ORIGINAL ARTICLE ASIAN JOURNAL OF MEDICAL SCIENCES

Effect of treatment of *Helicobacter pylori* with combination antibiotic therapy on iron deficiency anemia in patient with *H. pylori*-associated gastritis

Prashant Tanaji Dond[1], Rahul Deshpande[2], Shailesh Patil[3], Naresh Bhat[4]

[1,2,3]Assistant Professor, Department of General Medicine, Ashwini Rural Medical College, Hospital and Research Centre, Solapur, Maharashtra, [4]Chief, Department of Gastroenterology and Hepatology, Aster CMI Hospital, Bengaluru, Karnataka, India

Submission: 27-05-2023 Revision: 02-08-2023 Publication: 01-09-2023

ABSTRACT

Background: The failure to identify a cause of iron deficiency in a substantial subset of patients with low iron stores raises the question of whether there are additional as of yet unexplained causes of iron depletion. Recently, there has been a growing body of evidence to suggest a relationship between *Helicobacter pylori* gastritis and iron deficiency anemia (IDA) in the absence of peptic ulcer disease. **Aims and Objectives:** Therefore, the present study was undertaken to investigate the effect of treatment of *H. pylori* with combination antibiotic therapy on IDA in patient with *H. pylori*-associated gastritis. **Materials and Methods:** The present study was carried out at a tertiary care hospital catering to a large population in south Solapur and nearby areas. The study was conducted for 2 years. All patients with IDA attending outpatient department and admitted to the hospital for 2 years, were included in the present study. All patients who have IDA according to the World Health Organization criteria, as a hemoglobin concentration <13 g/dL for men and <12 g/dL for women, a mean corpuscular volume (MCV) <75 fL and a serum ferritin level <30 ng/mL, both in-patient and outpatient setting were evaluated with detail history, clinical examination, and investigation. **Results:** Baseline hemoglobin (Hb) in group I is 8.99 ± 1.23, while in group II 7.55 ± 2.08. All the parameters are comparable in groups I and II except baseline Hb%. There is a significant increase in Hb, packed cell volume (PCV), MCV, mean corpuscular hemoglobin (MCH), and MCH concentration (MCHC) after 2 months of treatment with oral iron therapy. There is a significant increase in Hb, PCV, MCV, MCH, and MCHC after 2 months of treatment with oral iron and triple therapy for *H. pylori*. **Conclusion:** Treatment of *H. pylori* infection was associated with more rapid and significant response to oral iron therapy in IDA as compared with the use of iron therapy alone.

Key words: Gastritis; *Helicobacter pylori*; Iron deficiency anemia

Access this article online

Website: http://nepjol.info/index.php/AJMS

DOI: 10.3126/ajms.v14i9.55198

E-ISSN: 2091-0576

P-ISSN: 2467-9100

INTRODUCTION

Iron deficiency anemia (IDA) is the commonest form of anemia worldwide, affecting nearly half a billion people.[1] It is also estimated to be the most common nutritional deficiency in both underdeveloped and developed nations, the most common cause of anemia, and possibly the most common organic disorder in clinical practice. As a results in impairment of immune, cognitive, and reproductive functions, as well as decreased work performance.

The incidence of IDA in developing countries like India is higher. It is a common problem encountered in our daily medical practice. Established causes for iron deficiency include inadequate intake, malabsorption, or excessive blood loss. In the absence of poor dietary intake or ongoing

Address for Correspondence:
Dr. Rahul Deshpande, Assistant Professor, Department of General Medicine, Ashwini Rural Medical College, Hospital and Research Centre, Kumbhari, Solapur, Maharashtra, India. **Mobile:** +91-8975578826. **E-mail:** drrahul2004@rediffmail.com

obvious blood loss, any patient who presents with IDA needs to undergo extensive gastrointestinal (GI) tract evaluation to look for the presence of an ongoing bleeding lesion. However, even a complete GI evaluation may be unrevealing in as many as 48% of cases.[2]

Among adolescents and pre-menopausal women, the incidence of IDA is higher. It is thought to be due to excessive menstrual loss and demands of pregnancy. Difficulty in accurately assessing the menstrual loss makes it impossible to identify excessive menstrual bleeding as the sole reason for the development of iron deficiency. However, a good number of patients in this group presenting with iron deficiency do not have a significant history of menorrhagia.

