Original Research Article

**Does *H. pylori* therapy augments the effect of iron therapy among children with iron deficiency anemia?**

**Arif Husain, Shrish Bhatnagar**

Department of Pediatrics, Eras Lucknow Medical College and Hospital, Lucknow, Uttar Pradesh, India

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*Correspondence:*
Dr. Shrish Bhatnagar,  
E-mail: drshrishbhatnagar@gmail.com

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**ABSTRACT**

**Background:** To assess beneficial effects of *H. pylori* therapy on children with pre-existing Iron Deficiency Anemia (IDA).

**Methods:** A total of 218 consecutive patients with iron deficiency anemia (Hb 6-11 gm/dl) were invited to participate in the study. Patients underwent endoscopic biopsy and rapid urease test for *H. pylori* detection. A total of three groups were formed- Group I (n=13) - positive for *H. pylori*, underwent treatment for *H. pylori* therapy and IDA, Group II (n=16) - positive for *H. pylori*, underwent treatment for IDA only, Group III (n=101) - negative for *H. pylori*, underwent treatment for IDA only. All the patients were followed up after every 4 weeks till week 12. Change in haematological parameters and anaemic and iron status was assessed. Chi-square paired ‘t’-test and ANOVA were used using SPSS 21.0.

**Results:** All the 3 groups showed a significant increase in S. Hb, Ferritin and iron levels and a decrease in S. TIBC levels. At 12 weeks, mean S. ferritin and S. iron levels were significantly higher in Groups I and III as compared to Group II while Mean S. TIBC levels were significantly higher in Group II as compared to that in Groups I and II. A total of 73.3% of Group III, 53.8% of Group I and 56.3% of Group II patients had hemoglobin levels >11 g/dl, but difference was not significant (p=0.175).

**Conclusions:** The findings of study showed that *H. pylori* therapy augments the effect of iron therapy among *H. pylori* positive children with iron deficiency anemia.

**Keywords:** *H. pylori* therapy, Iron deficiency anemia, Rapid urease test, S. Iron

**INTRODUCTION**

Iron Deficiency (ID), the most common nutritional disorder in the world, and Iron Deficiency Anaemia (IDA) affect 500-600 million people globally and represent a major public health problem particularly in developing countries affecting nearly 50% of children.\(^1\,^3\)

*Helicobacter pylori* is a common gut bacterium with predominantly affect the gastrointestinal tract.\(^4\) India is the prototypical developing country as far as *H. pylori* infection is concerned and more than 20 million Indians are estimated to suffer from peptic ulcer disease.\(^5\) The manifestations of *H. pylori* infection include gastritis, gastric atrophy, duodenal ulcer disease, gastric ulcer disease, primary gastric B-cell lymphoma, gastric adenocarcinoma, iron deficiency anaemia, and vitamin B12 deficiency.\(^5\,^10\)

The high prevalence of combined *H. pylori* infection and ID/IDA in developing countries suggests that infection with this bacterium may be a cause of ID/IDA. Possible
mechanisms include increased iron uptake by the *H. pylori* bacterium and blood loss due to gastric lesions as a consequence of *H. pylori* infection. Reduced iron absorption due to an elevated pH of gastric juice has also been attributed to *H. pylori* as there is transient hypochloridria of variable duration in the early phase of infection and gastric atrophic changes in the late stages of infection.

Considering the relevance of *H. pylori* infection as a cause of anemia and subsequently a barrier in treatment of IDA, the present study was undertaken to assess beneficial effects of *H. pylori* therapy on children with pre-existing iron deficiency anemia in our set up.

**METHODS**

The present study was carried out as a prospective observational cross-sectional study at pediatric gastroenterology unit of a tertiary care hospital in northern India during a period starting from January, 2015 to June, 2016 after taking approval from Institutional Ethics Committee and obtaining informed consent from the parents/guardians of all the patients. The inclusion criteria was children aged 3-16 years having Hb 6-11 gm/dl with iron profile- Serum ferritin <12 µg/L (for 3-5 years of age), <15 µg/L (for 6-16 years of age). The exclusion criteria was anemia due to causes other than Iron Deficiency. Children with symptomatic *H. pylori* infection such as gastric ulcer, duodenal ulcer and GERD, patients who received antimicrobial drugs, anticholinergic drugs and steroidal and non-steroidal anti-inflammatory agents and iron supplements for at least 30 days, patients who received proton pump inhibitors and H2 receptor antagonists for at least 15 days, patients with present or past history of chronic medical disease or underwent any abdominal surgery.

Initially, a total of 218 patients aged 3-16 years of age with Hemoglobin levels <11 g/dl with iron profile suggestive of iron deficiency (Serum ferritin <12 µg/L (for 3-5 years of age), <15 µg/L (for 6-16 years of age) were enrolled in the study.

