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Original Research Article

The effect of anti-helicobacter pylori with iron folate supplementation and only iron folate supplementation of helicobacter pylori infected CagA positive Indian non-pregnant women

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ABSTRACT

Background: *Helicobacter pylori* is a type of bacteria that infects our stomach and small intestine. This study aimed to evaluate response to *H. pylori* infection of the anti *H. pylori* therapy with iron folate supplementation and only iron folate supplementation of CagA positive and CagA negative women.
Methods: The non-pregnant Indian women (18-35 years) whose Hemoglobin<115 gm/dl, body mass index<20 kg/m2 and *H. pylori* positive status were recruited in our study. *H. pylori* positive strains women were divided two groups CagA positive and CagA negative. Depending on types of supplementations, both CagA positive and CagA negative women were divided by two groups treatment and Control. Treatment group received 7 days anti *H. pylori* therapy then 3 months iron folate supplementation. Control group received only iron folate supplementation for 3 months.
Results: Total 81 women were *H. pylori* infected and among them 65 (80.2%) were CagA positive and 16 (19.8%) were CagA negative. There were no significant correlations of hematological parameters between *H. pylori* infected CagA positive and CagA negative women. At baseline Hb, MCV, MCH and TIBC value was comparatively lower of CagA positive than CagA negative women. After 3 months intervention Hb, MCV and Ferritin were increased significantly ($p<0.05$) higher in treatment group than control group of CagA positive women.
Conclusions: After 3 months supplementation of anti *H. pylori* therapy with iron folate supplementation of CagA positive strains was better response than CagA negative strains of child bearing aged non pregnant women.

Keywords: Anemia, Anti *H. pylori* therapy, CagA, *Helicobacter pylori*, Iron folate supplementation

INTRODUCTION

Helicobacter pylori is a type of bacteria that infects our stomach and it is very common among the population of developing countries.[1] It can damage the tissue in our stomach and small intestine. It is often symptomless but it can increase the risk of ulcers, gastritis and cancers. It can also cause the painful inflammation and peptic ulcer.[2] *H. pylori* is a gram-negative pathogen that is wide spread all over the world, infecting more than 50% of the world's adult population.[3,4] *H. pylori* infection favors the development of gastro intestinal diseases, such as gastritis, ulcers, atrophy, lymphoma of the lymphoid tissue of the mucosa (MALT) and gastric adenocarcinoma.[5] *H. pylori* strain specific virulence factors play a major role in the pathogenesis.[6] One of the best characterized toxins of *H. pylori* is Cytotoxin associated gene A (CagA), the product CagA which is associated with enhanced induction of gastritis, peptic ulcer and high risk of gastric cancer (GC).[7] Chronic infection with *H. pylori* CagA positive strains is the strongest risk factor of GC.[8] It was first reported in 1995 that infection with CagA positive strains increased the risk of GC.[9,10] With a risk that was at least one order of magnitude higher risk than that of CagA negative strains.[11] CagA is one of the most important virulence

gene of H. Pylori. Moradi and colleagues showed that *H. pylori* CagA positive strains increase the GC susceptibility.[12] CagA positivity strains are more virulent and gastro duodenal diseases than CagA negative strains.[13] Though some environmental factors such as consumption of red meat and dairy products, high salt intake, consuming hot tea have increased GC and also *H. pylori* infection have been identified as an important risk factor for GC.[14]

Further this, some researchers showed that some scientific evidence indicates CagA, BabA, SabA as the virulence factors in H. Pylori, those are associated with GC.[15-17] One of the most important severity factors of *H. pylori* is the Cag pathogenicity island (Cag-PAI). CagA is located on the right half of Cag –PAI.[18] The treatment of *H. pylori* infection may reduce the risk of maternal health disease. We compared the hematological parameter of anti *H. pylori* therapy with iron folate supplementation and only iron folate supplementation of *H. pylori* infected CagA positive and CagA negative women. Furthermore, this study aimed to assess the women response to combined anti *H. pylori* triple therapy with iron folate supplementation compared to iron folate supplementation alone of *H. pylori* infected CagA positive and CagA negative women.