The failure to identify a cause of iron deficiency in a substantial subset of patients with low iron stores raises the question of whether there are additional as of yet unexplained causes of iron depletion. Recently, there has been a growing body of evidence to suggest a relationship between *Helicobacter pylori* gastritis and IDA in the absence of peptic ulcer disease.

A number of possible mechanisms have been invoked to explain the relationship between *H. pylori*-associated gastritis and refractory IDA including occult GI bleeding, alterations in gastric acidity, interference in absorption and competition for dietary iron by the bacteria.[3]

Chronic gastritis caused by *H. pylori* reduces stomach acid output and ascorbic acid levels, both of which are required for iron absorption. The duodenum and jejunum of the GI system absorb two types of iron: heme iron and non-heme iron. Heme iron is found mostly in meat and is easily absorbed.[4]

Another explanation for a relationship between *H. pylori* infection and IDA involves the possible effect of *H. pylori* gastritis on gastric acid secretion and iron absorption.

Ascorbic acid concentrations decreased as gastritis progressed in severity as well as extent, with involvement of the gastric body.[5] It has also been hypothesized that *H. pylori* may lead to IDA by sequestering and utilizing iron, thus competing with the human host.[6]

Though IDA is common in India, the occurrence of *H. pylori* infection as a contributory factor for IDA has not been evaluated extensively.

H. pylori infection is found to be very common in the developing countries due to poor sanitation and unhealthy food habits. However, many of those infected, remain asymptomatic for a long period. In a study done by Singh et al., the prevalence of *H. pylori* infection in India was 56.7% in asymptomatic and 61.3% in symptomatic (dyspepsia) individuals and 59.2% in the population overall.[7]

Besides the occult GI bleeding and competition for dietary iron, *H. pylori* infection can affect the gastric body and initiate the development of atrophic body gastritis that can, in turn, cause decreased gastric acid secretion and increased intragastric pH.

These findings suggest that the physiological mechanisms that are necessary for the absorption of alimentary iron in the duodenal mucosa are impaired in patients with *H. pylori*

gastritis and IDA. Thus, we planned to determine the relationship between *H. pylori* infection status and indices of IDA such as the peripheral haemogram and serum ferritin (SF). These indices were compared between group I, which received oral iron treatment only, and group II, which received combination antibiotic therapy combined with oral iron treatment.

Aims and objectives

To investigate the effect of treatment of *H. pylori* with combination antibiotic therapy on IDA in patient with *H. pylori* associated gastritis.

MATERIALS AND METHODS

The present study was carried out at a tertiary care hospital catering to large population in South Solapur and nearby areas. The study was conducted for 2 years. All patients with IDA attending outpatient department and admitted to the hospital in the aforementioned period were included in the present study.

Inclusion criteria

- Haemoglobin (Hb) <13 g/dL in males and <12 g/dL in females, peripheral blood smear suggesting IDA with mean corpuscular volume (MCV) <75 fL and SF <30 ng/mL.
- Patients in whom *H. pylori*-associated gastritis is the only pathological GI finding detected.

Exclusion criteria

- Patient with a history of consumption of nonsteroidal anti-inflammatory drug, anticoagulants, or corticosteroids
- Hematological disorder
- Stool sample positive for occult blood or hookworm ova
- Duodenal or gastric ulcer or carcinoma stomach at endoscopy
- Chronic renal failure

- Pregnancy (based on history in the span of 8 weeks)
- Hemorrhoids (proctoscopic examination)
- Patients with known causes of non-GI blood loss (history of menorrhagia or hemoptysis).

Data collection procedure

All patients who have IDA according to the World Health Organization criteria, as a hemoglobin concentration <13 g/dL for men and <12 g/dL for women, a MCV <75 fL and a SF level <30 ng/mL, both in-patient and outpatient setting were evaluated with detail history, clinical examination, and investigation.

Ethylenediaminetetraacetic acid blood (2 mL) was collected and analyzed for hemoglobin and red cell indices; SF level was determined by chemiluminescence. All patients who were found to have IDA by the above parameters underwent stool examination for the presence of hookworm ova on microscopy and for occult blood by benzidine test.

