

# The Efficacy and Safety of Oral Ferrous Gluconate in Premenopausal Women with Severe Iron Deficiency Anaemia

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## Abstract

**Objective:** To evaluate the efficacy and safety of ferrous gluconate, given orally thrice daily for three months, to pre-menopausal women with severe iron deficiency anaemia.

**Method:** A phase IV non randomized single arm open label drug trial was conducted at Gynaecology and Obstetrics Unit II in Abbasi Shaheed Hospital from Feb 2013 to March 2014, which is a 950 bedded public sector tertiary care hospital.

Total fifty premenopausal women with documented severe iron deficiency anaemia, haemoglobin (Hb) between 6-8 g/dl were enrolled after taking written informed consent. Clinical evaluation and lab investigation for serum ferritin and haemoglobin levels were conducted at baseline and after completion of treatment. A standardized proforma for data collection was developed. Ferrous gluconate soft gelatin capsules were given as one capsule during or after the meal 3 times daily, for three months. All patients were evaluated four times during study first at the time of enrolment and after 30, 60, and 90 days for clinical efficacy and safety assessment.

**Results:** In our study all fifty premenopausal women completed iron treatment. Analysis of therapeutic efficacy parameters i.e. haemoglobin, and serum ferritin levels showed improvement that was statistically significant. By the end of treatment with oral ferrous gluconate, significant improvement in Hb levels was observed ( $7.574 \pm 0.559$  g/dl vs  $11.020 \pm 0.718$ ,  $p < 0.0001$ ). Significant changes were noted in serum ferritin level ( $10.058 \pm 5.059$  ng/ml vs  $27.136 \pm 13.803$ ,  $p < 0.0001$ ) after 3 months therapy. Ferrous gluconate proved to be safe in women with severe iron deficiency anaemia. The treated women did not exhibit any major side effect, only one serious side effect was reported (erythema nodosum). Mild self-limiting side effects including black discoloration of stool in 54% cases, nausea in 6%, constipation in 2% and diarrhoea in 2% was observed.

**Conclusion:** Oral ferrous gluconate treatment for severe iron deficiency anaemia is well tolerated and highly effective in premenopausal women.

**Keywords:** Iron-deficiency anaemia, premenopausal, ferrous gluconate, haemoglobin, ferritin.

**IRB:** Approved by Ethical Review Committee, Karachi Medical and Dental College.

**Dated:** 26<sup>th</sup> February 2013.

(ASH & KMDC 22(1):5;2017).

## Introduction

Anaemia affects one-fourth of the world's population, accounting for 8.8% of the total global burden<sup>1</sup>. Iron deficiency is the most common form of malnutrition in the world, affecting more than 2 bil-

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Date of Submission: 31<sup>st</sup> July 2016  
Date of Acceptance: 28<sup>th</sup> February 2017

lion people globally. Iron deficiency anaemia (inadequate amount of red blood cells caused by lack of iron) is highly prevalent in less-developed countries but also remains a problem in developed countries where other forms of malnutrition have already been virtually eliminated. Iron deficiency is not the only cause of anaemia, but where anaemia is prevalent; iron deficiency is usually the most common cause<sup>2</sup>. In pre-menopausal women the prevalence of iron deficiency anaemia is 5-12%, usually due to menstrual blood loss or dietary deficiency<sup>3-5</sup>. In Pakistan, the prevalence of iron deficiency anaemia is much higher, reported about 30%<sup>6</sup>. Iron defi-

ciency anaemia usually present with fatigue, irritability, palpitation, tachypnea on exertion, impaired work capacity and reduce resistance to infection<sup>7</sup>.

Haemoglobin concentration and serum ferritin level can be used to diagnose the iron deficiency anaemia<sup>8,9</sup>. Treatment of underlying cause to prevent further iron loss is necessary in addition to iron supplementation for correction of anaemia and replenish the body iron store<sup>10</sup>. There are a wide variety of iron supplements in use around the world, and their quality varies. Oral iron therapy is the treatment of choice for the most of patients with iron deficiency anaemia. Conventional iron in form of ferrous sulphate is limited by gastro intestinal complaints. The use of ferrous gluconate as an alternative to these conventional ferrous salts offer less gastro intestinal upsets<sup>11,12</sup>. Iron deficiency anaemia (IDA) is associated with diminished quality of life, fatigue, impaired cognitive function, and subfertility but all these are reversible events<sup>12,13</sup>.

