

Treatment of Helicobacter Pylori Associated Iron Deficiency Anemia: Does Iron Supplementation Make Difference

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Abstract: Helicobacter pylori (H. pylori) infection is associated with high prevalence of iron deficiency anemia (IDA). Eradication of H. pylori is associated with improvement of IDA. The objective of this study was to assess the effect of H. pylori eradication with and without the use of iron supplementation on IDA among patients with H. pylori infection. It was a prospective therapeutic study on 36 patients tested positive ¹⁴C-urea breath test on screening for H. pylori infection, and had chronic mild to moderate IDA. Patients were divided randomly into two groups each of 18 patients. Group A patients were given anti-H. pylori eradication therapy plus oral iron supplementation for 2 months. Group B patients were given the same anti-H. pylori therapy but without the iron supplement. Hemoglobin, serum iron and serum ferritin were assessed and compared between the two groups at baseline, 1 month, and 2 months of therapy. Results were expressed as mean \pm SD. Paired t-test was used to compare quantitative values. P value significant if < 0.05 . It has been found that both groups showed significant increase in mean levels of hemoglobin, serum iron and serum ferritin at 1, and 2 months after successful H. pylori eradication ($p < 0.001$). However, the increase was more significant in Group A patients compared with group B patients ($p < 0.05$). At the end of the study, both groups showed normal mean levels of all these parameters. This study concluded that eradication of H. pylori infection plus simultaneous iron supplementation was associated with a faster and greater recovery from IDA as compared with eradication without iron supplement. However, H. pylori eradication without iron supplementation was also associated with significantly increased iron absorption and recovery from IDA.

Keywords: Iron Deficiency Anemia, Helicobacter Pylori, Eradication, Iron Supplementation

1. Introduction

Helicobacter pylori (H. pylori) infection is the most common chronic infection involving half of the population worldwide. [1] Numerous researches have focused on the role of H. pylori infection on a wide range of gastrointestinal disorders that vary from asymptomatic gastritis to peptic ulcer, and also gastric carcinoma and lymphoma. [2]

It has been reported that H. pylori may influence some extra-gastrointestinal diseases including iron deficiency (ID), and iron deficiency anemia (IDA). [1] ID is estimated to be the commonest nutritional deficiency in both developed and underdeveloped countries, and the most common cause of anemia. [3, 4] A moderate degree of IDA affects approximately 610 million people worldwide or 8.8% of the

population. [5] Mild IDA affects another 375 million. [5]

Several studies including meta-analysis have indicated an association between H. pylori infection and ID, and IDA. [6-13] Evidences to support the likelihood causative association between H. pylori gastritis and decreased iron stores comes also from case reports, epidemiologic studies and clinical trials. [13-21]

The hypothetical mechanisms by which H. pylori may produce IDA have been reviewed. Mechanisms include decreased iron absorption as a result of chronic gastritis which causes gastric hypochloridia/achloridia leading to reduced reduction of the non-heme iron from the ferric to ferrous form [22], and low gastric juice ascorbic acid with resulting decreased iron absorption. Also, persons with H. pylori infection and IDA appear more likely to have corpus

gastritis as compared to H. pylori-infected patients without anemia. [23] Corpus gastritis results in decreased gastric acid secretion and increase in intra-gastric pH that may impair iron absorption. Acid secretion returns to the normal range after eradication of H. pylori [24-26].

Studies including randomized controlled trials and four meta-analyses to assess the effect of H. pylori eradication combined with ferrous supplementation on the treatment of IDA have been available [7, 8, 16, 27-30] The conclusions suggest that H. pylori eradication therapy improves iron absorption, since H. pylori eradication combined with iron administration was more effective than iron administration alone for the treatment of IDA.

Moreover, there were multiple studies that reported improvement of IDA after eradication of H. pylori even without iron supplementation. [16, 19, 23, 31-35]

To the knowledge of the researcher, the difference in improvement of IDA and iron stores after eradication of H. pylori with and without iron supplementation has not been sufficiently assessed in previous studies. [16, 30] Therefore, the objective of this study was to compare the outcomes of eradication of H. pylori on IDA and iron stores with and without iron supplementation. Although the current study is small, but it is expected to add into the previous evidence.