After informed consent patients underwent gastroscopy with gastric antral and body biopsy. In selected patients duodenal biopsy specimens were also obtained to exclude celiac disease. The sample examined by conventional histology, *H. pylori* status was considered positive when the organism was detected on histological examination, on Giemsa stain and features suggestive of gastritis.

Patients with IDA and positive for *H. pylori* gastritis on histology were randomly assigned into two groups (Groups I and II).

- Group I - Received oral ferrous sulfate tablets 200 mg/day for 2 months
- Group II - Received oral ferrous sulfate 200 mg/day with a 14-day course of anti-*H. pylori* therapy.

Anti-*H-pylori* treatment - Consisting of Amoxicillin 750 mg BD, Tinidazole 500 mg BD, and Omeprazole 20 mg BD. Follow-up: The Hb, RBCs indices, the peripheral smear of the two groups were recorded after 2 months of treatment.

Statistical analysis

Descriptive statistical analysis has been carried out in the present study. Results on continuous measurements are presented on mean ± SD (min-max) and results on categorical measurements are presented in number (%). Student's t-test was used to find the significance of study parameters on a continuous scale between two groups. Chi-square/Fisher's exact test has been used to find the significance of study parameters on a categorical scale between two or more groups. A P<0.05 were considered statistically significant. Data analysis was performed using the statistical software Statistical Package for the Social Sciences v20.0.

RESULTS

Of the total 40 patients, the youngest was 9 years and the oldest patient was 80 years old. The mean age of the study population in group I and group II, 51 and 45 years, respectively. Those who were more than 40 years of age constituted 75% and the rest 25% were less than or to 40 years of age. 11 patients with IDA were in the age group of >60 years and constituted the largest group followed closely by patients in 41–50 year of age group.

Out of the 40 patients, 18 (45%) patients were males and 22 (55%) were females. The male-to-female ratio was (1:1.2).

The commonest symptom noted was easy fatiguability 75%, followed by DOE, giddiness, and headache. Pallor was present in all patients followed by glossitis (23%), koilonychia (13%), and platynychia (Table 1).

Baseline Hb in group I is 8.99±1.23, while in group II 7.55±2.08. All the parameters are comparable in groups I and II except baseline Hb%. SF varies between 1.30 to 25.8 ng/ml. The mean value in group I and II is 7.31 and 7.61, respectively (Table 2).

There is a significant increase in Hb, packed cell volume (PCV), MCV, mean corpuscular hemoglobin (MCH), MCH concentration (MCHC) after 2 months of treatment with oral iron therapy. Increase in Hb is 1.40±0.44 g/dL compared to the baseline which is statistically significant (<0.001) (Table 3).

There is a significant increase in Hb, PCV, MCV, MCH, and MCHC after 2 months of treatment with oral iron and triple therapy for *H. pylori*. Increase in Hb is 3.69±1.19 g/dl compared to the baseline which is statistically significant (<0.001) (Table 4).

The increase in Hb in group I (Iron only) is 1.40±0.44 while in group II is 3.69±1.19 (iron+anti-*H. pylori*) which is statistically significant. The increase in PCV, MCV, MCH, and MCHC is comparable in both groups (Table 5).

DISCUSSION

In the present study, the mean age is 48.5 years, which is equivalent to Chen et al., who reported the mean age of 53 years with range of 18–76 years.[8] In all of the research cited, female preponderance than male. In the present study, females make up 55% of the participants, while males make up 45%.

Comparison between baseline Hb between different studies

The baseline Hb in group I was 8.99±1.23, which is equivalent to the findings reported by Choe et al., as

Table 1: Baseline characteristics

Baseline characteristics	Group I		Group II	
	Number	Percentage	Number	Percentage
Age (years)				
≤20	1	5.0	1	5.0
21–30	1	5.0	2	10.0
31–40	3	15.0	1	5.0
41–50	3	15.0	10	50.0
51–60	5	25.0	2	10.0
>60	7	35.0	4	20.0
Mean±SD	51.75±16.37		45.35±15.02	
Gender				
Male	8	40.0	10	50.0
Female	12	60.0	10	50.0
Symptoms				
Easy fatiguability	15	75.0	14	70.0
Dyspnea on exertion	3	15.0	6	30.0
Palpitation	2	10.0	1	5.0
Headache	3	15.0	0	0.0
Giddiness	3	15.0	3	15.0
Irritability	0	0.0	1	5.0
Signs				
Pallor	20	100.0	20	100.0
Glossitis	5	25.0	4	20.0
Koilonychia	4	20.0	1	5.0
Platynychia	2	10.0	1	5.0