In a study conducted in Pakistan, it was concluded that low income, multiparity, poor diet and lack of supplements were the main contributors in development of anaemia<sup>14</sup>. A daily protocol of iron supplementation is recommended for treatment and prevention in the priority target groups. Iron supplements need to be administered in three times daily dosage and compliance is a major issue especially in low socioeconomic groups. However most of the women with severe iron deficiency anaemia are treated by intravenous iron or blood transfusion, hence, we wanted to try an oral haematinic and observe our patient's compliance and efficacy of the drug.

## Patients and Methods

This phase IV non-randomized single arm open clinical drug trial was conducted at Gynaecology and Obstetrics Unit II in Abbasi Shaheed Hospital which is a tertiary care public sector hospital affiliated with Karachi Medical and Dental College. The study went on during February 2013 to March 2014. An institutional ethical review board approved the study protocol prior to study initiation.

By using Rao soft sample size calculator, considering the proportion 43% of patients with iron deficiency anaemia with margin of error 5% and 95% confidence level, an estimated sample size of 50 was calculated<sup>15</sup>.

All women were enrolled after taking written informed consent in local language (Urdu). The premenopausal women included had moderate to severe anaemia with Hb 6 to 8 g/dl. Patients were excluded if they had anaemia other than iron deficiency, concomitant medical or surgical disease, and acid peptic ulcer, malabsorption, bleeding disorder, significant vaginal bleeding disorder or recent blood transfusion or were severely symptomatic. A standardized performa for data collection was developed. All patients were evaluated four times during study first at the time of enrolment and then after 30, 60, and 90 days for efficacy and safety assessment. Clinical evaluation in terms of fatigue, tiredness and dyspnoea was done before and after treatment on a 4 point scale as: nil, mild, moderate and severe. Labs including haemoglobin and serum ferritin levels were carried out prior to beginning of treatment and at the end of treatment. All the medications used in the study were provided by Merck Private Limited Pakistan. Each subject was provided one month of therapy, free of cost. On each visit counting the number of capsules returned and the capsules consumed during the previous visit assessed subject treatment compliance. All concomitant medication, unless considered absolute necessary for the welfare of the patient, were discontinued before study. Treatment was given as soft gelatine capsules that contain ferrous gluconate 250 mg three times daily.

Adverse reactions during study were evaluated by spontaneous reporting by patients at each visit as well as they were also given the contact number of investigator and to contact her in case of any adverse reaction associated with the treatment. Subject was withdrawn from study if she required any intervention due to deterioration of clinical symptoms and required blood transfusion, intravenous iron.

The tolerance of treatment protocol was assessed by the analysis of any side effects such as nausea, vomiting, constipation, black discoloration of stool and others reported by patients during treatment.

To report for all serious adverse events (SAEs) that were spontaneously reported, elicited or observed by investigator related to the drug. The women were provided the cell number to report adverse effects immediately. All SAEs were followed until satisfactory resolution or until the investigator or designee deems the event to be chronic or the patient to be stable.

Data were analysed by SPSS version 17. Student t test was used to compare values of haemoglobin and serum ferritin before and after completion of therapy. P-value less than 0.05 was considered statistically significant. Adverse drug reactions were assessed in the patients by computing the frequencies and percentages.

## Result

From February 2013 to March 2014, 68 anaemic premenopausal women were considered eligible for inclusion in the study. Out of 68 women 8 women did not sign the consent to participate. Therefore, 60 women were inducted. Fifty-one women were followed, whereas 9 women failed to come for follow up. Out of 51 women, one had to discontinue the treatment because she developed erythemanodosum. In our study, fifty premenopausal women completed iron therapy (Fig. 1).