199 who gave consent for endoscopy underwent rapid urease test during endoscopic evaluation. Those patients negative for *H. pylori* underwent iron therapy alone (Group 3). However, those who were positive for *H. pylori* were randomized into two equal groups - half the patients underwent iron therapy alone (Group 2) while remaining half were subjected to iron therapy with *H. pylori* therapy (Group 3). Iron therapy was done using Ferric Ammonium citrate (3 mg/kg/day) single dose daily for 12 weeks while *H. pylori* was done using the following regimen:

- Lansoprazole (1 mg/kg/day) in 2 divided doses for 14 days.
- Amoxicillin (50 mg/kg/day) in 2 divided doses for 14 days.
- Tinidazole (20 mg/kg/day) in 2 divided doses for 14 days.

All the patients underwent hematological assessment (Hb, S. Ferritin, S. Iron and TIBC) at baseline and after 12 weeks of intervention. Change in hemoglobin levels and iron reserves (S. Ferritin, S. Iron and S. TIBC) was evaluated.

**Statistical analysis**

Data was analyzed using Statistical Package for Social Sciences (SPSS) version 15.0. Chi-square, ANOVA and paired ‘t’-tests were performed. A ‘p’ value less than 0.05 indicated a statistically significant association.

**RESULTS**

During the course of study, a total of 218 patients were invited to participate in the study, however, only 199 consented to go for endoscopy. After endoscopic biopsy and Rapid urease test, a total of 92 (47.9%) were identified to be positive for *H. pylori* infection while remaining 107 (52.1%) were negative for *H. pylori*.

The 92 patients found positive for *H. pylori* were randomized into two groups of 46 patients each. A total of 46 were scheduled for iron supplementation and *H. pylori* eradication therapy and the other half (n=46) were scheduled for iron supplementation only. However, among those scheduled for iron supplementation and *H. pylori* eradication therapy, a total of 25 did not provide consent owing to financial implications, hence the sample size of this group was reduced to 21 patients only. Subsequently a total of 25 patients from amongst those scheduled for iron supplementation only were also dropped out for the purpose of matching the sample size with combined intervention group. Thus, the sample size of both the groups was reduced to 21 only. During the course of intervention, a total of 8 patients from combined therapy group and 5 patients from iron supplementation alone group did not complete the entire follow-ups and were subsequently considered as dropouts. Thus, the final sample size for combined therapy group reduced to 13 whereas for iron supplementation alone group, the sample size was reduced to 16.

In *H. pylori* negative group, all the 107 patients consented to participate in the study, however, a total of 6 were dropped out during the course of study and thus the final sample size was reduced to 101 (Figure 1).

Thus, a total of 130 patients completed the entire intervention - of these 13 (10.0%) comprised Group I (*H. pylori* positive patients receiving iron therapy with *H. pylori* therapy), 16 (12.31%) comprised Group II (*H. pylori* positive patients receiving iron therapy only) and remaining 101 (77.69%) comprised Group III (*H. pylori* negative patients receiving iron therapy only).
Age of patients ranged from 3 to 15 years. Mean age of patients in Groups I, II and III was 8.77±3.79, 8.69±2.92 and 8.87±3.12 years respectively. In Group I (69.23%) were males and in Groups II (56.25%) and III (54.46%) were females. However, the difference among groups was not significant statistically (p=0.259).

At baseline mean haemoglobin levels were 8.05±1.29, 8.28±1.56 and 8.47±1.49 g/dl respectively in Groups I, III and III. Mean S. ferritin levels were 9.99±2.48, 10.48±2.48 and 10.16±2.60 ng/ml, mean S. Iron levels were 43.26±6.84, 41.08±7.35 and 40.25±7.66 mcg/dl and mean TIBC levels were 508.06±100.08, 571.70±110.27 and 567.39±105.13 mcg/dl respectively in Groups I, II and III respectively (Table 1).

At 12 weeks, mean S. haemoglobin levels were 11.36±1.60, 11.13±2.20 and 11.93±1.67 g/dl respectively in Groups I, II and III. Statistically, there was no significant difference among groups (p=0.154). However, mean S. ferritin levels were significantly higher in Groups I (22.22±6.67 ng/ml) and III (22.39±6.85 ng/ml) as compared to that in Group II (17.34±5.29 ng/ml) (p<0.05).

Mean S. iron levels were also significantly higher in Groups I (99.12±24.89 mcg/dl) and III (89.90±20.27 mcg/dl) as compared to that in Group II (70.59±17.60 mcg/dl). Mean TIBC levels were maximum in Group II (333.48±79.96 mcg/dl) followed by Group I (313.31±76.56 mcg/dl) and Group III (284.06±73.19 mcg/dl) respectively. Statistically, there was a significant difference among groups with respect to S. ferritin, S. iron and TIBC levels (p<0.05) (Table 2).

