Clinical Obstetrics, Gynecology and Reproductive Medicine

Research Article

Heme iron to correct Iron deficiency anemia with pregnancy

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Abstract

Objectives: This study designed to evaluate the efficacy and tolerability of heme iron polypeptide (HIP) in treatment of iron deficiency anemia during pregnancy.

Methods: 150 pregnant women with hemoglobin <10 gm/dl due to iron deficiency included in this study and treated with HIP for correction of iron deficiency anemia during pregnancy. Treatment efficacy checked by comparing the pre-treatment values of hemoglobin, serum ferritin, reticulocytes, mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH) by the 3-months` post-treatment values.

Results: The mean pre-treatment hemoglobin significantly increased from 8.8 ± 3.7 to 11.4 ± 3.04 gm/dl and the mean pretreatment ferritin level significantly increased from 15.6 ± 6.3 to 118.4 ± 4.6 ug/l 3-months` after Proferrin treatment. In addition; the mean pre-treatment RBCs MCV significantly increased from 72.6 ± 5.2 to 92.1 ± 3.8 FL, and the mean -treatment RBCs MCH significantly increased from 24.5 ± 8.1 to 25.8 ± 6.6 pg 3-months` after Proferrin treatment. While, the mean pre-treatment reticulocytes count significantly decreased from 3.4 ± 4.2 to 1.2 ± 3.3 $10^6/mm^3$ 3-months` after Proferrin treatment.

Conclusion: HIP is safe, tolerable, effective, oral iron preparation to treat iron deficiency anemia with pregnancy; it increases the hemoglobin and replaces the depleted iron store.

Introduction

The World Health Organization defined hemoglobin below 11 gm/dl as anemia. Anemia is a public health problem and a direct cause of disability. Fifty-two percent (52%) of pregnant women in developing countries suffering from anemia compared to 23% in developed countries [1].

Causes of anemia include; iron deficiencies, poor nutrition, malabsorption, hookworm infestation, schistosomiasis, human immune deficiency (HIV) and hemoglobinopathies [1,2]. There is a high demand for iron during pregnancy (average 600 mg) and on top of the demands of pregnancy is the inevitable blood loss during deliveries [3,4].

A blood loss of ≥1 Liter occurs in 7% of vaginal deliveries and 23% of cesarean deliveries associated with 1000-1500 ml blood loss [3,4]. Maternal anemia is a leading cause of perinatal morbidity, adverse outcome in obstetrics, maternal mortality and blood transfusion [5-8]. Nissenson *et al.* [9] found that 6 months after evaluation of HIP (Proferrin®-ES) in hemodialysis patients who had been on maintenance intravenous iron therapy, the intravenous iron was discontinued and replaced with oral HIP. This study designed to evaluate the efficacy and tolerability of HIP (Proferrin®-ES) in treatment of iron deficiency anemia during pregnancy.

Methods

This comparative multicenter study conducted over 6 months in three private hospitals in Kuwait (Royal Hayat, Al Seef and Hadi), after approval of the study by the hospitals ethical committee. One hundred and fifty (150) pregnant women with hemoglobin level below 10 gm/dl due to iron deficiency anemia included in this study and treated with HIP (Proferrin®-ES) for correction of iron deficiency anemia during pregnancy after informed consent.

Inclusion criteria includes; pregnant women >18 years, 24-30 weeks` gestation with hemoglobin level between 8-10 gm/dl. Pregnant women with anemia due to causes other than iron deficiency and pregnant women received blood transfusion during current pregnancy excluded from this study. Eight (8) pregnant women excluded from this study because of travelling, preterm delivery and intolerance to Proferrin®-ES, so the study completed and statistical analysis done for one hundred and forty-two women (142).

Diagnosis of iron deficiency anemia confirmed by; hemoglobin concentration (gm/dl), serum ferritin (ug/l), mean Corpuscular Volume (MCV) and mean corpuscular hemoglobin (MCH) [6-8]. Heme Iron Polypeptide (Proferrin®-ES), (Nexgen Pharma Inc, Coloeado, USA) derived from bovine hemoglobin and it has unique carrier intestinal receptors Heme Carrier Protein-1 (HCP-1). HIP peptides content of the Proferrin tablets enhance the solubility of HIP and increase the bioavailable iron for absorption.

