thrombocytopenic purpura

Ravinder Naik Noonavath, Chandrasekharan Padma Lakshmi, Tarun Kumar Dutta, Vikram Kate

Ravinder Naik Noonavath, Department of Surgery, Jawaharlal Institute of Postgraduate Medical Education and Research, Pondicherry 605006, India

Chandrasekharan Padma Lakshmi, Department of Medical Gastroenterology, Jawaharlal Institute of Postgraduate Medical Education and Research, Pondicherry 605006, India

Tarun Kumar Dutta, Department of Clinical Hematology, Jawaharlal Institute of Postgraduate Medical Education and Research, Pondicherry 605006, India

Vikram Kate, Department of General and Gastrointestinal Surgery, Jawaharlal Institute of Postgraduate Medical Education and Research, Pondicherry 605006, India

Author contributions: Noonavath RN collected data, compiled the manuscript, literature review; Lakshmi CP performed data interpretation, literature review; Dutta TK contributed to data analysis, data interpretation, literature review, and supervised manuscript preparation; Kate V contributed to data analysis, design and overall conceptualization of the manuscript.

Correspondence to: Vikram Kate, MS, FRCS (Eng.), FRCS (Ed.), FRCS (Glasg.), PhD (Surg. Gastro.), MAMS, FIMSA, MASCRS, FACS, FACG, Professor of General and Gastrointestinal Surgery, Jawaharlal Institute of Postgraduate Medical Education and Research, Pondicherry 605006, India. drvikramkate@gmail.com

Telephone: +91-413-2203330 Fax: +91-413-2272066

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Abstract

AIM: To assess the effect of *Helicobacter pylori* (*H. pylori*) eradication on platelet counts in patients with chronic immune thrombocytopenic purpura (cITP).

METHODS: A total of 36 cITP patients were included in the study. The diagnosis of *H. pylori* was done by rapid urease test and Giemsa staining of the gastric biopsy specimen. All *H. pylori* positive patients received standard triple therapy for 14 d and were subjected for repeat endoscopy at 6 wk. Patients who continued to be positive for *H. pylori* on second endoscopy

received second line salvage therapy. All the patients were assessed for platelet response at 6 wk, 3rd and 6th months.

RESULTS: Of the 36 patients, 17 were positive for *H. pylori* infection and eradication was achieved in 16 patients. The mean baseline platelet count in the eradicated patients was $88615.38 \pm 30117.93/\text{mm}^3$ and platelet count after eradication at 6 wk, 3 mo and 6 mo was $143230.77 \pm 52437.51/\text{mm}^3$ ($P = 0.003$), $152562.50 \pm 52892.3/\text{mm}^3$ ($P = 0.0001$), $150187.50 \pm 41796.68/\text{mm}^3$ ($P = 0.0001$) respectively and in the negative patients, the mean baseline count was $71000.00 \pm 33216.46/\text{mm}^3$ and at 6 wk, 3rd and 6th month follow up was $137631.58 \pm 74364.13/\text{mm}^3$ ($P = 0.001$), $125578.95 \pm 71472.1/\text{mm}^3$ ($P = 0.005$), $77210.53 \pm 56892.28/\text{mm}^3$ ($P = 0.684$) respectively.

CONCLUSION: Eradication of *H. pylori* leads to increase in platelet counts in patients with cITP and can be recommended as a complementary treatment with conventional therapy.

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Key words: *Helicobacter pylori*; Immune thrombocytopenic purpura; Platelet counts

Core tip: Immune thrombocytopenic purpura (ITP) is an autoimmune haematological disorder in which destruction of platelets is mediated by auto-antibodies in the reticuloendothelial system. Some studies have demonstrated improvement in the platelet count after *Helicobacter pylori* (*H. pylori*) eradication in cITP. The present study describes the effect of *H. pylori* eradication on the platelet count in patients with cITP. It was found that following *H. pylori* eradication there was a significant sustained rise in the platelet count at 6 wk, 3rd and 6th months following eradication. In patients where conventional therapy was administered, although there was a significant rise in the platelet count at 6 wk and

3rd month, it was found that at 6th month the platelet count was similar to the baseline pre therapy level.