On evaluating the change in Hemoglobin, ferritin, iron and TIBC levels in different groups as compared to baseline, it was found to be significant for all the four parameters in all the three groups (p<0.05) (Table 2).
At 12 weeks, majority of patients in all the three groups had hemoglobin levels >11 g/dl. Proportion of those with S. ferritin levels >15 ng/ml was higher in Groups I (84.6%) and III (85.1%) as compared to that in Group II (50%). All the patients in Groups I and III (100%) achieved S. iron levels >50 µg/dl as compared to 3 (81.3%) in Group II. Proportion of patients with S. TIBC levels >425 µg/dl was higher in Groups III (37.6%) and I (23.1%) as compared to that in Group II (6.3%). Statistically, significant differences among groups were observed in the three groups with respect to S. ferritin, S. iron and S. TIBC status (p<0.05) (Table 3).

### Table 3: Intergroup comparison of anaemic status and iron stores status at 12 weeks.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group I (n=13)</th>
<th>Group II (n=16)</th>
<th>Group III (n=101)</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Haemoglobin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥11 g/dl</td>
<td>7</td>
<td>53.8</td>
<td>9</td>
<td>56.3</td>
</tr>
<tr>
<td>&lt;11 g/dl</td>
<td>6</td>
<td>46.2</td>
<td>7</td>
<td>43.8</td>
</tr>
<tr>
<td>S. Ferritin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥15 ng/ml</td>
<td>11</td>
<td>84.6</td>
<td>8</td>
<td>50.0</td>
</tr>
<tr>
<td>&lt;15 ng/ml</td>
<td>2</td>
<td>15.4</td>
<td>8</td>
<td>50.0</td>
</tr>
<tr>
<td>S. Iron</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 50 µg/dl</td>
<td>13</td>
<td>100.0</td>
<td>13</td>
<td>81.3</td>
</tr>
<tr>
<td>&lt;50 µg/dl</td>
<td>0</td>
<td>0.0</td>
<td>3</td>
<td>18.8</td>
</tr>
<tr>
<td>TIBC</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>250-425 µg/dl</td>
<td>10</td>
<td>76.9</td>
<td>15</td>
<td>93.8</td>
</tr>
<tr>
<td>&gt;425 µg/dl</td>
<td>3</td>
<td>23.1</td>
<td>1</td>
<td>6.3</td>
</tr>
</tbody>
</table>

**DISCUSSION**

In present study, H. pylori positivity rate was 46.2%. *H. pylori* positivity rates have been shown to be of higher order in different case series showing a variability from 31.7% to as high as 82%.17,18 The positivity rate close to this study has also been reported in a population based studies in India that have reported that by 10 years of age more than 50% and by 20 years more than 80% of population is infected with *H. pylori*.19-21 Another hospital based study on 400 patients (0 to 39 years of age) from Hyderabad, has shown the *H. pylori* positivity by PCR in saliva in 40% children by 10 years of age and this figure went up to 71% by 29 years of age.22 As such, no hospital based study evaluating prevalence of *H. pylori* infection in children with iron deficiency anemia has been carried out in Indian environment. In present study, a relatively lower prevalence of *H. pylori* infection in a rather high risk population might be attributed to the fact that in present study authors made the confirmed diagnosis on the basis of endoscopy result followed by Rapid urease test, thus the criteria used in present study was more robust and confirmatory. The findings of present study, are thus in agreement with different epidemiological studies conducted in India that report a prevalence of *H. pylori* in nearly half the patients.23,24 However, authors differ from the criteria for positivity as used in these studies which shows a high prevalence even in an asymptomatic population - compared to these the present study showed a relatively lower prevalence of *H. pylori* infection in a rather high-risk population.

In present study, authors used standardized iron-therapy for treatment of iron deficiency anemia among children. As far hemoglobin levels were concerned, authors could not find any difference in the outcome for different intervention methods and patient groups. Choe et al, in their study showed a significant increase in hemoglobin levels of patients receiving *H. pylori* eradication therapy with or without iron therapy as compared to those *H. pylori* infection patients who received iron supplementation alone.23 One of the reasons for the difference in outcome of present study as compared to the cited study might be difference in design of study. The present study compared outcome of iron supplementation in anemic children without *H. pylori* infection and two groups of *H. pylori* patients who received iron supplementation with or without *H. pylori* infected patients. Moreover, the *H. pylori* infected patients comprised only small study groups with sample size 13 and 16 only. In present study, as far as mean hemoglobin levels were concerned, addition of *H. pylori* eradication therapy did not add value, however, in terms of mean % increase in hemoglobin levels addition of *H. pylori* therapy with iron supplementation seem to prepare ground for maximum % increase in mean hemoglobin levels (41.2%) in Group I which is comparable to 40.9% increase in Group III which implies that addition of *H. pylori* eradication therapy in Group I made it feasible for Group I patients to achieve the % increase in mean Hb levels similar to that in iron supplemented patients without *H. pylori* infection. At the same time minimum mean % increase (34.5%) in Hb levels of those *H. pylori*
infected patients who received iron supplementation alone, indicated that eradication of *H. pylori* provides a basis for a better outcome. Observations to similar effect were also made by Valiyaveetil et al, while using a cross-over design for *H. pylori* eradication and comparing the same with iron-deficiency anemia patients without *H. pylori* infection brought home the same inference.26

