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# A Prospective Randomized, Open-Label, Parallel-Group Study to Evaluate the Efficacy and Safety of Two Different Iron Formulations

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***Abstract*: *Background*: Deficiency of iron, folic acid, and vitamin B12 (cobalamin) is common. Iron-deficiency is a common cause of anaemia world-wide. Nutritional deficiencies of folate, vitamin B12 and A, and C are other leading causes of anaemia.**
***Methods:* In this prospective, randomized, parallel-group study the efficacy and safety of tablet formulation containing combination of ferrous ascorbate, folic acid and cyanocobalamin (Treatment A) was evaluated and compared with tablet formulation containing combination of ferrous ascorbate and folic acid (Treatment B) in treatment of low hemoglobin level. The levels of haemoglobin, haematocrit, vitamin B12, ferritin, and total red blood cell count were assessed in each treatment group during screening, on Day 30, and Day 60. *Results:* Tablet formulation containing combination of ferrous ascorbate, folic acid and cyanocobalamin (Treatment A) demonstrated 23.52% rise in haemoglobin level from baseline to Day 60 whereas the rise in Treatment B, a combination tablet of ferrous ascorbate and folic acid was 14.15%. Similar result was obtained for all other haematological parameters, serum ferritin and vitamin B12. Both the treatments were safe and tolerable and no adverse events were reported in the study. *Conclusion:* Adding cyanocobalamin to iron supplements containing combination of ferrous ascorbate and folic acid provides better efficacy in improving haematological parameters (haemoglobin, haematocrit, and total red blood cell count), serum ferritin, and vitamin B12 level.**

***Keywords*: Anaemia, cyanocobalamin, efficacy, ferrous ascorbate, iron, rubired, safety, supplement, low haemoglobin**

## 1. Introduction

Anemia, a common blood disorder, in which hemoglobin (Hb) concentration and/or red blood cell (RBC) numbers are lower than normal and insufficient to meet an individual's physiological needs.1 It also occurs due to low intake or reduced absorption, and increased demands of iron during the period of growth and development as well as due to blood loss during menstruation.2 It can be of varying severity and fatal if left untreated. Although anemia can affect individuals of all ethnicity, race, gender, and age, it is more common among women than men.3 The most common cause of anemia worldwide is iron deficiency, resulting from prolonged negative iron balance, caused by inadequate dietary iron intake or absorption, increased needs for iron during pregnancy or growth periods, and increased iron losses as a result of menstruation and helminth (intestinal worms) infestation. Other important causes of anemia worldwide include infections, other nutritional deficiencies (especially folate and vitamins B12, A and C) and genetic conditions (including sickle cell disease, thalassaemia – an inherited blood disorder – and chronic inflammation) [4].

Published literature indicates the higher prevalence of nutritional anemia in India, with iron deficiency anemia (IDA) being the most common.5 Approximately 50% of the anemia affecting women globally is categorized as iron deficiency anemia (IDA).4 Iron is the critical part of hemoglobin, a protein in RBCs, which carries oxygen from lungs to the rest of the body.6 Measurement of serum ferritin level is considered to be the most accurate method to diagnose IDA [7].

As per World Health Organization, supplementation with iron is recommended in the management of IDA.8 IDA can be managed by identifying and treating the underlying cause along with the management of the current anaemic condition.2 About 65% infant and toddlers, 60% children aged 1-6 years, 88% adolescent girls (3.3% severely anaemic with haemoglobin <7.0 g/dL), and 85% pregnant women (9.9% severely anaemic) were found to be anemic. In addition, the prevalence rate in lactating mothers was higher than pregnant women.5

Regular intake of oral iron and folic acid supplements is recommended by WHO as part of antenatal care. It reduces the risk of iron deficiency, low birth weight, and maternal anemia. These formulations may also include other vitamins and minerals, as per the United Nations Multiple Micronutrient Preparation, to prevent and treat other micronutrient deficiencies in pregnant and lactating mothers. Supplementation with iron and folic acid has proven to reduce the prevalence worldwide, including India. In Gujarat, a state in