According to the manufacturer instructions, the HIP (Proferrin®-ES) tablets given to the studied women twice daily (1 tablet morning

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and 1 tablet evening) not related to meals till hemoglobin level of 11-12 gms/dl, then one tablet daily as maintenance dose [9]. After oral intake, Proferrin®-ES tablets, the iron content of the tablets absorbed by the HCP-1 receptors of the small intestine and the serum peak of iron reached within 2-4 hours. Each tablet of Proferrin®-ES increases the serum iron by 3.15 mg [9]. Oral folic acid given to the studied women with Proferrin®-ES to avoid folic deficiency and participants asked during each ante-natal care visit for any side effects related to Proferrin®-ES as gastrointestinal upset, metallic taste, constipation and/or intolerance. Efficacy of Proferrin®-ES treatment checked by comparing the pre-treatment by the 3-months` post-treatment of hemoglobin, ferritin, reticulocytes, MCV and MCH [10,11].

Sample size and statistical analysis

G* Power software used for calculation of the studied sample size, statistical analysis done using statistical package for social sciences (SPSS) version 20 (Chicago, IL, USA) and the Student's t-test used for quantitative data analysis. The significance level set as $p<0.05$.

Results

One hundred and fifty (150) pregnant women with hemoglobin level below 10 gm/dl due to iron deficiency anemia were included in this study and treated with HIP (Proferrin®-ES) for correction of iron deficiency anemia during pregnancy. Eight (8) pregnant women excluded from this study because of travelling (3 women), preterm delivery (2 women) and intolerance to Proferrin®-ES (3 women), so the study completed with one hundred and forty-two pregnant women (142) (Figure 1).

The mean age of the studied women was 25.4 ± 2.3, mean parity was 4.6 ± 6.3, mean weight was 82.6 ± 4.5, and the mean gestational age was 26.4 ± 3.3 weeks` gestation. The mean pre-treatment hemoglobin significantly increased from 8.8 ± 3.7 to 11.4 ± 3.04 gm/dl and the mean pre-treatment ferritin level significantly increased from 15.6 ± 6.3 to 118.4 ± 4.6 ug/l ($p<0.01$ and <0.001; respectively) 3-months` after Proferrin®-ES treatment.

In addition; the mean pre-treatment RBCs MCV significantly increased from 72.6 ± 5.2 to 92.1 ± 3.8 FL and the mean pre-treatment RBCs MCH significantly increased from 24.5 ± 8.1 to 25.8 ± 6.6 pg ($p<0.001$ and <0.01; respectively) 3-months` after Proferrin®-ES treatment. While, the mean pre-treatment reticulocytes count significantly decreased from 3.4 ± 4.2 to 1.2 ± 3.3 $10^6/mm^3$ ($p<0.01$) 3-months` after Proferrin®-ES treatment (Table 1).

Only 2.1% (3/142) of the studied women developed gastrointestinal intolerance and upset with oral Proferrin®-ES (insignificant difference and excluded from the study) and no other side effects recorded with oral Proferrin®-ES.

Discussion

The inevitable blood loss during deliveries aggravates maternal anemia and increases the need for blood transfusion [3,4,7,8]. One hundred and fifty pregnant women with hemoglobin level below 10 gm/dl due to iron deficiency anemia were included in this multicenter study and treated with HIP (Proferrin®-ES) for correction of iron deficiency anemia during pregnancy. Eight (8) pregnant women excluded from this study; because of travelling, preterm delivery and intolerance to Proferrin®-ES and the study completed with one hundred and forty-two pregnant women (142).

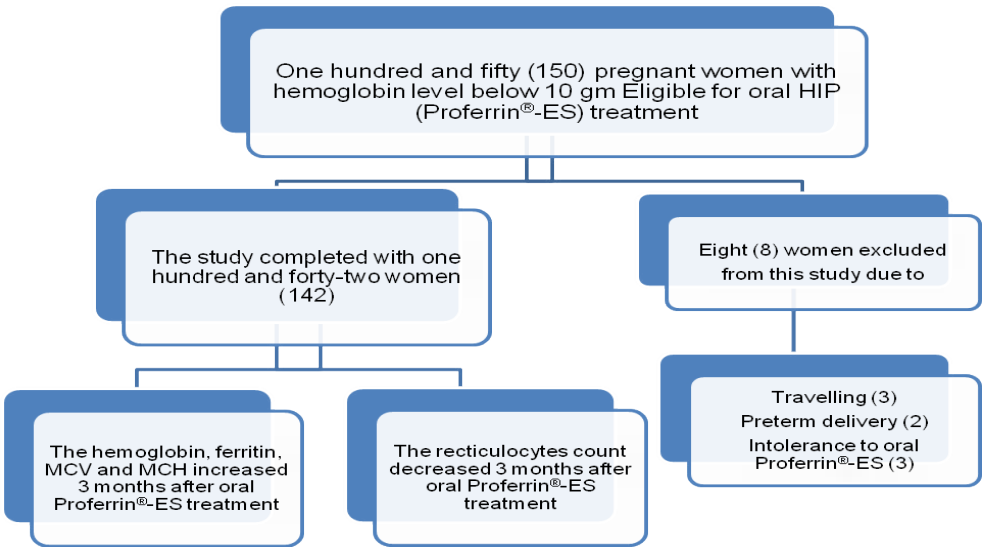

Figure 1. The study design and the results 3 months` after oral HIP (Proferrin®-ES) treatment.

