

Full Length Research Paper

Effect of Recombinant Erythropoietin in Pregnant Patients with Anemia not responding to Iron Sucrose in Egypt

Mahmoud Salah Mahmoud¹ and Mahmoud Saad Berengy²

¹ Obstetrics and Gynecology Department; Damietta Faculty of Medicine, Al-Azhar University

² Internal Medicine Department; Damietta Faculty of Medicine, Al-Azhar University

Article history

Received: 10-07-2016

Revised: 15-07-2016

Accepted: 20-07-2016

Corresponding Author:

Mahmoud S. Mahmoud

Obstetrics and

Gynecology Department;

Damietta Faculty of

Medicine, Al-Azhar

University

Abstract:

Objectives: Anemia is a common problem during pregnancy. This study was designed to evaluate the effectiveness of recombinant human erythropoietin (rhEPO) in pregnant patients with moderate and severe anemia not responding to intravenously administered iron. **Method:** Eighty women received a single dose of EPO (4000 IU subcutaneously) and hemoglobin concentration was evaluated. All women received oral iron supplementation. They met the following criteria for inclusion in the study: hemoglobin (Hb) concentration <8.5 g/dl, evidence of iron deficiency anemia, and absence of other pregnancy complications, or severe systemic diseases. **Results:** Patients treated with EPO had a significantly higher mean hemoglobin concentration than control patients. **Conclusion:** use of recombinant human erythropoietin safely enhanced the efficacy of iron sucrose in the treatment of gestational iron-deficiency anemia resistant to orally administered iron alone and is effective in decreasing the need for blood transfusion and the incidence of problems associated with anemia during pregnancy.

Keywords: Erythropoietin; Gestational Anemia; Iron-Deficiency Anemia; Iron; erythropoietin

Introduction:

A high proportion of women in the developing countries become anemic during pregnancy. Iron deficiency anemia is the most common type during pregnancy. However, many of these women were already anemic before pregnancy, the most common causes of anemia in Egypt are poor nutrition, deficiencies of iron and other micronutrients. Current knowledge indicates that iron deficiency anemia in pregnancy is a risk factor for preterm delivery and subsequent low birth weight. There is no sufficient data to determine the extent to which maternal anemia might contribute to maternal mortality. Iron supplements improve iron status during pregnancy. Maternal iron deficiency anemia is a risk for decrease iron stores in neonate in the first year in life. Serum ferritin usually falls markedly between 15 and 25 wks of gestation, as a result of iron utilization for expansion of the maternal red blood cell mass. When maternal iron status is poor, the placental transferrin receptors will increase so that more iron is taken up by the placenta (1).

There is a high risk of maternal morbidity and mortality with severe anemia especially in developing countries. The relation of maternal mortality with anemia reflected a greater extent of hemorrhage and late arrival at admission rather than the effect of anemic condition during pregnancy. The efficacy of iron supplementation for reducing maternal mortality will be difficult to conduct because it is unethical to not treat anemic women. Antenatal iron supplementation reduces maternal morbidity and mortality and subsequent iron stores in neonates. Lower birth weights in anemic women have been reported in several studies. However, some investigators reported a negative association between maternal serum ferritin and birth weight and a positive association between maternal anemia and lower infant Apgar scores was reported in some studies association with preterm delivery. Generally, the iron status of the fetus, and subsequently the infant, is quite independent of maternal iron status during pregnancy. Cord blood ferritin was related to maternal hemoglobin or maternal ferritin. Iron is obtained in the form of non-haem iron from vegetables and as haem iron from meat. Haem iron is absorbed about two to three times better than non-haem iron. A small amount of haem iron in the diet will improve absorption of non-haem iron.

Oral iron reduced the risk of anemia during the second trimester of pregnancy and that hemoglobin and serum ferritin levels were higher than the patient not taking iron antenatal). Higher doses of oral iron did not increase hematocrit values (5), but hematocrit increases when vitamin A was added to oral iron. Severely anemic pregnant women may require blood transfusion, which is not always feasible in many settings, especially in developing countries and it may even carry some risks for the woman. To avoid this, health services should implement a strategy for the control anemia in pregnant women, including early detection and appropriate management of the condition. Maternal hemoglobin at four weeks was higher (6, 7), and hemoglobin level > 11g/dl at birth was more

frequent, with intravenous iron, as compared with oral iron. Compared with oral iron, hematological parameters were better with intramuscular iron (8), and compared with intramuscular iron, the parameters were better with intravenous iron (9).

Intramuscular iron produced pain at the injection site. Skin discoloration at the injection site was more frequent with intramuscular iron than with intravenous iron.