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India, a weekly supplementation of iron-folic acid to 1.2 million reduced the prevalence from 74.2% to 53.5% within a year and the treatment compliance was found to be 90%.4

*1) Advantages of ferrous ascorbate over conventional iron therapy*

The primary merit of using ferrous ascorbate is the presence of ferrous ion and ascorbate in one compound. The higher in vivo absorption of iron from ferrous ascorbate than ferrous sulfate is due to (a) prevention or inhibition of oxidation of Fe(II) by ascorbate, and (b) the presence of Fe(II) in the form of chelate with ascorbate. Ascorbate acts as a solubility enhancer between pH 6 to pH 8, which could be the reason for increased iron absorption from this compound [9].

*2) Advantages of cyanocobalamin in combination with ferrous ascorbate and folic acid*

Deficiency of vitamin B12 (cobalamin) leads to a type of anaemia called pernicious anaemia, which lowers the absorption of vitamins and minerals, including vitamin B12 itself, folic acid, iron, and calcium.3 Cobalamin deficiency is also the second leading cause of megaloblastic anaemia; the first leading cause being folate deficiency.10 The malabsorption of these vitamins and minerals are observed in lactating women with pernicious anaemia, and those with gastrointestinal disorders or a history of malabsorptive bariatric procedure.11 Cyanocobalamin is useful in the management of vitamin B12 deficiencies. It is approved for the management of several indications, including pernicious anaemia, dietary deficiency of vitamin B12, malabsorption of vitamin B12, and malignancy of pancreas or bowel [12] Iron supplementation can be used as an intervention to prevent and treat IDA and iron deficiency in high risk populations. Prevalence of vitamin B12 deficiency is as high as 47% in India with only 26% population with vitamin B12 sufficiency (levels between 200-300 pg/ml are considered borderline deficient) [13,14]

Therefore, we conducted a prospective, randomized, comparative, open-label, parallel group study to evaluate and compare the efficacy and safety of tablet formulation containing ferrous ascorbate, folic acid and cyanocobalamin versus tablet containing ferrous ascorbate and folic acid in treatment of low hemoglobin level.

Table 1
Within Treatment Group Comparisons for Day30 and Day60 from Baseline

| Treatment | Treatment period | Haemoglobin (g/dL) | Haematocrit (%) | Serum Ferritin (ng/mL) | Vitamin $B_{12}$ (pg/mL) | Total RBC count (million/µL) |
|---|---|---|---|---|---|---|
| A | Baseline | 10.91 | 34.73 | 6.547 | 256.2 | 4.718 |
| | Day 30 | 12.74 | 39.62 | 23.311 | 332.8 | 4.960 |
| | Day 60 | 13.48 | 40.88 | 20.818 | 266.3 | 4.998 |
| | Mean change at Day 30ǂ | 1.83$ | 4.89$ | 16.764$ | 76.6$ | 0.242$ |
| | Mean change at Day 60ǂ (%mean change) ǂ | 2.57$ (23.52) | 6.14$ (17.69) | 14.271$ (217.99) | 10.1@ (3.95) | 0.280$ (5.93) |
| B | Baseline | 10.78 | 34.30 | 14.805 | 299.3 | 4.405 |
| | Day 30 | 11.78 | 36.81 | 42.054 | 243.4 | 4.544 |
| | Day 60 | 12.30 | 37.36 | 22.670 | 250.3 | 4.569 |
| | Mean change at Day 30ǂ | 1.00@ | 2.51@ | 27.25@ | -55.9$ | 0.139@ |
| | Mean change at Day 60ǂ (%mean change) ǂ | 1.53@ (14.15) | 3.06 @ (8.93) | 7.86@ (53.12) | -49.0@ (-16.37) | 0.164@ (3.72) |