METHODS

The non-pregnant women of child bearing age (18 to 35 years) with blood hemoglobin (Hb) of≤115 g/L, body mass index (BMI)<20 kg/m2 were included in the study. Additional inclusion criteria were no acute and chronic diseases, no antibiotics during the past one months and no blood transfusion or blood donation within the last 4 months and staying with a reasonable distance of the clinic (<3 km) and women to give a consent.

A longitudinal randomized study of the women was attended the well-baby clinic at the Infectious Diseases and Beliaghata General Hospital, Kolkata, India. This is a large general hospital run by the Govt. where the treatment is free or subsidized and serves the urban poor. The medical officer (S. J.) of the clinic invited the women in order of their registration and the first two eligible ones were recruited for the day. Written consent was obtained from the women. The recruitment and follow up was completed from 1st August 2012 through 28th June 2013.

Baseline history and clinical examination results on the women enrolled were recorded on a pretested data collection form. This included age, height, weight and selected socio-economic indicators. The tests done at admission to the study included determination of Hb, packed cell volume (PCV), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), iron, ferritin, transferrin, total iron binding capacity (TIBC), etc. and *H. pylori* serum IgG antibodies test to detect *H. pylori* infection. The blood tests were repeated after 3 months of intervention. This study was approved by the Ethical Review Committee of Society for Applied Studies, Kolkata, India and the University of Alabama, Birmingham, USA.

Sample size

The study women were divided two groups GrA (*H. pylori* positive, CagA positive) and GrB (*H. pylori* positive, CagA negative). We estimated that about 39 women (taking into account 10% drop out) would be required for each group to detect differences between the groups with an alpha level=0.05 and power=80%.

We wanted to recruit initially about 41 *H. pylori* infected women in each group. Considering further a success rate of eradication of about 90%, based on our previous experience, therefore, a total of 105 *H. pylori* infected, undernourished and Fe-deficient were recruited.

(^{13}C) urea breath test

The (^{13}C) urea breath test has high specificity and sensitivity and is widely accepted as a non-invasive technique for diagnosing current *H. pylori* infection. (^{13}C) Urea is degraded rapidly in the presence of *H. pylori* urease to $^{13}CO_2$ and NH_3 and the former is excreted in the breath.[19] A baseline sample of expired breath was collected (0 hour) in a 10 vacutained (Beckton Dickin son, New Jersey, USA)) tube.

The women ate 0.1N citric acid (200 ml) and Sucralose as sweetner (25 mg) and after 10 minutes late collected baseline breath sample and kept it in a vacutainer tube. After that the woman drank 75 mg (^{13}C) urea with 50 ml water.

After 30 minutes later, collected the 2nd breath samples and kept it in a vacutainer tube. Samples were analysed using isotope ratio mass spectrometry (Europe Scientific, Crews, UK). The test was considered positive for *H. pylori* infection positive when delta over baseline (dob) was>5%.

Laboratory measurements

Each participant had 5 ml of blood drawing in the morning. There was analysis of Hb, Erythrocytes, MCV, PCV, MCH, MCHC and RDW (CV). Reference range values for Hb, Erythrocytes, PCV, MCV, MCH, MCHC, RDW (CV) was (12-15) g/dl; (3.8-4.8) mill/c.mm, (37-48) %, (83-100) fl, (27-32) pg, (31.5-34.5) g/dl and (11.6-14) % respectively. The remaining 2.5 ml of blood was collected into a serum tube for measurement of iron related parameters including serum iron, ferritin, transferrin, Iron, TIBC, %saturation measured by spectrophotometer, transferrin serum by Nephelometry and Ferritin serum by Chemiluminescence.