Table 2: Comparison of laboratory investigations in group I and group II – Baseline

Investigations	Group I	Group II	P-value
Initial Hb	8.99±1.23	7.55±2.08	0.011*
TC	7060±1522.26	7632.50±2813.98	0.429
Platelet	3.65±1.22	3.49±1.38	0.709
PCV	26.75±6.07	26±6.04	0.698
MCV	62.15±5.99	64.85±5.51	0.146
MCH	18.35±3.51	19.00±3.76	0.575
MCHC	27.6±3.19	27.9±3.63	0.783
SF	7.31±6.27	7.61±5.51	0.873

Hb: Hemoglobin, TC: Total count, PCV: Packed cell volume, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, MCHC: Mean corpuscular hemoglobin concentration, SF: Serum ferritin

7.7±1.3,[9] and the baseline Hb in group II was 7.55±2.08, which is akin to the findings reported by Vijayan et al., as 7.42±1.90.[10]

Comparison of baseline SF

SF levels in the present study were 7.31±6.27 in group I and 7.61±5.51 in group II, which is equivalent to Choe et al., reported as 5.1 ±2.6 in group I and 4.6±1.6 in group II.[9] There is no statistically significant difference in SF levels between the two groups. Some studies have identified a link between *H. pylori* infection and lower ferritin levels.[11]

Increase in Hb after treatment in group I (iron only)

The increase in Hb in the present study is 1.40±0.44 g/dL, which is comparable to the 1.1 (1 month) reported by Valiyaveettil et al.,[12] and the 1.07 (1 month) reported by Vijayan et al.[10]

Increase in Hb after treatment in Group II (iron + anti *H. pylori*)

When compared to the baseline, there is a considerable increase in Hb. The mean increase in Hb in group II of the current study is 3.69±1.19 g/dL, which is comparable to the 3.6 (2 months) reported by Valiyaveettil et al.,[12] and the 4.1 (2 months) reported by Choe et al.[9]

Mean rise in Hb in groups I and II

Hb levels are much higher in group II (iron+anti-*H. pylori*) 3.69±1.19 than in group I, 1.40±0.44. In the current study, the increase in Hb in group I is 1.40 mg/dL, while it is 3.69 g/dL in group II. A similar findings were observed in studies conducted by Valiyaveettil et al., reported as After *H. pylori* infection was treated in Group II, the median rise in Hb was equivalent to those in Groups I and III (3.7 g/dL vs. 2.5 g/dL and 2.5 g/dL, respectively)[12] and Choe et al., reported, after 8 weeks, subjects in groups A (iron+eradication) and B (eradication+placebo) had significantly higher Hb levels than those in group C (iron+placebo).[9]

Whereas some other studies reported as, for up to 2 years of follow-up, Tseng et al., reported that, no significant improvement in IDA after *H. pylori* therapy.[13] A cross-sectional study of older people found no relationship between iron deficiency anemia and *H. pylori* infection.[14]

H. pylori gastritis is increasingly being investigated as a probable cause of IDA that is resistant to oral iron treatment, and *H. pylori* treatment may be followed by a

Table 3: Evaluation of blood parameters in baseline and 2 months after in Group I

Blood investigations	Baseline	After 2 months	Mean difference	95% CI	P value
Hb	8.99±1.23	10.39±1.13	1.40±0.44	1.19–1.60	<0.001**
TC	7060±1522.26	7210±1246.85	150.0±1513.24	558.42–858.23	0.663
Platelet	3.65±1.22	3.18±0.76	−0.47±1.05	−0.03–0.96	0.065+
PCV	26.75±6.07	35.15±5.36	8.40±5.67	5.74–11.05	<0.001**
MCV	62.15±5.99	81.40±5.11	19.25±5.62	16.61–21.88	<0.001**
MCH	18.35±3.51	28.90±3.60	10.55±3.52	8.90–12.19	<0.001**
MCHC	27.6±3.19	31.80±1.82	4.20±3.95	2.35–6.05	<0.001**

Hb: Hemoglobin, TC: Total count, PCV: Packed cell volume, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, MCHC: Mean corpuscular hemoglobin concentration, SF: Serum ferritin, **: Highly significant, +: Not significant