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INTRODUCTION

Helicobacter pylori (*H. pylori*) is a spiral shaped microaerophilic gram-negative bacterium, first isolated from gastric biopsy by Robin Warren and Barry J. Marshall in 1984. *H. pylori* has been implicated in the aetiology of many upper gastrointestinal disorders like acid peptic disease, chronic gastritis and gastric lymphoma (MALToma)^[1]. Recently, *H. pylori* has been found to be associated with various extra-intestinal and immune mediated diseases, including pernicious anemia, idiopathic thrombocytopenic purpura (ITP), rheumatoid arthritis, auto immune thyroiditis and Sjogren's syndrome^[2,3].

Some studies have shown an increased prevalence of *H. pylori* infection in patients with chronic ITP (cITP) compared to the general population^[4]. The prevalence of *H. pylori* infection in cITP patients varies according to the geographic region^[5]. Some studies have demonstrated significant improvement in the platelet count after *H. pylori* eradication in cITP patients^[2,3,6-8]. Several mechanisms have been proposed to explain the association of *H. pylori* infection and ITP. *H. pylori* surface antigen, such as cytotoxin associated gene A protein (CagA) evokes host systemic immune response that produces auto antibodies which cross-reacts with host platelets^[9].

However, some studies have reported that there was no significant improvement of platelet counts after eradication of *H. pylori* infection in cITP patients^[10,11].

To the best of our knowledge, no studies have been reported from India regarding the association of *H. pylori* and cITP. Hence, this study has been done to evaluate the role of *H. pylori* infection in cITP and the response of *H. pylori* infected cITP patients to the eradication of *H. pylori*.

MATERIALS AND METHODS

All the patients attending the haematology clinic of JIPMER hospital, Puducherry in-between September 2011 to July 2013 with the diagnosis of cITP were included in the study. The diagnosis of cITP was confirmed by a haematologist according to the standard criteria proposed by the American Society of Haematology guidelines^[12]. cITP was defined as ITP that persists for more than 6 mo^[13]. The study was conducted after obtaining clearance

from the Institute Research Council and Ethics Committee. Informed written consent was obtained from all the patients included in the study.

After enrolment in the study, all the patients had baseline platelet counts, complete blood count and serology for hepatitis B, hepatitis C and human immunodeficiency virus analysis done. A baseline platelet count of less than 120000/mm³ and stable treatment for 3 wk prior to study entry were included in the study.

Patients with other causes of thrombocytopenia such as Hepatitis C virus, Human Immunodeficiency virus or Hepatitis B virus infections were excluded. The patients also were excluded if they had received eradication therapy for *H. pylori* infection within the previous 2 years of enrolment or an antibiotic or proton pump inhibitor within the previous 4 wk. Those patients who had active life threatening bleeding at the time of enrolment were also excluded.

All cITP patients underwent diagnostic upper gastrointestinal endoscopy (UGIE). Four gastric mucosal biopsies were taken (two from the antrum and two from the body) and subjected to rapid urease test and histology by Giemsa staining for the diagnosis of *H. pylori* infection. A biopsy of mucosa is taken from the stomach and placed into the solution containing urea with phenol red as indicator and observed for 24 h. The urease produced by *H. pylori* catalyzes the urea to ammonia, which raises the pH of the solution, and changes the colour from yellow (negative) to red (positive). This urease test was earlier standardized in our institution, which contained 250 mg urea, 400 µL of gentamycin (40 mg/mL), and 400 µL of phenol red in 15 mL of distilled water^[14].

Any one or both above mentioned tests, if positive, were considered to be positive for *H. pylori* infection. Eradication of *H. pylori* was defined when a patient was negative for urease test and *H. pylori*. After endoscopy and biopsy, the patients were divided into two groups.