Therapy response assessment

Women who were discovered to have GrA (*H. pylori* positive and CagA positive) and GrB (*H. pylori* positive and CagA negative). GrA were subdivided randomly into two groups: GrA1, GrA2. Similarly, GrB were sub divided GrB1 and GrB2. GrA1 and GrB1 received 7 days triple (anti *H. pylori*) therapy for *H. pylori* eradication (Clarithromycin 250 mg bid, lansoprazole 30 mg bid and tinidazole 500 mg bid) and after 1 weeks, they received 3 months iron folate supplementation i.e., FeFA (Ferrous sulphates 150 mg (50 mg elemental iron) and folic acid 0.5 mg) 2 capsules per day. GrA2 and GrB2 received only FeFA capsules per day 2 capsules for 3 months.

RESULTS

Ninety-four women were assessed for eligibility in our study (Figure 1). Among these women, 81 (86.2%) were *H. pylori* positive and 13 (13.8%) were *H. pylori* negative. Of the 81 *H. pylori* positive women, 65 (80.2%) were CagA positive (GrA) and 16 (19.8%) were CagA negative (GrB).

Baseline demographic and clinical characteristics of GrA and GrB were compared in Table 1 and 2. Mean age of these study population was 24.64±5.20 years (18-35) years. In terms of socioeconomic factors were not associated with CagA status (Table 3).

There was no significant correlation between *H. pylori* infected CagA status and hematological parameters. Due to the process of randomization for allocating a woman to treatment and control group be similar with regard to socio demographic and clinical characteristics and hence these were studied as single group for these characteristics.

Sixty-five women (GrA) were randomized by two groups, GrA1 (n=33, treatment group) and GrA2 (n=32, control group). Similarly, CagA negative (GrB) 16 women were randomized in two groups GrB1 (n=8, treatment group) and GrB2 (n=8, control group). GrA1 and GrB1 received triple therapy for 7 days then oral iron folate supplementation for 3 months. Again, GrA2 and GrB2 received only oral iron folate supplement for 3 months.

After 3 months supplementation, GrA1 showed statistically significant increase in Hb, MCV and serum Ferritin (p=0.0013, p=0.003 and p=0.002) respectively. On the other hand, MCV and Ferritin (p=0.101, p=0.05) respectively were not significant of GrA2.

Again Hb, Erythrocyte, MCH, PCV and iron were significantly (p<0.05) increased from baseline to after 3 months of GrA2. Total 21 women were drop out from our study. After 1st month 10 women, 2nd month 6 women and after 3rd month 5 women were drop out from our study. So finally, we analysed total 60 (49 CagA positive and 11 CagA negative) women.

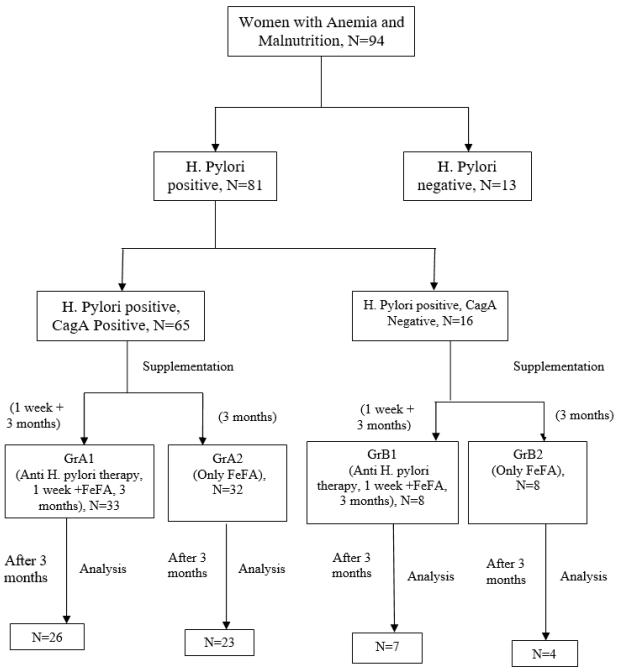

Figure 1: Flow chart of the research study group.