Subjects and methods

This study was designed at new Damietta hospital Al-Azhar University from (August's 2015 till February 2016). consent from all patients were taken. Treatment was not started before 20 weeks of gestation and was continued for 4 weeks until the target Hb level of 11.0 g/dl was reached.

Inclusion Criteria

Patients had iron deficiency anemia, i.e. an Hb level 10.0g/dl and a ferritin level 15 g/l. All patients had received oral iron supplements during pregnancy after 20 weeks gestation.

Exclusion Criteria

Patients with anemia from causes other than iron deficiency as thalassemia, sickle cell anemia or anemia of chronic disease. Eighty patients included in this study fifty patients with severe anemia (group A) and thirty patients with moderate anemia (group B)

Group A: Patients with Hb level between 8.5 g/dl and 10.0 g/dl received 200 mg (10 ml) iron sucrose intravenously twice weekly.

Group B: If response to therapy was poor (i.e., Hb increase less than 0.6 g/dl) after 2 weeks patients additionally received 10,000 U rhEPO in both group therapy was continued for a maximum of 4 weeks or until the target Hb level of 11.0 g/dl was reached

Blood samples were taken once weekly immediately before therapy for routine hematologic examination, including hemoglobin level, platelet count and serum samples for determination of iron status [ferritin level, transferrin saturation, which were determined using a flow cytometric hematology analyzer (Chiron Diagnostics, USA). Erythropoietin (EPO) level was measured by enzyme-linked immunosorbent assay (Abingdon,).

Results

Eighty patients were included in this study. All patients were of Egyptian ethnicity. In new Damietta Al-Azhar university. Fifty patients (groups A) had a baseline Hb level between 9.0 and 9.9 g/dl, of whom 30 women responded poorly to the initial therapy, receiving additional rhEPO injections the target Hb level was 11.0 g/dl for both groups. Therapy was stopped after the target Hb level was 11.0 g/dl or after a maximum iron dose of 1,500 mg. The overall Hb level after therapy was 11.0 g/dl. Thirty patients had an Hb level between 9.9 and 10.9 g/dl, and 50 patients had an Hb level of 11.0g/dl or higher. The mean duration of therapy was 6 weeks (7 infusions).

Patients with severe anemia, group A treated initially with a combination of iron sucrose and rhEPO, showed an immediate response to therapy. Twenty patients had an Hb level 7.0g/dl, 5 patients had an Hb level between 9.9 and 10.9g/dl, of whom 3 patients was not able to complete therapy as she gave birth at term after the second infusion. Patients with moderate anemia (9.0 ^ Hb ! 10.0 g/dl) were initially treated with iron sucrose alone twice weekly. Of the 50 patients, 30 responded poorly to therapy according to our protocol (Hb increase! 0.7 g/dl within 14 days, i.e., after 4 infusions of 200 mg iron sucrose) and received additional rhEPO as therapy continued. In the 50 patients responding well to therapy (group A), the mean Hb level after therapy was 11.1 g/dl (8 0.4, range 10.1–12.0 g/dl) after a mean duration of therapy of 2.5 weeks (5 infusions).

The remaining 30 patients (group B) had a mean Hb level of 10.9 g/dl (8 0.4, range 10.0–11.7g/dl) after a mean of 4 weeks of therapy (8 infusions). Patients in group A presented statistically significantly higher Hb values compared to patients in group B from day 4 until day 22 of therapy (day 4, p = 0.005; day 8, p = 0.0001; day 11, p = 0.003; day 15, p = 0.0001; days 18 and 22, p = 0.005) and also compared to patients in group C from day 4 until day 15 (days 4, 8, 11, and 15, p = 0.0001). Hb value in group B was statistically significantly higher on days 4 and 8 compared to group C (day 4, p = 0.0001; day 8, p = 0.005). The course of Hb in both groups during treatment.

Those patients identified as poor responders to intravenous iron therapy (group B) showed statistically significantly lower eEPO levels compared to patients of group A who had the same degree of anemia (46.6 8 29.8 vs. 69.3 8 42.8 U/l; p ! 0.05). Furthermore, the transferring receptor-ferritin index (TfR-F index) was statistically significantly lower in these patients compared to group A (10.9 8 5.7 vs. 16.1 8 8.7; p = 0.05). The index is calculated as sTfR at baseline/log serum ferritin at baseline, serving as an established tool for detection of iron deficiency anemia. The ferritin level at baseline was also statistically significantly higher in those patients compared to group A (7.8 8 3.7 vs. 5.4 8 2.3 g/l; p = 0.05). Transferrin saturation increased from overall baseline 9.1% (8 7.7, range 2.0–40.1%) to overall 19.6% (8 8.9, range 6.1–51.2%) at the end of therapy. At inclusion, transferring saturation was significantly lower in group B. There was no statistically significant difference between both groups at the end of therapy. sTfR was elevated in both groups at

baseline, was statistically significantly higher values in group A compared to group B. This difference remained throughout the course of therapy (days 8 and 15: group A, $p = 0.001$, vs. group B, $p = 0.0001$; day 22.