Study group - *H. pylori* positive patients (Cases) were given standard first line eradication therapy for *H. pylori* (capsule- amoxicillin 1 gm twice daily, tablet- clarithromycin 500 mg twice daily, and capsule- omeprazole 20 mg twice daily for 14 d).

Control group - This group included cITP patients negative for *H. pylori*. The conventional therapy for ITP was continued (Prednisolone/Dapsone/azathioprine) for them.

Regular follow up was done at the end of 6 wk, 3 mo, and 6 mo following completion of eradication therapy. Study group were subjected for repeat UGIE with rapid urease test and histology by Giemsa stain to confirm the eradication of *H. pylori* at the end of 6 wk. The patients who continued to be positive for *H. pylori* on second endoscopy received second line salvage regime with amoxicillin 1 mg twice daily, levofloxacin 500 mg twice daily, and omeprazole 20 mg twice daily for 14 d, to eradicate *H. pylori*. In both the groups the platelet counts were estimated at 6 wk, 3 mo and 6 mo follow up.

Table 1 Prevalence of *Helicobacter pylori* in patients with immune thrombocytopenic purpura (*n* = 36)

ITP Patients	<i>n</i> (%)
<i>H. pylori</i> positive	17 (47.2)
<i>H. pylori</i> negative	19 (52.8)
Total	36 (100)

ITP: Immune thrombocytopenic purpura; *H. pylori*: *Helicobacter pylori*.

Statistical analysis

Statistical analysis was done by using SPSS 19.0 software version for windows. The following variables were analyzed to identify factors associated with the improvement in the platelet count after eradication therapy: age, sex, disease duration, duration of *H. pylori* eradication therapy, platelet count before and after *H. pylori* eradication, endoscopic and histopathological findings.

The χ^2 *t* tests was used for comparison of age and gender distribution, disease duration, and mean baseline platelet counts between *H. pylori* negative and *H. pylori* positive cITP patients. χ^2 test was used for comparison of UGIE findings and platelet response between *H. pylori* eradicated and *H. pylori* negative cITP patients. Unpaired student *t* test was used for comparing platelet count response between *H. pylori* eradicated and *H. pylori* negative patients during follow up period. A *P* value of less than 0.05 was considered as statistically significant.

RESULTS

A total of thirty seven patients were enrolled in the study. Out of these, 36 patients underwent UGIE and biopsies were taken and subjected to rapid urease test and histology by Giemsa stain for the diagnosis of *H. pylori*. After endoscopy and biopsy, patients were divided into two groups.

Total of seventeen patients were diagnosed to have *H. pylori* infection with cITP. Table 1 shows the prevalence of *H. pylori* infection in the study population (47.2%). The mean age in both the groups was similar. In *H. pylori* positive cITP patients the mean age was \pm SD of 29.1 ± 10.9 years and in *H. pylori* negative patients the mean age was \pm SD of 29.8 ± 9.2 years, ($P < 0.0830$). Most of the patients 15/36 (41.5%) were in the age group of 21-30 years with a mean age of 29.5 ± 9.92 years (range: 14-52 years).

The gender distribution between the groups was similar. Among *H. pylori* positive patients, 2 were males and 15 were females and in *H. pylori* negative group, 5 were males and 14 were females ($P \leq 0.271$). In the present study, the most common symptom was gum bleeding 18 (52.9%) followed by menorrhagia 11 (32.4%), petechiae 4 (11.8%) and epistaxis 1 (2.9%).

The mean cITP duration between *H. pylori* positive and *H. pylori* negative patients was 2.09 ± 1.9 years *vs* 5.3 ± 6.4 years ($P \leq 0.057$). The mean baseline platelet count between *H. pylori* positive and *H. pylori* negative patients

was $81588.2 \pm 7100/\text{mm}^3$ *vs* $34294.8 \pm 33216.5/\text{mm}^3$, ($P = 0.354$).