The mean age of women was  $34.20 \pm 7.706$  years. The study showed oral ferrous gluconate was effective in increasing mean haemoglobin concentration i.e. 3.44 g/dl after 3 months of treatment. Mean Hb concentration was increased from  $7.574 \pm 0.559$  to  $11.020 \pm 0.718$  g/dl that was statistically significant  $p < 0.000$  as shown in Table 1.

Significant increase was observed in serum ferritin level from baseline value to three months. The serum ferritin level at the beginning of treatment

was  $10.058 \pm 5.059$  ng/ml and after 90 days it was  $27.136 \pm 13.803$  ng/ml with a  $p < 0.000$  (Table 1).

The study showed significant improvement in clinical parameters. At the beginning of therapy 72% women had mild fatigue and tiredness while 28% had moderate symptoms. Mild dyspnoea was present on routine activity in 46 cases. However, at the end of therapy all patients improved symptomatically.

It was found that 64% women had adverse effects after ingestion of oral ferrous gluconate. The commonest adverse events were black discoloration of stool in 54%, nausea in 6%, and constipation in 2% and diarrhoea in 2% (Fig. 3).

Only one patient developed erythema nodosum after 15 days of treatment, she was a diagnosed case of pelvic tuberculosis and was taking anti-tuberculosis treatments, but was not disclosed by the patient. The patient recovered completely after 2 weeks of dermatological treatment. However we stopped her oral iron therapy.

Table 1. Comparison of haemoglobin and serum ferritin level prior and after treatment.

| S. No | Characteristic         | Baseline values Mean±S.D | At completion of therapy Mean±S.D | p-value |
|-------|------------------------|--------------------------|-----------------------------------|---------|
| 1     | Haemoglobin (g/dl)     | $7.574 \pm 0.559$        | $11.020 \pm 0.718$                | <0.0001 |
| 2     | Serum Ferritin (ng/ml) | $10.058 \pm 5.059$       | $27.136 \pm 13.803$               | <0.0001 |

p-value = significant at 5<sup>th</sup> level of significance

## Discussion

Iron deficiency anaemia is the most common disorder around the globe. Oral iron therapy is usually adequate for most patients and is currently the treatment of choice for patients with mild to moderate iron deficiency anaemia; it is an efficient, well-tolerated and cost-effective way to replace iron stores. Ferrous gluconate is one of the oral therapy produced significant improvement in haemoglobin.

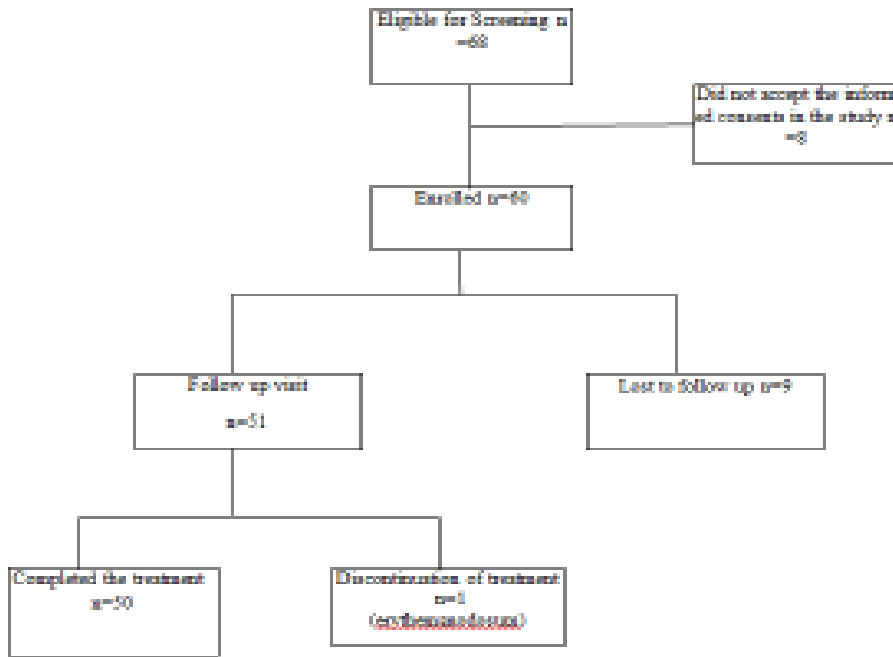


Fig 1. Flow diagram showing the total study population.

