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COMPARATIVE EFFICACY OF INTRAVENOUS IRON SUCROSE VERSUS INTRAVENOUS IRON SUCROSE AND ERYTHROPOIETIN THERAPY IN MODERATE AND SEVERE ANEMIA OF PREGNANCY

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ABSTRACT

Aim: The aim of the study was to evaluate the efficacy of intravenous iron sucrose versus intravenous iron sucrose and erythropoietin in moderate and severe anemia of pregnancy.

Methods: A total of 50 women with hemoglobin of less than 8 g/dl inthe second or third trimester of pregnancy were enrolled to receive either 1000 mg of intravenous iron sucrose as 5 doses of 200 mg on alternate days (Group I) or to 500 mg of parenteral iron as above with 3 doses of subcutaneous 6000 units each of erythropoietin (Group II).

Results: There was a mean rise of 1.4 g with intravenous iron sucrose there was a mean increaseof 2.8 g/dl with intravenous iron sucrose and erythropoietin therapy. There was significantly high rise in serum iron, serum ferritin, and transferrin saturation. There was no anaphylaxis in any group with iron sucrose and erythropoietin therapy as compared to iron sucrose alone.

Conclusion: Addition of erythropoietin to intravenous iron sucrose gives superior results inimproving hematological parameters in moderate and severe anemia during pregnancy and can obviate the need for blood transfusion.

Keywords: Anemia, Pregnancy, Erythropoietin, Intravenous iron sucrose

INTRODUCTION

Iron deficiency is the most common nutritional disorder in the world, affecting approximately 25% of the world's population.[1] Pregnant women are particularly at high risk for iron deficiency and iron-deficiency anemia because of increased iron needs during pregnancy. Anemia during pregnancy causes significant maternal mortality and morbidity and may be responsible for up to 40% of maternal deaths in low income countries.[2,3] It also causes perinatal mortality and morbidity due to increased risk of preterm deliveries, low birth weight infants, small

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gestational age infants, low iron stores in infants, cognitive and affective dysfunction and lower mental development in infants.[4,5] The global prevalence of iron-deficiency anemia in pregnant women is 38.2% being 3-4 times higher in lower income countries as compared to high income countries. The prevalence is 24.4% in America, 25.8% in Europe, 43.6% in Africa and 48.7% in South east Asian regions.[6] India has one of the highest incidence of anemia with small incidence being 55.3% (38.6% mild anemia, 15% moderate anemia, 18% severe anemia).[7] It is probably due to dietary habits, consumption of low iron bioavailability cereal diet with vegetarian diet low in vitamin C with low excess of inhibition of iron (Fe) absorption (like phytaes), high prevalence of worm infestations and repeated pregnancies at shorter intervals.[8–10] Diet alone cannot supply the 30–40 mg Fe that is required for absorption of the 4–6 mg iron per day needed during the latter stages of pregnancy.[11]

Iron supplementation is therefore recommended for all pregnant women in developing countries.[10] Oral iron intake is the treatment of choice, and almost all women can be treated effectively with oral preparations.

However oral Iron supplementation is not always sufficient for a quick and effective treatment of anemia in pregnancy. Ministry of Health, Government of India recommends 200 mg elemental iron with 1 mg folic acid for treatment of anemia until Hb levels come back to normal, followed by 100 mg per day as maintenance therapy during 3 months of puerperium for replenishing the iron stores.[12] Parenteral iron therapy is only indicated when the pregnant woman is unable to take oral iron due to side effects or is non-compliant as both oral iron and parenteral iron have been found to be equally efficient in the studies.[13] The advantage of parenteral iron is its certainty of administration while iron sorbitol can only be given intramuscularly. Iron dextran can be given both intramuscularly and intravenously.[10,13] However, both these preparations though economical, run the risk of allergic and anaphylactic reactions and are going out of favor. Currently, intravenous iron sucrose is the preferred treatment due to its efficacy and safety (rare chance of anaphylaxis) although more expensive than iron dextran and iron sorbitol as 200 mg intravenously twice or thrice weekly. It raises Hb and Ferritin levels significantly and faster.[14–16] Newer iron preparations like ferric carboxymaltose has no iron dextran and has high molecular weight and high stability. It can be given as 1000 mg high dose intravenously in one sitting. Although found to be safe for use even during pregnancy, it has not yet been approved for use during pregnancy by US FDA and drug controller of India.[17,18] However, it has been approved for postpartum anemia where it is considered to be drug of first choice as single injection can be used and patient can be discharged early.[17,18] Blood transfusion is widely used as a last resort, despite its controversial use and safety and the risk of complications, such as viral infections, or noninfectious and immunological adverse effects. Synthetic agents such as recombinant human erythropoietin (rHuEPO) have traditionally been used as therapeutic means for anemia of chronic renal disease with low endogenous erythropoietin production.[19]