Treatment A= Ferrous Ascorbate 100 mg, Folic Acid 1.5 mg and Cyanocobalamin IP 7.5 mcg Tablet
Treatment B: Ferrous Ascorbate 100 mg + Folic Acid 1.5 mg Tablet
ǂ: Changes indicate from baseline
Note: Within treatment comparison, by statistical method paired t-test,
$ Statistical significant P-value<0.05
@ Statistical insignificant P-value>0.05

## 2. Methods

This study was conducted in accordance with the Good Clinical Practice Guidelines and other guidelines applicable to the study and approval was obtained from ethics committee prior to the conduct of the study.

*1) Screening and eligibility criteria*

Adult men or women aged above 18 years who had low hemoglobin level, were not participating in any other interventional trials, able to provide voluntary informed consent, able to comply with the procedures in the study, willing to consume deworming medication were included in the study.

Known hypersensitivity to the study treatment active ingredients, frequent blood donation; bleeding due to hemorrhoids, active hemorrhage; unable to take or tolerate study medications, ongoing oral iron supplementation; history of use of any of the study treatment within the last 3 months; blood transfusion or intravenous iron administration or erythropoiesis-stimulating agent administration within 1 month prior to randomization; active drug or alcohol dependence or abuse within 12 months prior to screening; heavy menstrual bleeding; and any clinically significant acute or chronic illness or circumstance that could compromise the integrity of study data, affect the analyses or place participants at risk in the study, in the opinion of the investigator, haemoglobin >12.9 g/dL in men and >11.9 g/dL in women, were considered as exclusion criteria for the study.

*2) Treatment groups and dosing regimen*

The two treatments in the study were:

- *Treatment A:* Ferrous Ascorbate 100 mg, Folic Acid

1.5 mg and Cyanocobalamin IP 7.5 mcg Tablet

- *Treatment B*: Ferrous Ascorbate 100 mg + Folic Acid 1.5 mg Tablet

The study treatments, Treatment A Rubired® Tablet and Treatment B Orofer® XT Tablet were purchased from the market.

*3) Statistical analysis*

Statistical analysis was performed using Statistical Analysis System® (SAS®), (SAS Institute Inc., Cary, USA) Version 9.4. Intent-to-treat (ITT) population (N=17) defined as all randomized population who received at least one dose of study treatment were included for primary efficacy and safety analysis. Paired t-test method was used for within treatment comparison. Statistical significance for the result was indicated at 5% level of significance.

*4) Primary efficacy analysis*

- Mean of haemoglobin, haematocrit, total RBC, serum ferritin and vitamin B12 from baseline to Day 30 and Day 60 within each treatment groups were analyzed
- Percentage mean change of haemoglobin, haematocrit, total RBC, serum ferritin and vitamin B12 from baseline to Day 60 for each treatment group was presented.

*5) Study assessments*

Hematological parameters, hemoglobin, haematocrit, and total RBC count and vitamin B12, serum ferritin, were assessed in each treatment group during screening, on Day 30 and Day 60. Occurrence of adverse event was monitored throughout the study period.

## 3. Results

A total of seventeen (N=17) adult men or women aged above 18 years of age and fulfilling the eligibility criteria received Treatment A (n=9) or Treatment B (n=8). The efficacy and safety outcomes are described below.

*1) Primary efficacy endpoints*

The mean of each hematological parameter, and serum ferritin was increased from baseline at Day 30 and Day 60 in both Treatment A and Treatment B groups. Paired t-test was used to analyze the mean change at Day 30 and Day 60 from baseline within each treatment group. The mean change at Day 30 and Day 60 from baseline was statistically significant for all hematological parameters and serum ferritin ($P<0.05$) in Treatment A group whereas in Treatment B group no statistical significance was observed. (Table 1, Figure 1)

The percentage mean change in hemoglobin, haematocrit, total RBC, and serum ferritin increased at Day 60 from baseline in Treatment A as compared to Treatment B. The Vitamin B12 percentage mean change increased only in Treatment A group. The percentage mean changes for each hematological parameter, serum ferritin, and Vitamin B12 are presented in Figures 2 to 6.