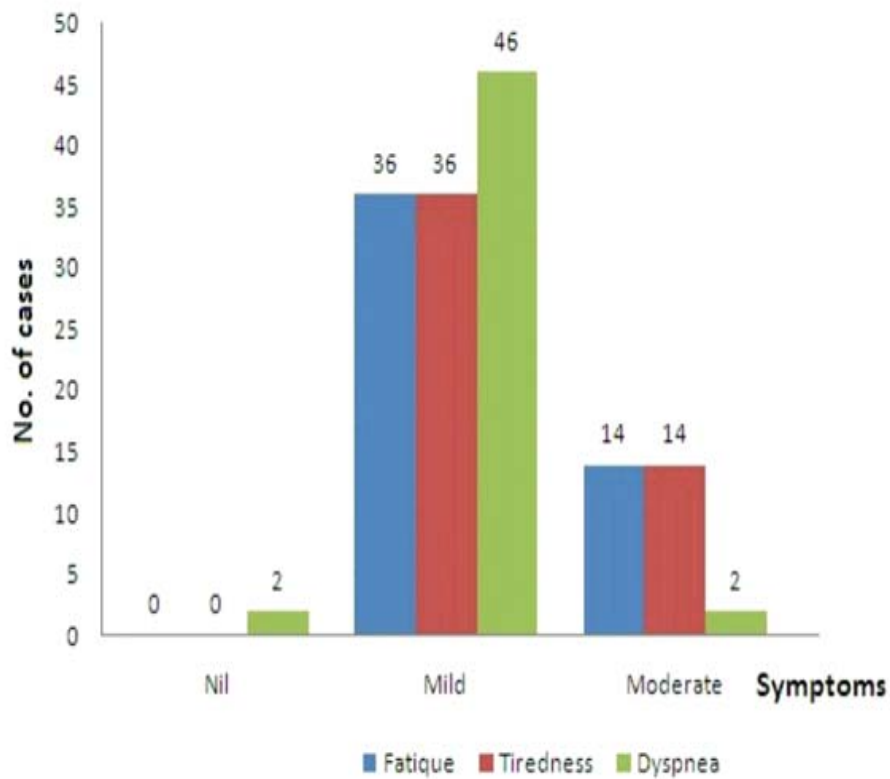
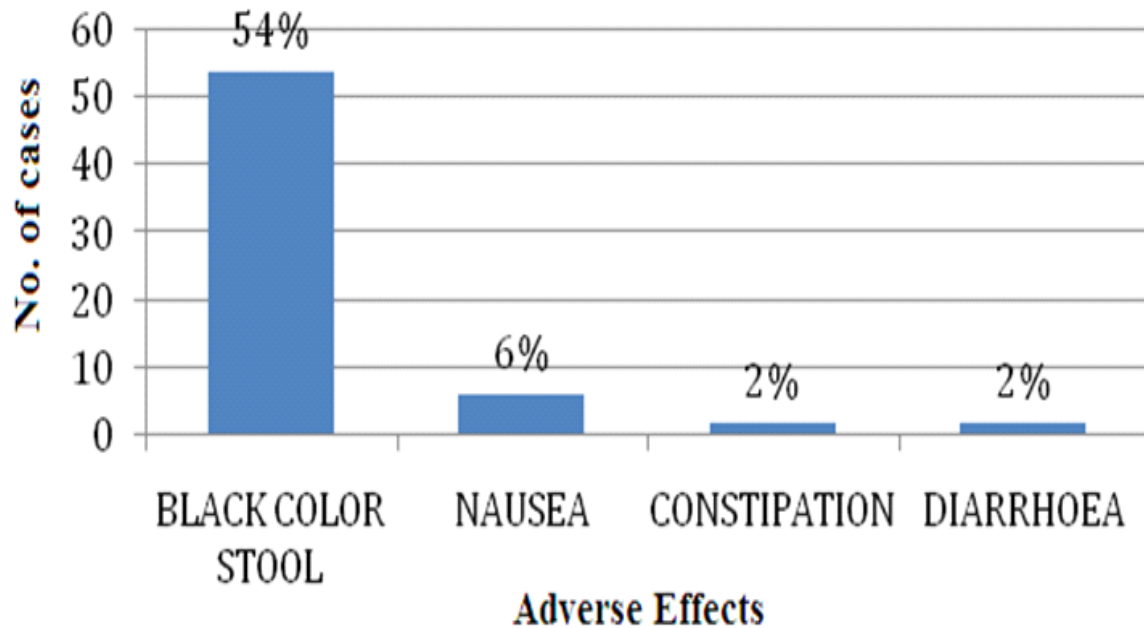