During the last decade, rHuEPO supplementation has also been used in the treatment of anemia in pregnancy and postpartum.[20–23] However, such treatment during pregnancy still remains controversial and of limited use.

The objective of this study was to investigate the therapeutic efficacy of rHuEPO combined with intravenous iron sucrose, in the treatment of moderate and severe iron deficiency anemia of pregnancy that didn't respond to iron supplementation alone.

MATERIALS AND METHODS

It was a prospective, randomized study consisting of 60 women in second or third trimester of pregnancy with a hemoglobin value <8 g/dL. It was conducted between Jan 2006-May 2012. The study was approved by ethics committee and all women gave informed consent.

Inclusion Criteria

All subjects had severe iron deficiency anemia with hemoglobin 8 g/dL. All patients had received oral iron (elemental iron=100 mg) for at least fourweeks before starting injectable therapy.

Exclusion Criteria

Women with anemia due to other causes than iron deficiency and those not willing to participate in the study were excluded.

Study Group

All patients were recruited on a consecutive and prospective basis from our antenatal clinic if they fulfilled our inclusion and exclusion criteria. Sixty patients were randomly assigned to two treatment groups of 30 patients each. The aim was to include enough patients so that a true difference of 1 g/dL in haemoglobin increase from baseline to day 7 would have a 90% chance of giving significance in a 2-sided

test at the 5% risk level. Since, enough empirical evidence with respect to haemoglobin levels changes due to intravenous iron sucrose vs iron sucrose and erythropoietin therapy were not available, the adequate sample size could not be calculated. Therefore, the present study was initiated by taking 30 patients in each group.

Group I: 200 mg of intravenous iron sucrose on alternate days for 5 injections.

Group II: Intravenous iron sucrose as above with 3 doses of subcutaneous 6000 units each of erythropoietin on day 1, 3 and 5.

The first dose of iron sucrose was administered in labor room keeping injection adrenaline, hydrocortisone and chlorpheniramine maleate and oxygen cylinder ready for any anaphylactic reactions. Further doses were given in labor room or in outpatient department.

Laboratory tests:

A detailed history was taken from all the women, and a complete physical examination and an obstetric examination were performed at the time of recruitment.

The study protocol was cleared by the Ethics Committee of the Institute. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. An informed written consent was taken from all the patients who were participating in the study after explaining to them in detail about the protocol in the local and regional language of the patient. Detailed history taking, complete physical and obstetrical examination and routine antenatal investigations were performed in all pregnant women. Among the patients who were detected as anemic, a hemoglobin electrophoresis study was carried out to rule out thalassemia and other hemoglobinopathies. Upon recruitment, a 5 ml blood sample was taken from each patient and was sent and processed in the Hematology Department laboratories of the Institute for the following investigations which were conducted free of cost.

1. The routine hematological indices (Hb, MCV, MCH, MCHC) were measured by the *Coulter H 750 Analyser*: MCV = PCV/RBC count, MCH = Hb/ RBC count, MCHC = Hb/PCV. A peripheral smear was also made.
2. Serum iron studies: for this test, the patients were asked to stop iron intake for 7 days. Around 4 ml of clotted blood was taken in an iron- free test tube provided, from which 1 ml of serum was taken for serum iron studies and 2 ml of serum for serum ferritin levels. An ELISA kit for serum iron studies (serum iron, % saturation of iron, TIBC) from *FAR Diagnostics, USA* was used and the various concentrations of each component was measured with the *Genius WD 21B machine*.
3. Serum ferritin levels: a 2 ml serum sample was separated as discussed above. For measuring the serum ferritin levels, the *Ferritin Enzyme Immuno Assay* from *Orgentech, USA* was used (optical density was proportional to concentration).
4. Serum transferrin receptor level: A 2 ml serum sample was taken from the above sample and processed using the *Human sTfR ELISA kit* form *Bio Vendor LLC, Candler, NC 28715, USA*.