Table 4: Evaluation of blood parameters in baseline and 2 months after in Group II

Blood investigations	Baseline	After 2 months	Mean difference	95% CI	P-value
Hb	7.55±2.08	11.24±1.53	3.69±1.19	3.13–4.25	<0.001**
TC	7632.50±2813.98	7825±1601.93	192.50±2342.5	−903.9–−1288.9	0.717
Platelet	3.49±1.38	3.16±0.91	−0.33±1.12	−0.19–0.85	0.208
PCV	26±6.04	36.90±5.34	10.90±5.13	8.49–13.30	<0.001**
MCV	64.85±5.51	81.90±3.97	17.05±7.24	13.65–20.44	<0.001**
MCH	19.00±3.76	28.75±2.65	9.75±4.47	7.66–11.84	<0.001**
MCHC	27.9±3.63	32.65±1.63	4.75±3.49	3.11–6.39	<0.001**

Hb: Hemoglobin, TC: Total count, PCV: Packed cell volume, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, MCHC: Mean corpuscular hemoglobin concentration, SF: Serum ferritin, **: Highly significant

Table 5: Comparison between rise in Hb in group I and II

Delta values	Group I	Group II	P-value
Initial Hb	1.40±0.44	3.69±1.19	<0.001**
TC	150.0±1513.24	192.50±2342.5	0.946
Platelet	−0.47±1.05	−0.33±1.12	0.691
PCV	8.40±5.67	10.90±5.13	0.152
MCV	19.25±5.62	17.05±7.24	0.290
MCH	10.55±3.52	9.75±4.47	0.533
MCHC	4.20±3.95	4.75±3.49	0.644

Hb: Hemoglobin, TC: Total count, PCV: Packed cell volume, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, MCHC: Mean corpuscular hemoglobin concentration, SF: Serum ferritin

better response to oral iron in previously refractory IDA patients.

Nonetheless, an Egyptian study of 90 chronic renal disease patients on hemodialysis found no significant differences between *H. pylori*-positive and -negative groups in any of the variables investigated, including Hb, serum iron, ferritin, and transferrin saturation.[15]

In a country like India, where cost-effective solutions must be pursued, it may be worthwhile to consider treating iron-deficient patients for *H. pylori* blindly.

Limitations of the study

We did not confirm the eradication of *H. pylori* infection after 2 weeks of anti-*H. pylori* treatment. SF level not done at end of 2 months because of financial constraint. Patient in group I (iron only) was started on Anti- *H. pylori* treatment at the end of 2 months, follow-up of these patients not included in this study.

What this study adds

Our study provides further data that patients with unexplained IDA benefit from testing and treatment for *H. pylori* infection. Given the relative ease and simplicity of *H. pylori* treatment and the encouraging results in literature, *H. pylori* testing and treatment for persons with unexplained IDA appear to be clinically indicated. In a country like India where cost-effective strategies have to be implemented, it may be worthwhile to consider blindly treating refractory iron-deficient patients for *H. pylori*.

CONCLUSION

The treatment of *H. pylori* infection was associated with a more rapid and significant response to oral iron therapy in IDA as compared with the use of iron therapy alone. Our study provides further data that patients with unexplained IDA benefit from testing and treatment for *H. pylori* infection.

ACKNOWLEDGMENTS

The authors are acknowledged all staff that helped a lot during this research work.

REFERENCES

1. DeMaeyer E and Adiels-Tegman M. The prevalence of anaemia in the world. World Health Stat Q. 1985;38(3):302-316.
2. Rockey DC and Cello JP. Evaluation of the gastrointestinal tract in patients with iron-deficiency anemia. N Engl J Med.