As regards UGIE findings, 18 (50.0%) had gastritis, 15 (41.7%) had normal study and 3 (8.3%) had ulcer. The UGIE findings were similar in both *H. pylori* positive and *H. pylori* negative patients and the difference was not significant ($P = 0.66$).

Comparison of the platelet count at 6 wk, 3 mo and 6 mo between *H. pylori* eradicated and *H. pylori* negative patients from the baseline count is shown in the Table 2, Table 3 and Table 4 respectively. Eradication of *H. pylori* in the patients with cITP achieved a significant increase in the platelet count at 6 wk, 3 mo and 6 mo follow up, whereas with conventional therapy in *H. pylori* negative patients although there was short term benefit in the platelet response at 6 wk and 3 mo follow up, the platelet count reduced a 6 mo follow up closer to the baseline counts ($P = 0.0001$).

Table 5 shows the comparison of platelet response in the patients with successful eradicated and *H. pylori* negative patients. Among sixteen *H. pylori* eradicated patients, 13 had a complete response (CR), 3 had partial response (PR) and in 19 *H. pylori* negative patients, 5 had complete response, 5 had partial response and 9 patients did not have any response (NR) ($P = 0.002$).

In the present study, platelet response (CR, PR and NR) was assessed between the successful *H. pylori* eradicated (13/3/0) and *H. pylori* negative patients (5/5/9), and it was statistically significant ($P = 0.002$).

Assessment of platelet response was done as per the following criteria - CR - platelet count of at least 120000 for more than 2 mo, PR - platelet count of at least 20000 and at least doubling the base line count over a period of more than 2 mo. NR - platelet counts below 20000 or when the counts do not increase to more than 50% of the pretreatment level.

DISCUSSION

ITP is an autoimmune hematological disorder in which destruction of the platelets is mediated by anti-platelet auto-antibodies in reticuloendothelial system^[15]. The mechanisms of anti-platelet auto-antibodies development are still not yet known. In recent years, several studies have proposed that *H. pylori* infection may be associated with extra gastrointestinal diseases, especially haematological disorders like iron deficiency anaemia and immune thrombocytopenic purpura^[15].

In 1998 Gasbarrini, for the first time proposed that *H. pylori* infection may be associated with ITP and showed that, there was a significant improvement of platelet counts in *H. pylori* positive ITP patients after eradication of *H. pylori* infection^[2]. Emilia *et al*^[16] have demonstrated that *H. pylori* eradicated cITP patients exhibited a significant increase in the platelet count. Sato *et al*^[8] and Inaba *et al*^[7]. Demonstrated a favourable platelet response in the patients in whom *H. pylori* was successfully eradicated

In the present study, the results are similar to that of

Table 2 Comparison of platelet count at 6 wk follow up between *Helicobacter pylori* eradicated patients and *Helicobacter pylori* negative patients (n = 32)

Groups	n	Platelet count (mean ± SD)/mm ³	P value ¹	CI
<i>H. pylori</i> eradicated	13		0.003	-89230.8 - -20000
Baseline count		88615.38 ± 30117.93		
Count at 6 wk		143230.77 ± 52437.51		
<i>H. pylori</i> negative	19		0.001	-104526 - -2736.8
Baseline count		71000.00 ± 33216.46		
Count at 6 wk		137631.58 ± 74364.13		

¹Unpaired t test. *H. pylori*: *Helicobacter pylori*.**Table 3 Comparison of platelet count at 3 mo follow up between *Helicobacter pylori* eradicated patients and *Helicobacter pylori* negative patients (n = 35)**

Groups	n	Platelet count (mean ± SD)/mm ³	P value ¹	CI
<i>H. pylori</i> eradicated	16		0.0001	-100118.68 - -36256.32
Baseline count		84375.00 ± 33372.39		
Count at 3 mo		152562.50 ± 52892.3		
<i>H. pylori</i> negative	19		0.0050	-91249.09 - -17908.79
Baseline count		71000.00 ± 33216.46		
Count at 3 mo		125578.95 ± 71472.1		