For iron reserves the differences among groups were quite differentiating notwithstanding the fewer number of patients in *H. pylori* infected groups. In present study, mean S. ferritin and S. iron levels of Group I and Group III patients were significantly higher as compared to those of Group II patients at the end of follow-up period (12 weeks), thus establishing the usefulness of *H. pylori* eradication therapy as an adjuvant to iron supplementation among the children with *H. pylori* infection.

The percentage increment in mean S. ferritin level in Groups I and III were comparable (104.4% and 120.4% respectively) and were much higher than that in Group II (65.5%). Similarly, S. Iron levels also showed a much higher % increment in Groups I and III (129.1% and 123.4% respectively) as compared to Group II (71.8%). However, despite these iron reserves showing a beneficial effect of adjuvant use of *H. pylori* therapy, the trends indicated for S. TIBC levels did not show a similar picture. As a matter of fact, TIBC levels showed a minimum % decline in Group I (38.3%) as compared to Groups II and III respectively for a decline of 41.7% and 49.9% respectively. The findings underscore the observation made by Cardenas et al, who observed that *H. pylori* infection is associated with a decrease in serum ferritin and hence iron supplementation alone does not complement the loss of serum ferritin levels owing to decrease in Serum ferritin levels induced by an active *H. pylori* infection.27 However, when *H. pylori* eradication therapy is added in the management of these patients, some promising results can be expected as observed in present study.

While leaving aside the non-infected group, the present study showed a significant difference in treatment outcome between *H. pylori* infected patients with and without *H. pylori* eradication therapy for iron reserve replenishment. Similar observations were also made by Chen et al.28

Some of the disagreements in results in different studies could be owing attributed to inability to measure the stage at which infection was detected. In present study, authors did not find a positive impact on hemoglobin levels. DiGirolamo et al, observed that relationship between *H. pylori* and anaemia/iron deficiency might depend on the phase of infection and as such the phase of infection could also interfere with the response to treatment.29,30

In present study, increased S. ferritin and S. iron levels among Group I patients as compared to Group II showed that iron supplementation related outcomes were impaired in the absence of *H. pylori* eradication therapy. Thus, indicating that in the absence of *H. pylori* eradication therapy, some of the benefits of iron supplementation are lost. In a study Yokata et al, reasoned out that strains of *H. pylori* derived from patients with iron-deficiency anemia showed enhanced Fe ion uptake and Fe ion-dependent rapid growth compared with those from patients with non-iron-deficiency anemia.11 Thus *H. pylori* with enhanced Fe ion-uptake ability may be a causative factor for iron-deficiency anemia and hence might impair the benefits of iron supplementation to a certain extent as observed in present study.

Some of the studies in past have established *H. pylori* as the etiological or causative factor for iron deficiency anemia in children.31 If this relationship is assumed to be true then without eradication of *H. pylori*, the iron supplementation will be just like pouring a glass of milk in a sieved bucket and then expecting the bucket to be full. The findings of present study highlighted this hypothesis in terms of relatively lesser improvements in serum iron reserve levels among non-*H. pylori* therapy recipients with *H. pylori* infection.

The findings in present study, thus in essence supported the use of *H. pylori* eradication therapy for getting a beneficial impact of iron supplementation among children positive for *H. pylori* infection. However, it is noteworthy that despite iron supplementation in all the groups and *H. pylori* eradication therapy in the designated group, all the three groups had some patients in whom neither iron deficiency nor anemia could be rectified completely. These findings in turn indicate that iron supplementation alone does not necessarily change the anemic status, unless some reinforcement from change in dietary pattern and habits is made. These findings indicate the need for proper dietary counselling of affected children and their parents. Role of dietary adequacy differences affecting the outcome can also not be ruled out in view of the small groups of *H. pylori* infected children in this interventional study. Owing to these limitations, the results of present study should view as indicative and not conclusive and further studies on a larger sample size with longer duration of follow up are recommended.

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**Conflict of interest:** None declared

**Ethical approval:** The study was approved by the Institutional Ethics Committee

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