*2) Safety endpoint*

No adverse events were reported in any of the treatment groups throughout the study period, and both the treatments were safe and tolerable.

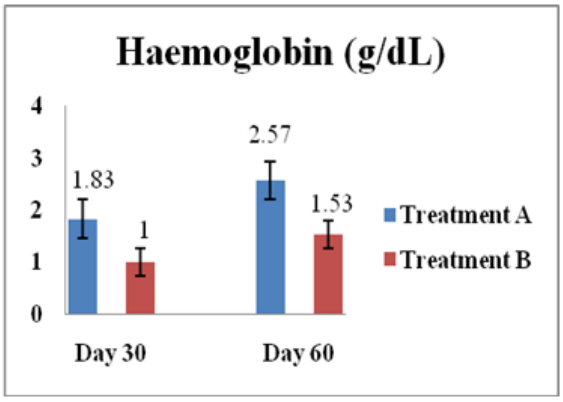


Fig. 1. Mean change in haemoglobin at Day 30 and Day60

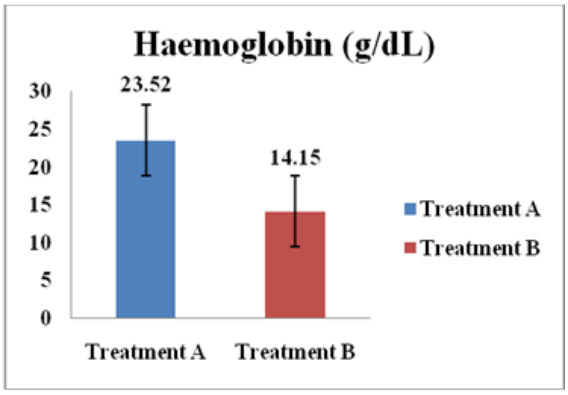


Fig. 2. Percentage mean change in haemoglobin at Day 60

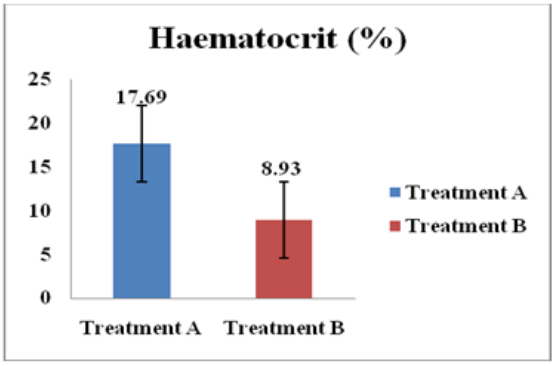


Fig. 3. Percentage mean change in hematocrit at Day 60

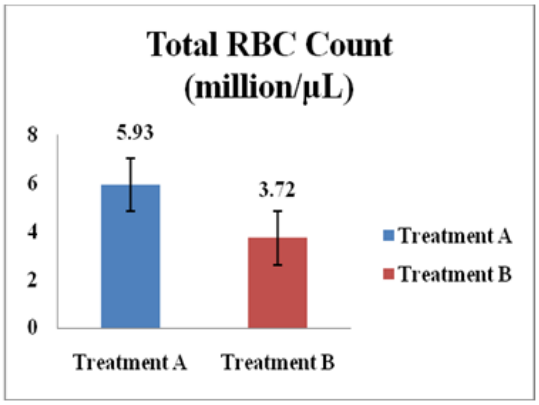


Fig. 4. Percentage mean change in total RBC count at Day 60

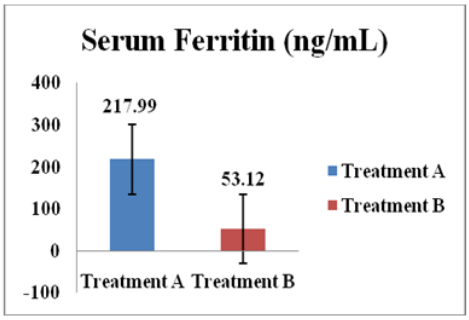


Fig. 5. Percentage mean change in serum ferritin at Day 60

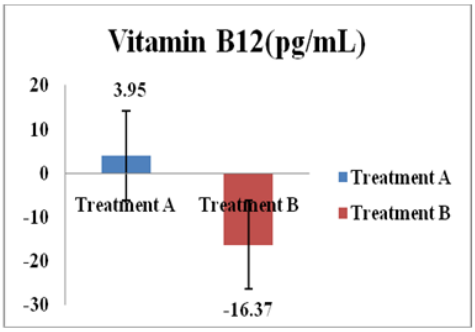


Fig. 6. Percentage mean change in vitamin B12 at Day 60

## 4. Discussion

Deficiency of iron, folic acid, and vitamin B12 (cobalamin) is common. Iron-deficiency is a common cause of anaemia world-wide. Nutritional deficiencies of Folate, Vitamin B12 and A, and C are other leading causes of anaemia.4, 10 The deficiency of vitamin B12 not only affects its own further absorption in the body, but also affects the absorption of other vital constituents, such as iron and folic acid. This suggests the reason for better efficacy of Treatment A (Ferrous Ascorbate, Folic acid and Cyanocobalamin tablet), which has the extra component-cyanocobalamin (vitamin B12). Statistical significant improvement in levels of all haematological parameters, serum ferritin, and vitamin B12 analyzed in this study were noted with Treatment A as compared to Treatment B (Ferrous Ascorbate and Folic acid tablet).

Along with iron and vitamin B12, folic acid is the central component involved in human erythropoiesis. Although folate is widely distributed in various food items, its dietary deficiency causing megaloblastic anaemia is seen globally. Fishman SM et al. indicated that folate and vitamin B12 supplementation can be useful to prevent megaloblastic anaemia. 10