Fig 2. Evaluation of symptoms before treatment



**Fig 3.** Adverse event profile of the iron supplementation

The present study is therefore targeted to observe the therapeutic efficacy of oral ferrous gluconate in premenopausal women with severe iron deficiency anaemia.

Women with severe iron deficiency anaemia are treated by intravenous iron or blood transfusion as no convincing data of oral iron regarding efficacy and compliance was available in our women who come from poor or low middle class background. With this study it could be demonstrated that ferrous gluconate is an effective oral iron therapy in severe iron deficiency anaemia, which is indicated by mean increase in Hb and serum ferritin level. Raise serum haemoglobin (Hb) by 2 g/dl every two weeks ultimately restoring iron store at least 3 months after iron therapy. Successful iron repletion is possible with lower doses such as 50 mg elemental iron per day<sup>16</sup>. Our study shows mean rise in Hb concentration 3.44 g/dl after 3 months of treatment

Oral therapy provides benefit of avoidance of risk of intravenous therapy associated with adverse reactions as well as eradicate need of blood trans-

fusion and its related transmission of infection<sup>17,18</sup>. Serum ferritin level reflects iron stores and is the most accurate test to diagnose iron deficiency anaemia. Low serum ferritin level is the first abnormal biochemical parameter which indicates iron deficiency<sup>8</sup>.

In our study, ferrous gluconate significantly replenished iron stores from  $10.058 \pm 5.059$  ng/ml to  $27.136 \pm 13.803$  ng/ml ( $p < 0.0001$ ) after 3 months of treatment.

Correction of iron deficiency along with achieving normal haemoglobin is also important in improving tiredness and mental concentration<sup>19,20</sup>.

In our study, improvement in all clinical signs and symptoms (fatigue, tiredness and dyspnoea) was observed. The physician and patient assessment of the treatment seems to favour in oral ferrous gluconate form in severe anaemia.

All adverse effects are dose related adverse effects can occur in upto 20% of patients, impairing compliance<sup>19</sup>.

Our study shows only one serious side effect; erythema nodosum. Erythema nodosum is a cutaneous inflammatory reaction located on the anterior aspects of lower extremities. It may be associated with a wide variety of diseases, including infections, inflammatory, bowel disease, medications, autoimmune disorder, pregnancy and malignancies. In this study, the women developed erythema nodosum after 2 weeks of treatment, but she was diagnosed as a case of pelvic tuberculosis and was taking anti-tuberculosis treatment without revealing this information. So it cannot be excluded that the concomitant medication might have contributed to the event or has to be considered as causal related to event. We have not found any case of erythema nodosum after taking ferrous gluconate in literature search. Ferrous gluconate is safe and associated with mild self-limited side effects. This study also highlights the advantage of oral iron supplementation in low resource setting and the overall benefit to the health care setting of a country aligned to World Health Organization (WHO) principles of IDA management. The most frequently reported side effect black stool is in fact considered as an undesirable effect, but does not represent a negative medical impact to the health of the patients.

Limitations of this study are that of a small sample size and it does not include the comparison with other iron therapy, further studies needed to explore on these aspects.

## Conclusion

This study revealed that oral ferrous gluconate is effective treatment in severe iron deficiency anaemia in premenopausal women with minimal side effects.

## Acknowledgement

We would like to acknowledge Merck pharma limited for assistance with the laboratory work and provision of medicines in this study.

## Conflict of interest

Authors have no conflict of interest. Funding for this study was provided by Merck pharma limited for provision of medicines and laboratory investigations, free of cost.

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