2. Subjects and Methods

This was a prospective therapeutic study of patients who attended the family medicine clinic of the university medical center of Umm Alqura University, Makkah, Saudi Arabia during the period of November 2014 to December 2015. Patients were included if they were 18-49 years old, of either gender with all of the following: (1) H. pylori infection as tested positive by ^{14}C -urea breath; (2) chronic mild to moderate IDA as defined according to WHO definition as hemoglobin ≥ 8 to < 13 g/dL in men, and ≥ 8 to < 12 g/dL in women, peripheral blood smear with microcytosis and hypochromia consistent with IDA, serum iron < 65 $\mu\text{g/dL}$ in men, and < 50 $\mu\text{g/dL}$ in women, and serum ferritin < 15 $\mu\text{g/L}$ in men and women; [36] (3) normal physical examination; (4) absent intestinal helminthes including hook worms on stools examination using formol ether concentration technique; (5) negative three consecutive samples of faecal tests for occult blood by benzidine test; (6) normal blood analysis (including routine blood biochemistry, and vitamin B₁₂ levels). For female patients, only those with regular menstruation and menstrual period of ≤ 5 days with mild to moderate amount of bleeding (change 1-2 napkins/day) were included.

Patients with the following conditions were excluded from the study: (1) obvious blood loss (melena, haematochezia, haematuria, recurrent epistaxis); (2) conditions which cause anaemia including haematological disorders, malignancy, connective tissue disease, chronic diseases such as chronic renal failure, chronic liver disease, severe cardiac and respiratory disease, and previous gastrointestinal surgery; (3) frequent (three times a week or more) intake of non-steroidal

anti-inflammatory (NSAID) drugs or salicylates during the previous 6 mo; (4) on anticoagulants or corticosteroids (5) those with history of duodenal or gastric ulcers or carcinoma stomach at endoscopy (6) history of alcoholism; (7) pregnancy or lactation; (8) heavy menstrual flow (cycles > 5 d, associated with passage of clots after the three first days) and/or metrorrhagia; (9) adherence to vegetarian or iron-deficient diet. The patients were excluded from the study due to any of the exclusion criteria following critical review of their electronic medical charts.

The study was approved by the Ethics and Research Committee of the Faculty of Medicine, Umm Alqura University and all patients provided informed consent.

After simply explanting the aim of the study and its process, consenting patients were randomly assigned into two groups according to the order of their entry to the study, where patients with single digits have been in group A, and those with binary digits have been in group B.

Baseline hemoglobin, serum iron and serum ferritin were done for both groups, then, patients in Group A received oral ferrous sulfate tablets 200 mg three times a day for 3 months, and a 14-day course of anti-H. pylori therapy for eradication of H. pylori consisting of clarithromycin 500 mg *bid*, pantoprazole 40 mg *bid* and amoxicillin 1000 mg *bid*. Those in Group B received the same anti-H. pylori therapy without iron supplementation. H. pylori eradication have been assessed at 4 weeks of the end of the course of anti-H pylori therapy by ^{14}C -urea breathe test. At the same time, hemoglobin, serum iron and serum ferritin were tested to evaluate the effect of therapy. Patients with failing of eradication of H. pylori were given a rescue therapy consisting of the sequential quinolone (levofloxacin) based therapy for 10-days, and re-tested again for eradication of H pylori 4 weeks after the end of the course of anti-H. pylori therapy by ^{14}C -urea breath test. Serum hemoglobin, serum iron and serum ferritin were tested to evaluate the effect of therapy at 1 month, and 2 months of the end of successful eradication for H. pylori in both groups.

For the ^{14}C -urease breath test to be done, patients were asked to fast overnight, and then were asked to ingest urea labeled with 37 kBq of ^{14}C dissolved in water. Breath samples were collected before and 15 min after ingestion. The ^{14}C content in breath was measured in Bq mode using a liquid β -scintillation counter. Samples with ^{14}C content in breath < 3.33 Bq were considered negative for H. pylori, while samples with > 3.33 Bq were considered positive.

For hematological study, about 3 ml of venous blood was collected on EDTA, then analyzed using Sysmex K-21 hematology analyzer. Biochemical assays for serum iron and hemoglobin were performed as routine. Serum ferritin level was determined by ELISA using human ferritin enzyme immunoassay test kit.

Adherence to therapy was assessed on follow up using patient's response to direct question about adherence, pill count, and empty blister foils.

The results were collected, tabulated and statistically analyzed by SPSS software program (Statistical Program for

Social Science), Version 20. Quantitative data were expressed as mean and standard deviation. To assess the differences in frequencies on quantitative variables, paired t test was used with p value at < 0.05 level of significance.