Table 1. Pre-treatment hemoglobin, reticulocytes count, ferritin level, MCV and MCH compared to 3-months` post-treatment values.

Variables	Pre-treatment values	3-months` Post-treatment values	*P* value (95% CI) Significance
Hemoglobin (gm/dl)	8.8 ± 3.7	11.4 ± 3.04	0.01* (-3.4, -2.6, -1.8)
Reticulocytes count ($10^6/mm^3$)	3.4 ± 4.2	1.2 ± 3.3	0.002* (1.3, 2.2, 3.07)
Ferritin level (ug/l)	15.6 ± 6.3	118.4 ± 4.6	0.0001* (-104, -102.8, -101.5)
RBCs MCV (FL)	72.6 ± 5.2	92.1 ± 3.8	0.0001* (-20.5, -19.5, -18.4)
RBCs MCH (pg)	24.5 ± 8.1	25.8 ± 6.6	0.007* (-3.0, -1.3, 0.4)

*= significant difference; CI = Confidence interval; Data presented as mean and ± SD; MCH = Mean corpuscular hemoglobin; MCV = Mean corpuscular volume; RBCS = Red blood cells; Student's t-test used for statistical analysis.

The mean pre-treatment hemoglobin and ferritin levels significantly increased 3-months` after Proferrin®-ES treatment. In addition; the mean pre-treatment RBCs MCV and MCH significantly increased 3-months` after Proferrin®-ES treatment. While, the mean pre-treatment reticulocytes count significantly decreased 3-months` after treatment.

Barraclough *et al.* [12] designed a multicenter study in 2009; to provide evidence to the nephrologists and their peritoneal dialysis whether HIP (Proferrin®-ES) administration effectively augments the iron stores than conventional oral iron supplementation or not [12].

Barraclough *et al.* [13], concluded that; HIP showed no clear safety or efficacy in peritoneal dialysis patients compared with conventional oral iron supplements. The reduction in serum ferritin levels and high costs associated with HIP (Proferrin®-ES) therapy suggest that this agent is unlikely to have a significant role in iron supplementation in peritoneal dialysis patients.

Although, Barraclough *et al.* [13] concluded that HIP (Proferrin®-ES) showed no clear safety or efficacy in peritoneal dialysis patients compared with conventional oral iron supplements. Nissenson *et al.* [9], found that 6 months after evaluation of HIP (Proferrin®-ES) in hemodialysis patients who had been on maintenance intravenous iron therapy, the intravenous iron was discontinued and replaced with oral HIP.

In addition; this study concluded that the hemoglobin, ferritin, MCV and MCH significantly increased 3-months` after Proferrin®-ES treatment in anemic pregnant women. Moreover; significant decrease in reticulocytes count observed 3-months` after Proferrin®-ES treatment. Gastrointestinal side effects are very common problem with oral iron preparations. Al Momen *et al.* [14], in their study compared 52 women treated with intravenous iron sucrose and 59 women treated with 300 mg oral iron sulfate, found that 18 (30 %) of the oral iron group complained of disturbing gastrointestinal symptoms and 18 (30 %) had poor compliance [14].

While, in this study; only 2.1% (3/142) of the studied women developed gastrointestinal intolerance and upset with oral Proferrin®-ES (insignificant difference and excluded from the study) and no other side effects recorded with oral Proferrin®-ES. The anemic pregnant women developed gastrointestinal disturbance with Proferrin®-ES treated with intravenous iron sucrose because they cannot tolerate oral iron preparation other than Proferrin®-ES.

To the best our Knowledge, the current study was the first study designed and conducted to evaluate the efficacy and tolerability of heme iron polypeptide (HIP) in treatment of iron deficiency anemia during pregnancy. The limited data and studies available about HIP (Proferrin®-ES) was the only limitation faced during conduction of this study. More comparative studies needed to compare the efficacy of HIP (Proferrin®-ES) in treatment of iron deficiency anemia during pregnancy with the available oral or intravenous iron preparations.

Conclusion

HIP is safe, tolerable, effective, oral iron preparation to treat iron deficiency anemia with pregnancy; it increases the hemoglobin and replaces the depleted iron store.

Acknowledgment

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Declaration of interest

Authors declare no conflict of interest related to this study.

Financial disclosure

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