Oral Iron was given for haemoglobin of >8 g/dl while parenteral Iron was given for <8 g/dl. Apart from the iron treatment, all the women were advised dietary changes in terms of green leafy vegetables and other iron rich foods. The women were also regularly followed up in the antenatal clinic.

RESULTS

Baseline patient characteristics:

All patients had used oral iron for at least two weeks. There was no intolerance or noncompliance to oral iron. Hemoglobin in all these patients was ≤ 8 g/dL. Iron deficiency anemia was confirmed in all these patients by a serum ferritin value of less than 1.5 µg/dL. The mean age, parity and gestation were similar in two groups (Table 1). There were no significant differences between the groups (Student's *t* test or chi-square test). There was no history of blood transfusion or clinical evidence of infection.

Table1: Baseline patient characteristics in the 2 groups

Characteristic	Group I Iron sucrose alone N=30	Group II rhEPO+ iron sucrose N=30	P- Value
Age (year)			
Range	19-33	20-38	
Mean	22±3.8	24±2.8	0.0238
Body Mass Index			
Range	19-31	20-32	
Mean	22.5±2.8	23.1±2.4	0.3765
Gestation at initiation of treatment (week)			
Range	20-34 weeks	22-36 weeks	
Mean	28±3.6	29±2.8	0.2346

Table 2 shows the mean value and range of hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular haemoglobin, mean corpuscular

Table 2: Mean value and range of hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular haemoglobin, mean corpuscular Hb concentration (MCHC), serum iron, total iron binding capacity (TIBC), transferrin saturation and serum ferritin at recruitment and after completion of therapy

Parameters	Group I Iron Sucrose alone		Group II rhEPO+ iron Sucrose		Post-treatment rise/Fall*		P-value
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Group I	Group II	
Hb(g/dl) Mean Range	6.8±0.58 5.2-8	8.2±0.76 6.3-9.1	6.7±0.56 5.0-7.5	9.5±0.80 6.5-10	1.4±0.4 0.7-1.9	2.8±0.8 2.0-3.1	0.001
Hematocrit(%) Mean Range	22.4±3.2 17.4-26.2	27.2±3.6 21-32	21.8±2.9 16.6-25.2	32±3.8 28-34	4.8±0.5 3.1-6.2	10.2±0.7 7.4-18.2	0.001
Mean corpuscular volume (fl) Mean Range	77±5.1 69-83	83±2.8 74-92	76±4.5 71-88	88±2.1 82-95	9±0.8 6-14	12±0.9 8-18	0.001
Mean corpuscular Hemoglobin (MCH) pg Mean Range	21.8±2.4 20-24.2	28.2±2.6 22.2-30.2	21.6±2.3 20.2-24.8	32.4±2.6 28.2-36.0	6.4±1.2 3.2-8.2	10.6±1.8 7.6-12.5	0.001
Mean corpuscular Hb concentration (MCHC%) Mean Range	26.6±1.8 22-30	34.2±2.2 27.6-38.0	28.6±1.9 25.8-32.2	38.2±2.8 30.2-42.2	5.6±0.4 31-72(**?)	9.6±1.2 5.2-11.2	0.001
Serum iron µg/dl Mean Range	31.48±4.84 26.37-40.85	48.79±10.4 38.42-59.45	30.87±4.38 25.88-39.42	56.67±13.2 42.54-67.38	17.31±2.45 12.45-24.25	25.80±3.82 19.48-38.45	0.001
Total iron binding capacity (TIBC)* µg/dl Mean Range	368.2±39.4 332.4-388.9	324.4±12.6 312.4-338.5	362.6±38.7 329.2-387.4	321.3±11.8 309.4-331.7	43.4±2.8 20.2-58.4	41.3±2.4 19.8-59.5	0.003
Transferrin saturation (%) Mean Range	11.2±2.1 9.2-18.4	28.0±3.4 12.8-39.5	10.6±1.9 7.8-19	38.0±3.8 14.8-44.7	16.8±2.2 11.5-23.2	27.4±2.8 20.2-32.5	0.001
Ferritin concentration (µg/l) Mean Range	6.8±3.2 4.8-12	38.9±11.2 9.2-52.8	7.2±3.4 3.4-14	60.2±19.8 11.2-90.2	30.1±9.8 12.3-45.2	53.0±1.45 22.5-68.5	0.001

Hb concentration (MCHC), serum iron, total iron binding capacity (TIBC), transferrin saturation and serum ferritin at recruitment and after completion of therapy. At recruitments the two groups did not differ much in term of hemoglobin, hematocrit, blood indices, serum iron, TIBC or serum ferritin values.