3. Results

One hundred-sixty consecutive adult patients with positive ^{14}C -urea breathe test for *H. pylori* infection, and fulfilling the inclusion criteria during the study period were screened. Thirteen patients were excluded due to presence of exclusion criteria; four patients with frequent oral intake of NSAID in the past 6 months, two patients with presence of faecal occult blood, two patients with history of gastric ulcer at upper endoscopy, three patients with occasional bleeding haemorrhoids, and two female patients with heavy menstrual flow. Of the remaining 147 patients, forty-three patients (29.2%) showed evidence of mild to moderate IDA and were included in the study. During the study, there were three patients with failure of eradication of *H. pylori* with first line and alternative treatment, two patients were intolerant to oral iron and withdrawn from the study, and two additional patients (5%) were lost in follow-up before achieving the effect of therapy on their anemia. However, there were no significant differences in demographic data between included patients and those lost in follow-up. Thus, 36 patients were finally included in the study (23 men and 13 women). Mean

age: 38.0 ± 6.3 years.

All patients were found to be adherent to treatment on checking the empty blister packs. Mean age, and mean baseline values for hemoglobin, serum iron levels and serum ferritin levels were comparable in the two groups (Table 1; $p > 0.05$). Anemia in both groups was mild to moderate in severity (mean hemoglobin 9.1 ± 0.8 g/dL vs. 9.2 ± 0.7 g/dL; Group A and Group B respectively).

Response to therapy: Both groups showed significant increase in the mean levels of hemoglobin, serum iron and serum ferritin levels from baseline to 1 month, and from 1 month to 2 months ($p < 0.001$).

Comparison of the two groups (Table, 1): At the end of the first month, Group A patients showed a statistically significant increase in mean hemoglobin level (9.1 ± 0.8 g/dL vs. 11.7 ± 0.8 g/dL respectively; $p < 0.05$), and mean serum iron level (83.8 ± 12.2 mg/dL vs. 57.8 ± 9.8 mg/dL respectively; $p < 0.05$) compared to Group B patients. However, there was no significant difference in mean serum ferritin between the two groups at 1 month ($p > 0.05$). At the end of the second month, Group A patients continued to show statistically significant increase in mean hemoglobin, and mean serum iron ($p < 0.05$), and also significant increase in mean serum ferritin ($p < 0.05$) compared to Group B patients. However, at the end of the two months, the two groups had mean hemoglobin, serum iron and ferritin levels at the normal values.

Table 1. Changes in hemoglobin and iron indices with therapy in the two groups at different time intervals.

Parameter	Time interval	Group I (n=18)	Group II (n=18)	P value
Hemoglobin	Baseline	9.1 ± 0.8 (8-11)	9.2 ± 0.7 (8-11)	> 0.05
	1 month	12.6 ± 0.8 (11.5-14.5)	11.7 ± 0.8 (10-13.5)	0.003
	2 months	15.5 ± 0.7 (14.2-16.6)	14.4 ± 0.7 (13-16)	< 0.001
P value*		< 0.001	< 0.001	
P value**		< 0.001	< 0.001	
Serum Iron	Baseline	23.1 ± 7.1 (11-34)	21.1 ± 6.01 (10-29)	> 0.05
	1 month	83.8 ± 12.2 (64-102)	57.8 ± 9.8 (30-70)	< 0.001
	2 months	120.9 ± 24.6 (89-158)	85.1 ± 11.5 (68-102)	< 0.001
P value*		< 0.001	< 0.001	
P value**		< 0.001	< 0.001	
Serum Ferritin	Baseline	11.1 ± 2.5 (5-14)	11 ± 1.7 (7-13)	> 0.05
	1 month	27.2 ± 3.1 (13-55)	24.8 ± 5.4 (16-35)	> 0.05
	2 months	99.4 ± 17.5 (72-134)	80.2 ± 14.4 (60-112)	0.002
P value*		< 0.001	< 0.001	
P value**		< 0.001	< 0.001	

P*: difference between baseline and 1 month

P**: difference between 1 and 2 months

4. Discussion

Numerous studies in the literature have investigated the association between *H. pylori* infection and IDA, and the outcomes of *H. pylori* eradication on IDA.

This study was purposed to investigate the association between *H. pylori* infection and IDA, and the outcomes on IDA as regard hemoglobin, serum iron and serum ferritin, after eradication of *H. pylori* with and without the use of iron supplementation.

The association has been supported by evidences from

case reports, clinical trials, double-blind, placebo-controlled trials, and met-analysis. [6-9, 11, 14-16, 21, 37- 40] However, other studies from Latin American countries by Santos et al [41] showed no association between *H. pylori* infection and IDA, whereas a study in Haiti by Shak et al [42] showed an opposite association. Fraser et al [43] and Kermatiet al [44] reported no association between *H. pylori* infection and Hgb/HCT levels.