Table (1):

Parameter	Group A	Group B	P value
Gestational age, weeks	30.786.5 (16–38)	28.885.1 (16–37)	n.s.
Hb concentration, g/dl	9.480.3 (9.1–9.9)	9.380.3 (9.0–9.9)	<0.001
Hematocrit, %	28.381.3 (26.9–32.0)	27.981.5 (26.3–31.9)	<0.001
Mean corpuscular volume, fl(80–100)	78.786.8 (66.5–93.0)	81.886.9 (69.2–93.9)	<0.001
Mean corpuscular Hb, pg (26–34)	24.882.9 (20.6–31.5)	26.383.0 (21.3–31.5)	<0.001
Mean corpuscular Hb concentration, g/dl	33.481.2 (29.7–34.0)	33.981.3 (30.6–36.2)	<0.001
Reticulocyte count, % (0–1.5)	2.680.9 (1.2–5.6)	2.180.9 (0.5–4.8)	n.s.
Reticulocyte corpuscular Hb, pg (25–28)	28.884.2 (21.5–38.0)	28.283.3 (19.4–33.3)	<0.001
Hypochromic red blood cell population, (<2.5)	8.889.3 (0.4–37.0)	6.888.3 (0.1–32.2)	<0.001
Microcytic red blood cell population, % (<2.5)	6.388.4 (0.4–31.9)	4.987.1 (0.2–30.3)	<0.05
EPO concentration, U/l (<20)	67.3842.8 (21.4–173.0)	46.6829.8 (10.0–138.0)	<0.05
Ferritin concentration, g/l (15–150)	5.471.3 (2.0–12.0)	7.862.7 (3.0–15.0)	<0.05
Transferrin saturation, % (>20)	9.133.2 (2.4–40.1)	11.536.4 (3.3–30.8)	<0.05
sTfR concentration, μ g/ml (2.2–5.0)	10.237.3 (4.8–20.5)	8.473.3 (2.4–16.1)	<0.05
TfR-F index (<3.8)	16.1687.7 (5.9–42.9)	10.974.7 (2.4–25.4)	<0.05

Discussion

The present study shows an effective treatment of iron sucrose alone or in combination with rhEPO for patients with various degrees of iron deficiency anemia in pregnancy. All patients developed anemia despite routine prescription of oral iron supplements (60 mg per day) from the beginning of the second trimester. Patients with severe anemia treated with the combination of rhEPO and iron sucrose show a rapid response as indicated by the increases in Hb and reticulocyte count. It was known that rhEPO therapy delivers optimal results when combined with an effective iron supplement to avoid at least decrease iron deficiency anemia. Especially when iron stores are empty before starting therapy, only parenterally administered iron sucrose. [10]

In our patient's iron deficiency anemia was already present at the start of therapy and did not increase during the observation period. Due to the fact that in those patients treated with rhEPO and iron sucrose iron deficiency anemia was still present at the end of therapy. When iron stores are empty before therapy, only parenterally administered iron (i.e., iron sucrose) is able to increase iron stores [10, 11]. In our patients' iron deficiency anemia was already present at the start of therapy and did not worsen during the period of therapy. Due to the fact that in those patients treated with rhEPO and parenteral iron sucrose iron deficiency anemia was still present at the end of therapy.

In patients with moderate iron deficiency anemia treated with iron sucrose alone we observed variable response. the aim of our study was to discriminate so-called 'non-responders' from patients with moderate anemia who show a good responder to parenteral intravenous iron sucrose. To identify those patients who might benefit from an additional subcutaneous rhEPO therapy, Hb increase of 0.6 g/dl after 4 infusions of 200 mg iron sucrose each within 14 days. [14].