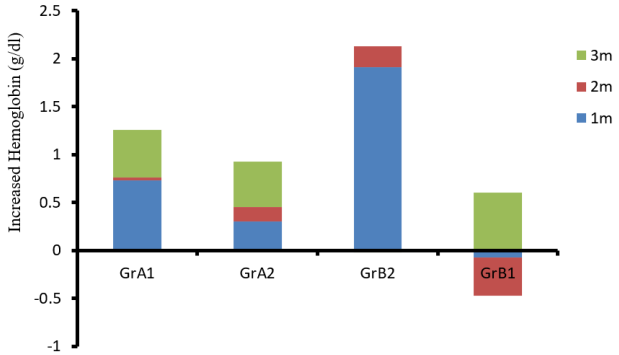

Figure 2: Average haemoglobin increases/ decreases in from baseline to 3 months supplementation.

GrA1→ H. Pylori positive, CagA positive women (1-week anti H. Pylori therapy and 3 months iron folate supplementation) GrA2 → H. Pylori positive, CagA positive women (only 3 months iron folate supplementation). GrB1 → H. Pylori positive, CagA negative women (1-week anti H. Pylori therapy and 3 months iron folate supplementation). GrB2 →H. Pylori positive, CagA negative women (only 3 months iron folate supplementation).

■→ Baseline to 1st month Haemoglobin increases/ decreases

■→ 1st month to 2nd month Hemoglobin increases/ decreases

■→ 2nd month to 3rd month Hemoglobin increases or decrease

After 3 months supplementation of CagA positive women, mean Hb had increased significantly (1.27 p=0.001, 1.03 p=0.0003) GrA1 and GrA2 respectively. But 3 months supplementation of CagA negative women, Hb had not significantly (p>0.05) increased (1.2 p=0.36, 0.2 p=0.67) of GrB1 and GrB2 respectively. All treatment and control group, Hb had increased from baseline to 1st month, 2nd month and 3rd month (Figure 2).

One important finding was that both Hb concentrations values after 3 months of iron folate supplementation and anti *H. pylori* therapy were adversely affected by the presence of CagA positive of *H. pylori* infected women. Iron folate supplementation with and without anti *H. pylori* therapy on Hb, iron and ferritin after 3 months supplementation was compared. A trend for a negative interaction was noted for Hb concentration (-0.006, 95% CI -0.62, 0.61) and ferritin (-3.05, 95% CI -12.14, 6.05). But a positive interaction was seen for iron concentrations (21.43, 95% CI -6.72, 49.58). Comparing hematological indices of all *H. pylori* CagA positive and CagA negative women at admission and after 3 months intervention data were showed in table 4.

Table 1: Baseline characteristics and comparison between *H. pylori* positive infected CagA positive (GrA) and CagA negative (GrB) women.

Characteristics	GrA (n=65)	GrB (n=16)	P value
Age groups (in years)			
≤20	22(33.85%)	4 (25%)	
21-25	17 (26.15%)	3 (18.75%)	0.58
26-30	17 (26.15%)	7 (43.75%)	
>30	9 (13.85%)	2 (12.5%)	
Education status			
Illiterate	15 (23.08%)	3 (18.75%)	
Can sign only	11 (16.92%)	2 (12.5%)	
Primary School	12 (18.46%)	1 (6.25%)	0.47
Secondary School	20 (30.77%)	6 (37.5%)	
Madhyamik passed and above	7 (10.77%)	4 (25%)	
Income			
<Rs. 5000	36 (55.38%)	11 (68.75%)	0.33
≥Rs. 5000	29 (44.62%)	5 (31.25%)	
Living number of rooms			
1	44 (67.69%)	11 (68.75%)	
2	19 (29.23%)	4 (25%)	0.81
≥3	2(3.08%)	1 (6.25%)	
Total family members			
<5	31 (75.61%)	10 (24.4%)	
≥5 and <7	25 (89.39%)	3 (10.7%)	0.33
≥7	9 (75%)	3 (25%)	
ID (Iron deficiency)			
Yes	45 (69.23%)	11 (68.75%)	0.97
No	20 (30.77%)	5 (31.25%)	
IDA (Iron deficiency anemia)			
Yes	53 (81.54%)	12 (75%)	0.56
No	12 (18.46%)	4 (25%)	
Anthropometric parameters			
Height (cm)	148.91±5.53	151.31±6.84	0.14
Weight (kg)	39.42±4.78	40.97±5.84	0.27
BMI	17.75±1.61	17.84±1.77	0.85