¹Unpaired t test. Post salvage therapy 3 patients added to *H. pylori* eradication Group. *H. pylori*: *Helicobacter pylori*.**Table 4 Comparison of platelet count at 6 mo follow up between *Helicobacter pylori* eradicated patients and *Helicobacter pylori* negative patients (n = 35)**

Groups	n	Platelet count (mean ± SD)/mm ³	P value ¹	CI
<i>H. pylori</i> eradicated	16		0.0001	-93120.40 - -38504.60
Baseline count		84375.00 ± 33372.39		
Count at 6 mo		150187.50 ± 41796.68		
<i>H. pylori</i> negative	19		0.6840	-36862.56 - 24441.51
Baseline count		71000.00 ± 33216.46		
Count at 6 mo		77210.53 ± 56892.28		

¹Unpaired t test. *H. pylori*: *Helicobacter pylori*.**Table 5 Comparison of platelet response in patients with successful eradication and *Helicobacter pylori* negative patients**

Groups	n	Response		P value ¹	CI
		Yes (CR/PR)	No (NR)		
<i>H. pylori</i> eradicated	16	16 (13/3)	0	0.002	0.2835-0.6308
<i>H. pylori</i> negative	19	10 (5/5)	9		

¹Unpaired t test. *H. pylori*: *Helicobacter pylori*.

the previous studies, and at 6 wk follow up in patients with *H. pylori* eradication there was a significant increase in the mean platelet count from the baseline value (88615 ± 30117/mm³ vs 143230 ± 52437/mm³, $P \leq 0.003$), whereas, *H. pylori* negative patients also had a significant increase in the platelet count (137631 ± 74364/mm³) from the baseline value (71000 ± 33216/mm³, $P \leq 0.001$).

In the present study, at 3 mo follow up in the patients with *H. pylori* eradication there was a significant increase

in the mean platelet count from the baseline value (84375 ± 33372/mm³ vs 152562 ± 52892/mm³, $P \leq 0.0001$), whereas, *H. pylori* negative patients also had a significant increase in the platelet count (125578 ± 71472/mm³) from the baseline value (71000 ± 33216/mm³, $P \leq 0.005$).

In the present study, at 6 mo follow up in the patients with *H. pylori* eradication there was a significant increase in the mean platelet count from the baseline value (84375 ± 33372/mm³ vs 150187 ± 41796/mm³, $P < 0.0001$),

whereas, in *H. pylori* negative patients who received conventional therapy had a drop in mean platelet count close to the baseline value ($71000 \pm 33216/\text{mm}^3$ vs $77210 \pm 56892/\text{mm}^3$, $P < 0.684$).

It appears from the present study, in the short term such as at 6 wk and 3 mo follow up, *H. pylori* eradication therapy or conventional therapy achieved a significant increase in the platelet count. However, at 6 mo follow up it was found that patients without *H. pylori* infection who received conventional therapy had a drop in platelet count close to the baseline level, whereas in patients with *H. pylori* eradication there was sustained increase in the platelet counts. Eradication of *H. pylori* was achieved in 94% of patients with standard triple therapy and salvage therapy. This could be due to long term effect of *H. pylori* eradication therapy in *H. pylori* positive chronic ITP patients.

In contrast to our study, Stasi *et al*^[17] reported that *H. pylori* eradication therapy had no effect on the platelet counts in the patients with cITP. Ahn *et al*^[11] too reported a poor response to *H. pylori* eradication therapy in patients with cITP in Western countries.