Patil P et al. conducted a randomized controlled trial to compare the therapeutic efficacy of ferrous ascorbate and iron polymaltose complex (IPC) in IDA. At the end of 3-month treatment, both the groups showed improvement in haematological parameters. Although both the iron salts showed statistically significant improvement in haematological parameters from baseline, the results was better in ferrous ascorbate group, the haemoglobin increase at 1 month and 3 month were found to be statistically better in ferrous ascorbate group than iron polymaltose complex [15].

Other studies such as Yewale VN et al. indicated higher mean rise in haemoglobin in ferrous ascorbate group than the colloidal iron group (3.59±1.67 g/dL vs. 2.43± 1.73 g/dL; P<0.01). Significantly higher proportion of those receiving ferrous ascorbate (64.86% vs. 31.03%; P<0.01) became non-anaemic at the end of 12-week treatment period.16

In this study Treatment A showed higher probability of improvement in all haematological parameters, serum ferritin, and Vitamin B12.

## 5. Conclusion

Regular intake of oral iron and folic acid supplements reduces the risk of iron deficiency, low birth weight, and maternal anaemia. Ferrous ascorbate supplements lead to higher rise in haemoglobin levels as compared to other ferrous salts. Adding cyanocobalamin to iron supplements gives added benefit in improvement in vitamin B12 as its deficiency is one of the most important causes of anaemia. This was demonstrated in our study wherein the treatment containing ferrous ascorbate, folic acid and cyanocobalamin showed better efficacy in improving haematological parameters of haemoglobin, haematocrit, total red blood cell count, and serum ferritin and vitamin B12 level.

## 6. Declarations

- *Funding:* This study was funded by Macleods Pharmaceuticals Ltd.
- *Conflict of interest:* All authors and statistician are full-time employees of Macleods Pharmaceuticals Ltd.
- *Ethical approval:* This study was approved by Ethics Committee

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