Table 2. Admission laboratory findings of CagA positive (GrA) and CagA negative (GrB) *H. pylori* infected women (values are means±standard deviations).

Variables	Over all	*H. pylori* positive		95% CI	P value
	N=81	GrA (N=65)	Gr B (N=16)		
	(Mean±SD)	(Mean±SD)	(Mean±SD)		
Hemoglobin (g/dl)	9.78±1.25	9.75±1.22	9.87±1.38	-0.58 to 0.81	0.74
Erythrocyte (mill/c.mm)	4.07±0.46	4.1±0.47	3.94±0.38	-0.41 to 0.10	0.23
PCV (%)	32.94±2.86	33.10±2.93	32.33±2.56	-2.36 to 0.82	0.34
MCV (fl)	79.98±9.69	80.05±9.22	79.7±11.74	-5.76 to 5.07	0.90
MCH (pg)	25.53±3.37	25.44±3.26	25.9±3.90	-1.43 to 2.34	0.63

Continued.

Variables	Over all	*H. pylori* positive		95% CI	P value
	N=81 (Mean±SD)	GrA (N=65) (Mean±SD)	Gr B (N=16) (Mean±SD)		
MCHC (g/dl)	31.58±1.02	31.57±0.96	31.61±1.28	-0.53 to 0.60	0.90
RDW (%)	15.52±2.27	15.52±2.07	15.75±3.02	-1.09 to 1.50	0.72
Iron (µg/dl)	58.75±33.94	60.37±35.53	50.8±24.59	-33.22 to 14.09	0.42
TIBC (µg/dl)	410.58±78.99	411.96±83.46	403.8±54.73	-63.48 to 47.16	0.77
Saturation (%)	15.07±9.10	15.43±9.34	13.3±8.02	-8.48 to 4.23	0.51
Transferrin (mg/dl)	264.31±77.37	265.13±82.38	260.3±48.60	59.05 to 49.39	0.85
Ferritin (ng/dl)	20.44±20.83	20.29±19.47	21.2±27.86	-13.69 to 15.51	0.90

Table 3: Binary logistic regression analysis for factors associated with *H. pylori* CagA infected women.

Variable	Odds ratio (95% CI)	P value
Age group (in years)		
≤20	Ref	
21-25	1.03 (0.2-5.23)	0.971
26-30	0.44 (0.11-1.76)	0.246
>30	0.82 (0.13-5.29)	0.833
Education Status		
Illiterate	Ref	
Can sign only	1.1 (0.16-7.74)	0.924
Primary school	2.4 (0.22-26.12)	0.472
Secondary school	0.67 (0.14-3.11)	0.606
Madhyamik passed and above	0.35 (0.06-2.04)	0.238
Income		
<Rs 5000	Ref	
≥Rs 5000	1.77 (0.55-5.68)	0.34
Family member		
<5	Ref	
≥5 and <7	2.69 (0.67-10.83)	0.164
≥7	0.97 (0.22 to 4.29)	0.97
Room status		
1	Ref	
2	1.19 (0.34 to 4.21)	0.79
More than 2	0.50 (0.04 to 6.03)	0.59
Marital Status		
Unmarried	Ref	
Married	1.27 (0.31 to 5.28)	0.743
Iron deficiency (ID)		
No	Ref	
Yes	0.98 (0.30-3.19)	0.97
Iron deficiency anemia (IDA)		
No	Ref	
Yes	0.68 (0.19-2.48)	0.55
Height <145cm		
No	Ref	
Yes	0.60 (0.18 to 2.03)	0.414
BMI (<18.5 kg/m^2)		
No	Ref	
Yes	1.52 (0.50 to 4.63)	0.461

Table 4: Comparison of haematological parameters among the study groups before and after intervention.