1993;329(23):1691-1695.

https://doi.org/10.1056/NEJM199312023292303

3. Hershko C, Hoffbrand AV, Keret D, Souroujon M, Maschler I, Monselise Y, et al. Role of autoimmune gastritis, *Helicobacter pylori* and celiac disease in refractory or unexplained iron deficiency anemia. Haematologica. 2005;90(5):585-595.

   https://doi.org/10.3410/f.4034.461526

4. Lee JY, Kim SE, Park SJ, Park MI, Moon W, Kim JH, et al. *Helicobacter pylori* infection and iron deficiency in non-elderly adults participating in a health check-up program. Korean J Intern Med. 2022;37(2):304-312.

   https://doi.org/10.3904/kjim.2020.433

5. Husson MO, Legrand D, Spik G and Leclerc H. Iron acquisition by *Helicobacter pylori*: Importance of human lactoferrin. Infect Immun. 1993;61(2):2694-2697.

   https://doi.org/10.1128/iai.61.6.2694-2697.1993

6. Barabino A, Dufour C, Marino CE, Claudiani F and De Alessandri A. Unexplained refractory iron-deficiency anemia associated with *Helicobacter pylori* gastric infection in children: Further clinical evidence. J Pediatr Gastroenterol Nutr. 1999;28(1):116-119.

   https://doi.org/10.1097/00005176-199901000-00027

7. Singh V, Trikha B, Nain CK, Singh K and Vaiphei K. Epidemiology of *Helicobacter pylori* and peptic ulcer in India. J Gastroenterol Hepatol. 2002;17(6):659-665.

   https://doi.org/10.1046/j.1440-1746.2002.02746.x

8. Chen LH and Luo HS. Effects of *H pylori* therapy on erythrocytic and iron parameters in iron deficiency anemia patients with *H pylori*-positive chronic gastritis. World J Gastroenterol. 2007;13(40):5380-5383.

   https://doi.org/10.3748/wjg.v13.i40.5380

9. Choe, YH, Kim, SK, Son, BK, Lee DH, Hong YC and Pai SH. Randomized placebo-controlled trial of *Helicobacter pylori* eradication for iron-deficiency anemia in preadolescent children and adolescents. Helicobacter. 1999;4(2):135-139.

   https://doi.org/10.1046/j.1523-5378.1999.98066.x

10. Vijayan G, Sundaram RC, Bobby Z, Hamide A, Selvaraj N and Dasse NR. Increased plasma malondialdehyde and fructosamine in anemic *H pylori* infected patients: Effect of treatment. World J Gastroenterol. 2007;13(5):796-800.

    https://doi.org/10.3748/wjg.v13.i5.796

11. Gheibi SH, Farrokh-Eslamlou HR, Noroozi M and Pakniyat A. Refractory iron deficiency anemia and *Helicobacter pylori* infection in pediatrics: A review. Iran J Ped Hematol Oncol. 2015;5(1):50-64.

12. Valiyaveettil AN, Hamide A, Bobby Z and Krishnan R. Effect of anti-*Helicobacter pylori* therapy on outcome of iron-deficiency anemia: A randomized, controlled study. Indian J Gastroenterol. 2005;24(4):155-157.

13. Tseng DS, Li D, Cholleti SM, Wei JC, Jodesty Y and Pham HV. Effect of *Helicobacter pylori* treatment on unexplained iron deficiency anemia. Perm J. 2019;23:18-195.

    https://doi.org/10.7812/TPP/18-195

14. John S, Baltodano JD, Mehta N, Mark K and Murthy U. Unexplained iron deficiency anemia: Does *Helicobacter pylori* have a role to play? Gastroenterol Rep (Oxf). 2018;6(3):215-220.

    https://doi.org/10.1093/gastro/goy001

15. El-Said H, Attallah AH and Ali-Eldin ZA. Does *Helicobacter pylori* infection play a role in iron deficiency anemia in hemodialysis patients? Clin Nephrol. 2017;88(4):177-180.

    https://doi.org/10.5414/CN109034

Authors' Contributions:
PTD- Concept and design of the study, prepared first draft of manuscript and revision of the manuscript; **RD-** Statistical analysis, Interpreted the results; reviewed the literature and manuscript preparation; **SP-** Concept, statistical analysis and interpretation, **NB-** Preparation of manuscript and revision of the manuscript.

Work attributed to:
Ashwini Rural Medical College, Hospital and Research Centre, Solapur.

Orcid ID:
Dr. Prashant Tanaji Dond - https://orcid.org/0009-0008-9489-7395
Dr. Rahul Deshpande - https://orcid.org/0009-0004-3515-0188
Dr. Shailesh Patil - https://orcid.org/0009-0007-7706-5717
Dr. Naresh Bhat - https://orcid.org/0009-0006-9446-9994

Source of Support: Nil, **Conflicts of Interest:** None declared.