The prevalence of *H. pylori* infection in cITP patients varies according to the geographical location^[5]. The prevalence of *H. pylori* in cITP patients in most of the Asian countries such as Japan, Iran and South Korea is high at 50% to 85%^[10,18-20]. However, the prevalence of *H. pylori* in cITP patients in the Western countries is lower at 22% to 30%^[10,18-21]. In the present study, the prevalence of *H. pylori* infection in cITP patients was 47.2%. This was lower than the prevalence of *H. pylori* in cITP patients in other Asian countries^[10,18-20]. This may be due to differences in the socioeconomic status, hygiene factors, *H. pylori* strains and widespread use of antimicrobials for treatment of various infections in the childhood^[22,23].

Stasi *et al*^[17] and Fujimura *et al*^[6] reported better platelet response in patients with shorter duration of cITP and mild thrombocytopenia than in patients with long duration of cITP and severe thrombocytopenia. In the present study, there was no significant difference between the *H. pylori* positive and *H. pylori* negative patients with regard to duration of cITP ($P < 0.057$) and the baseline platelet count ($P < 0.354$).

In *H. pylori* positive and *H. pylori* negative patients with cITP did not show difference in the baseline characteristics such as age, gender, symptoms and UGIE findings.

The main limitations of the present study are: (1) the sample size of the study was not larger ($n = 36$); and (2) follow up period of the study was limited.

The eradication of *H. pylori* in the patients with cITP was effective in restoring platelet counts at 6 mo follow up ($P \leq 0.0001$), whereas in *H. pylori* negative patients with cITP there was a transient improvement in the platelet count with conventional therapy ($P < 0.684$). The persistent increase in the platelet count in *H. pylori* eradicated patients could be due to long term efficacy of *H. pylori* eradication therapy in cITP patients.

Therefore we conclude that *H. pylori* eradication

therapy was effective in *H. pylori* positive cITP patients in increasing the platelet count. Further studies are required to identify other possible causative factors involved in the platelet recovery, and to understand the mechanism underlying the response to eradication therapy.

COMMENTS

Background

Immune thrombocytopenic purpura (ITP) is an autoimmune hematological disorder. Some studies have suggested an association between chronic ITP (cITP) and *Helicobacter pylori* (*H. pylori*) infection and improvement in the platelet count following its eradication. This study was done to determine the effect of *H. pylori* eradication on platelet count in patients with cITP.

Research frontiers

H. pylori is a most common gastrointestinal pathogen. It has been implicated in the aetiology of many upper gastrointestinal diseases like acid peptic diseases, chronic gastritis and gastric lymphoma. Recently, *H. pylori* has been found to be associated with various extra-intestinal and immune mediated diseases including pernicious anaemia, ITP. Some studies have demonstrated significant improvement in the platelet count after *H. pylori* eradication in cITP patients. However, some studies have reported that there was no significant improvement of platelet counts after eradication of *H. pylori* infection in cITP patients. Hence, this study has been done to evaluate the role of *H. pylori* infection in cITP and the response of *H. pylori* infected cITP patients to the eradication of *H. pylori*.

Innovations and breakthroughs

Many studies have demonstrated that there was a significant improvement of platelet count after eradication of *H. pylori* in cITP patients. In the present study it was found that there was a significant and sustained increase in the platelet count when compared to that of the baseline level following eradication of *H. pylori* in cITP patients, whereas in *H. pylori* negative patients with cITP there was a transient improvement in the platelet count with conventional therapy. Eradication of *H. pylori* should be recommended in patients with cITP and *H. pylori* infection.

Applications

Several mechanisms have been proposed to explain the association of *H. pylori* infection and ITP. *H. pylori* surface antigen, such as cytotoxin associated gene A protein evokes host systemic immune response that produces auto antibodies which cross-reacts with host platelets. The authors found that eradication of *H. pylori* infection in patients with cITP showed a significant and sustained increase in the platelet count. This therapy of *H. pylori* eradication in patients with cITP and *H. pylori* infection can be a more acceptable alternative to surgical therapy such as splenectomy.

Peer review

This is a valuable contribution from India relating to the beneficial effect of *H. pylori* eradication in the treatment of thrombocytopenic purpura.

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