	GrA1 (*H. pylori* positive, CagA positive)–Treatment (n=26)			GrA2 (*H. pylori* positive, CagA Positive)-Control (n=23)			GrB2 (*H. pylori* positive, CagA Negative) Control (n=4)			GrB1 (*H. pylori* positive, CagA Negative)-Treatment (N=7)		
	At baseline	**After follow up**	**P value**	**At baseline**	**After follow up**	**P value**	**At baseline**	**After follow up**	**P value**	**At baseline**	**After follow up**	**P value**
Hemoglobin (g/dl)	9.57±1.15	10.84±1.07	0.001	10.12±1.12	11.15±1.09	0.003	9.83±1.42	11.02±0.87	0.36	10.2±1.08	10.4±1.08	0.68
Erythrocyte (mill/cmm)	4.16±0.51	4.18±0.52	0.67	4.11±0.47	4.33±0.46	0.009	4.15±0.47	4.43±0.63	0.08	4.07±0.28	4.03±0.25	0.53
PCV (%)	33.09±2.86	34.23±2.71	0.18	33.77±2.60	36.10±2.85	0.006	32.55±2.86	36.5±1.07	0.14	33.34±1.29	32.61±2.69	0.35
MCV (fl)	78.22±8.81	81.57±7.99	0.003	81.89±9.07	83.47±8.67	0.101	78.73±12.83	82.3±8.13	0.25	81.51±6.95	80.17±7.63	0.41
MCH (pg)	25.03±2.93	26.16±3.35	0.06	25.88±3.12	26.79±3.17	0.04	24.85±4.88	26.15±3.20	0.26	25.7±2.99	25.83±3.01	0.79
MCHC (g/dl)	31.53±0.82	32.0±1.64	0.2	31.59±0.82	32.06±1.18	0.13	31.43±1.36	31.68±0.95	0.62	31.43±1.09	32.17±1.71	0.25
RDW (%)	15.76±1.92	15.30±2.18	0.27	15.27±2.22	14.99±1.95	0.26	17±3.82	14.75±1.13	0.31	14.93±0.88	15.99±2.07	0.17
Iron (µg/dl)	63.15±42.51	75.12±32.86	0.24	57.22±26.11	90.61±33.49	0.002	35.5±18.34	106.25±39.20	0.08	61±23.97	79.33±37.70	0.22
TIBC (µg/dl)	426.88±78.69	411.38±88.90	0.23	395.09±87.18	390.33 ± 75.33	0.73	439±39.68	377.25±103.26	0.98	380±52.42	379.67±64.01	0.99
Saturation (%)	15.5±10.37	18.8±7.25	0.18	15.34±8.25	23.78±9.01	0.002	8.25±4.79	30±15.90	0.12	16.67±8.26	22.5±13.1	0.24
Transferrin (mg/dl)	271.65±62.61	253.88±73.46	0.15	257.75±101.22	249.30 ± 74.27	0.61	286.25±44.40	248±58.35	0.48	243±43.86	244.67±46.60	0.95
Ferritin (ng/dl)	14.07±12.12	24.32±15.64	0.002	27.32±23.71	34.51±23.37	0.05	6.35±5.81	24.6±12.91	0.09	31.1±32.91	32.3±26.04	0.85

DISCUSSION

The present study confirmed that the prevalence of *H. pylori* infection is high in women from among the urban poor in India. In our previous study, also we showed, "*H. pylori* infection is high in children from among the urban poor in India".[19] In our present study, there were no statistically significant associations between *H. pylori* infected CagA status and socio demographic characteristics (age group, marital status, educational background, occupational status and no. of living rooms).