For the patients receiving additional subcutaneous rhEPO therapy (group B) statistically significantly lower rhEPO levels at compared to patients of group A who had the same degree of anemia. there was a statistically significantly lower ferritin level in group A compared to group B, although both baseline ferritin mean values were well below 10 g/l. sTfR concentration was not statistically significantly different in both groups, but when the sTfR/ferritin ratio was calculated, the so-called non-responders (group B) showed statistically significantly lower values compared to group A. The TfR-F index issued to distinguish iron deficiency anemia from anemia of infection and represents a combination of measurements of iron stores (ferritin) and functional tissue iron (sTfR) [16]

Another explanation might lie in the fact of considerable variations in the degree of hemodilution in pregnant women. [14], the Hb concentration may vary up to 3 g/dl. It is known that Hb as a single parameter is not valid for estimation of the iron status. patients successfully treated with iron alone (group A) and the so-called non-responders (group B), it is evident that for the same degree of anemia

In conclusion, iron sucrose given intravenously is a safe option for the treatment of iron deficiency anemia in pregnancy, to avoid side effects of high-dose oral iron supplementation, i.e., constipation or abdominal pain. In cases of severe iron deficiency anemia even a combination with subcutaneous rhEPO might be considered, especially if further risk factors are noted, such as placenta previa, or abruptio placenta. If a patient's not responding well to therapy with iron sucrose alone, additional treatment with subcutaneous rhEPO might be considered.

References

- 1- World Health Organization: The World Health Report 2002: Reducing Risks, Promoting Healthy Life. Geneva, World Health Organization, 2002, chapt 4: Quantifying Selected Major Risks to Health, pp 52–54.
- 2- Milman N, Bergholt T, Byg K, Eriksen L, Graudal N: Iron status and iron balance during pregnancy. A critical reappraisal of iron supplementation. *Acta Obstet Gynecol Scand* 1999; 78: 749–757.
- 3- Levy A, Fraser D, Katz M, Mazor M, Sheiner E: Maternal anemia during pregnancy is an independent risk factor for low birth weight and preterm delivery. *Eur J Obstet Gynecol Reprod Biol* 2005; 122: 182–186.
- 4- Williamson L, Lowe S, Love EM, Cohen H, Soldan K, McClelland D, et al: Serious hazards of transfusion (SHOT) initiative: analysis of the first two annual reports. *BMJ* 1999;319: 16–19.
- 5- Breymann C, Visca E, Huch R, Huch A: Efficacy and safety of intravenously administered iron sucrose with and without adjuvant recombinant human erythropoietin for the treatment of resistant iron-deficiency anemia during pregnancy. *Am J Obstet Gynecol* 2001; 184: 662–667.
- 6- Bayoumeu F, Subiran-Buisset C, Baka N, Legagneur H, Monnier-Barbarino P, Laxenaire M: Iron therapy in iron deficiency anemia in pregnancy: intravenous route versus oral route. *Am J Obstet Gynecol* 2015; 186: 518–522
- 7- Ganz T: Hcpidin and its role in regulating systemic iron metabolism. *Hematology Am Soc Hematol Educ Program* 2006;29–35.
- 8- Milman N: Iron and pregnancy – A delicate balance. *Ann Hematol* 2015; 85: 559–565.
- 9- Danielson B, Geisser P, Schneider W: *Iron Therapy with Special Emphasis on Intravenous Administration*, ed 1. St Gallen, ECV, Vifor International, 1996.
- 10- Perewusnyk G, Huch R, Huch A, Breymann C: Parenteral iron therapy in obstetrics: 8 years experience with iron-sucrose complex. *Br J Nutr* 2002; 88: 3–10.
- 11- Huch A, Eichhorn KH, Danko J, Lauener PA, Huch R. Recombinant human erythropoietin in the treatment of postpartum anemia. *Obstet Gynecol* 1992; 80:127–131.
- 12- Richardson D. Clinical factors influencing sensitivity and response to epoietin. *Nephrol Dial Transplant* 2002;17(S1):53–59.
- 13- Petitti D. *Meta-analysis, Decision Analysis, and Cost-effectiveness Analysis: Methods for Quantitative Synthesis in Medicine*. New York/Oxford: Oxford University Press; 2000.
- 14- Arthur W, Bennett W, Huffcut A. *Conducting Meta-Analysis Using SAS: Multivariate Applications*. Mahwah, NJ: Lawrence Erlbaum Associates, Inc.; 2011.
- 15- Kashiwagi M, Breymann C, Huch R, Huch A. Hypertension in a pregnancy with renal anemia after recombinant human erythropoietin (rhEPO) therapy. *Arch Gynecol Obstet* 2012; 267:54–56
- 16- Brown MS, Keith JF. Comparison between two and five doses a week of recombinant human erythropoietin for anemia of prematurity: a randomized trial. *Pediatrics* 1999; 104:210–215.