The outcomes of the current study advocate the *H. pylori* infection as a frequent cause of IDA in adult patients in whom the standard diagnostic work-up does not recognize

the presence of other cause of anemia. In this study, 43 of 147 (29.2%) *H. pylori* infected patients were diagnosed with IDA; a finding comparable with that of a larger study by Kibru et al [45] where the estimated prevalence of IDA in *H. pylori* infected patients was 31%.

Also, the current study showed that, after confirmation of eradication of *H. pylori*, the mean values of hemoglobin and iron indices including ferritin have improved significantly in group B patients without the use of iron supplementation which indicates improved absorption of dietary iron with subsequent improvement of IDA. This finding is coincident with studies that indicate improvement of IDA after eradication of *H. pylori* without iron supplement. [14, 16, 23, 31-33]

In addition, a quite number of studies have suggested *H. pylori* infection as a reason of refractory IDA (IDA that does not respond properly to oral iron supplementation) in patients with no obvious other cause of anemia. [46, 48] In one study, 58% of pre-adolescent children and adolescents with IDA were *H. pylori* positive at endoscopy. [16] Another study showed that 61.9% of patients with IDA had *H. pylori* infection. [49] A different study showed that 62% of patients with IDA were *H. pylori* positive. [30]

Moreover, in the current study, before the completion of *H. pylori* eradication, there were no significant differences in parameters reflecting hemoglobin and iron status between the two studied groups. After the 1 month triple therapy was finished, the current study indicated that the response to treatment was significantly greater in group A, who received anti-*H. pylori* eradication therapy plus iron supplementation, than in group B, who did not receive iron supplement with anti-*H. pylori* treatment. It has been obviously demonstrated in earlier studies that *H. pylori* eradication can reverse the negative influence of *H. pylori* infection on iron absorption and lead to improvement of IDA in case series and in clinical trials in both children and adults. [6, 7, 16, 27-30, 32, 40]

All the above mentioned findings argue in favor of causality of *H. pylori* infection.

The magnitude of improvement in group A is comparable with that in a study by Valiyaveetil et al [30] who found 3.6 g/dl increase in median hemoglobin during the first month of treatment of *H. pylori* with simultaneous use of oral iron supplement, and comparable with results by Choe et al [16] who found that patients who underwent *H. pylori* treatment, with or without iron, had a significantly greater rise in hemoglobin level at 8 weeks after therapy compared with those who received only iron supplementation without *H. pylori* eradication therapy. This is explained by increased absorption of iron after eradication which has been given in the supplement.

In this study, baseline ferritin was below normal value. This is in agreement with results of a study of Korean children by Seo et al [50] who found that serum ferritin levels were significantly lower in *H. pylori*-seropositive children than in seronegative controls (24 vs. 39 ng/mL). Similar results were found in a study of 2794 Danish adults by Milman et al., [51] as well as a cross-sectional national

health survey from Germany by Berg et al. [11]. In the recent study by Darvishi et al, [52] initial ferritin was found to be significantly lower in the *H. pylori*-positive group than in the *H. pylori*-negative and the control groups. However, Valiyaveetil et al [30] on their study on Indian adults, and Choi et al, [53] on their study of Korean children did not find difference in iron indices between sero-positive and sero-negative *H. pylori*.

In this study, there was significant improvement serum ferritin after eradication of *H. pylori*; a result consistent with other studies. [6, 7, 16, 29, 30] Although in both groups, serum ferritin significantly increased after 1 month compared to baseline, there was no significant difference in mean serum ferritin between group A and B at 1 month ($p > 0.05$), and the increase was greater at 2 months ($p < 0.05$). This is explained by the body use of the oral iron supplement for heme production, and not to replenish stores until hemoglobin values normalize which occurred after 2 months of therapy.

At the end of 2 months of therapy, both groups had recovered from IDA.

5. Conclusion

This study concludes that, eradication of *H. pylori* infection is associated with recovery from the accompanying IDA. However, the rate of recovery is faster and greater when oral iron supplementation is given simultaneously with anti-*H. pylori* eradication therapy. Hence, clinicians might reserve oral iron supplementation for severe cases of IDA for a faster and greater recovery, while mild and moderate IDA could be treated with anti-*H. pylori* therapy alone, or according to the patient's preferences.

6. Limitations

This study is small, and did not exclude other causes of IDA by extensive laboratory work and interventions including upper and lower endoscopy because it has been done in a family medicine setting where these interventions are not available. However, the study considered only mild and moderate degrees of anemia, excluded severe anemia to be referred for gastroenterology assessment outside the study setting, patients above 49 years have been excluded for the increased risk of colon cancers and subsequent IDA, and the mean values of hematological parameters were considered for statistical analysis.

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