Also, this is similarly found in the study of Kitila and colleagues.[20] Lower age group women had higher rates of *H. pylori* infected CagA positive status. In our study, *H. pylori* infected CagA positive women was higher in the 24 years or below age group compared to the above 24 years. Similarly, the proportion of illiterate women was marginally higher in the *H. pylori*-CagA positive. Low family income women had comparatively a higher rate of *H. pylori* infected CagA positive.

Several studies have assigned the gastric carcinogenesis of *H pylori* bacteria to the cytotoxin associated with antigen A (CagA).[21] It has been found that the presence of CagA positive *H. pylori* strains may influence ferritin levels in infected individuals. CagA has been shown to interact with cellular signaling pathways and disrupt normal cellular processes, including iron metabolism.[22]

In our study, all women were anemic and mal nourished (Hb less than 11.5 g/dl and BMI<20 kg/m2). Some variables (Hb, PCV, MCH, MCHC, RDW and ferritin) were lower of CagA positive women than the CagA negative women. There was no significant difference found between CagA positive and CagA negative women. Iron deficiency (ID) and iron deficiency anemia (IDA) was higher in CagA positive women than CagA negative women.

In our study, anti *H. pylori* therapy with iron folate supplementation was more affected of hematological parameter than only iron folate supplementation of CagA positive women. Many studies showed that *H. pylori* were significantly associated with iron deficiency (ID) and iron deficiency anemia (IDA).[23,24] Some studies showed that *H. pylori* infection and IDA was not significant.[25-27] In our present study, the CagA positive

women did not significantly associated with iron deficiency (ID) and iron deficiency anemia (IDA) (χ^2=0.0014, p=0.97 and χ^2=0.3463, p=0.556) respectively. Among these women, only 30.8% women were ID and 18.5% IDA of 65 women with CagA positive. Response to iron, Ferritin and Hb was compared between iron folate supplementation with and without anti *H. pylori* therapy of *H. pylori* infected CagA positive women between baseline and after 3 months therapy. After intervention of 3 months therapy, Hb had significantly increased both treatment and control groups. MCV and ferritin had increased significantly ($p<0.05$). Similarly, for control groups, erythrocyte, PCV, iron and saturation had increased significantly ($p<0.05$). CagA is able to alter the polarity of the transferring, transferring receptor iron uptake system, which allows the bacterium to shuttle iron across the epithelium.[28,29] Malik and his colleagues showed that in pregnant women with IDA, the response to anti *H. pylori* therapy with oral iron folate supplementation was significantly better than only iron folate supplementation.[30]

Some limitation inherent to the current study's design may have influenced the overall findings. First, the sample size was very small. Second, the recruited subjects were child bearing aged (18-40 years) non pregnant women only. Third, the study was conducted on low socio-economic status women who lived 10 km radius of our study area, the Government Hospital of Kolkata, India. These limits generalized in a small population. So, above all these limitations should be considered in our future study.

In developing countries, anemia is a major public health problem in infants and young children. Some researchers showed that West Bengal had the highest percentage of anemia prevalence for SC and ST (76.14%), general (68.65%) women and non-pregnant women of child bearing age (19-45) were (71.7%).[31]

CONCLUSION

In our present study, conducted in child bearing aged Indian women with *H. pylori* infected CagA positive and anemia, the response to GrA1 were better response than the GrA2. *H. pylori* infected CagA infected treatment group showed significantly a better response in mean Hb, MCV and Ferritin levels than the control groups. Serum MCH, RDW, TIBC and Transferrin levels also showed a better improvement in *H. pylori* CagA positive women. So iron folate with and without anti *H. pylori* therapy was better response of CagA Positive than CagA negative non pregnant childbearing aged Indian women.

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

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