Response to therapy:

After 2 weeks of therapy there was a significant improvement in all the parameters in both the groups. The range of post therapy hemoglobin was 6.3 to 9.1 g/dl with mean of 8.2 g/dl in-group I in contrast to 6.5 to 10.0 g/dl with mean of 9.4 in Group II (p=0.001). Thus while there was a mean rise of 1.4 gm with parenteral iron there was a mean increase of 2.8 g/dl with parenteral iron and erythropoietin therapy (p=0.001). Both groups showed an increased hematocrit response to therapy. At two weeks of therapy in Group II the mean hematocrit was 32 compared to 27.2 in Group I (p=0.001). Mean corpuscular volume increased in both groups and was higher in Group II than Group I at two weeks (88 vs. 83 fl; p value=0.001). MCH and MCHC increased over two weeks in both the groups but, the increase was subsequently more in group II than in group I (p=0.001) Serum iron increased significantly more in group II than in group I (p=0.005) while TIBC decreased significantly more in group II than in group I (p=0.003). Transferrin saturation increased significantly in both the groups but the increase was higher in group II (p=0.001). Serum Ferritin concentration increased from 6.8±0.32 µg/dL in group I to 38.9±1.12 µg/dL while the increase was significantly higher in group II than in group I (p=0.001) (increased from 7.2±0.34 µg/dL to 60.2±1.98 µg/dL). There was no anaphylactic reaction in any group. One patient in intravenous iron sucrose group had thrombophlebitis at injection site which healed of its in one week. None of the women needed additional ante partum and postpartum blood transfusion.

DISCUSSION

Iron deficiency anemia during pregnancy continues to be a major public health problem especially in developing countries causing significant maternal and perinatal mortality and morbidity.[1–6] The prevalence is particularly high in India (55.3%) due to dietary habits, worm infections and repeated pregnancy at shorter intervals.[7–10]

Iron supplementation with folate is recommended to all pregnant women in dose of 100 mg oral iron with 1 mg folate per day while for treatment double dose (200 µg elemental iron and 200 mg folate) are recommended.[11,12] Then efficacy of oral and parenteral iron is equal.[13,14] The only advantage of parenteral iron is certainty of administration. Traditional parenteral iron preparations like iron dextran and iron sorbitol, though economical, can cause allergic reactions including anaphylactic reactions.[13] New iron preparations like iron sucrose, though more expensive, is associated with least risk of anaphylaxis and is highly effective.[15,16] Ferric carboxymaltose is a newer iron preparation which can be given as 1000 mg dose but is not licensed yet for administration during pregnancy but is suitable for postpartum anemia.[17,18] For severe anemia, traditional treatment especially in late pregnancy is blood transfusion which can be associated with viral transmission and blood related reactions and should only be given for antepartum hemorrhage or severe anemia near term. Erythropoietin therapy has traditionally been recommended for renal disease with anemia but has been found to be safe for severe anemia during late pregnancy to avoid blood transfusions.[19–23]

This study shows that combination of erythropoietin with intravenous iron sucrose increases the hematological response compared to intravenous Iron sucrose alone. Also the mean increase of hemoglobin and hematocrit was higher and anemia was corrected earlier in combination group. The hemoglobin increase observed after 2 weeks corresponds to the expected rise after transfusion of two units of blood, similar to that observed previously in a retrospective study of women with postpartum anemia.[24] As it was an outpatient therapy, no admission was required and treatment was completed in one week.

Several studies have described the role of recombinant erythropoietin in non-renal obstetric anemia during pregnancy.[25] The combination of erythropoietin with parenteral iron increases the efficacy by stimulating erythropoiesis at the time iron is delivered for hemoglobin synthesis and storage.[20] Continued supplementation with oral iron after completion of parenteral iron therapy helps in replenishing iron stores. Because intravenous iron sucrose is also safe and effective, the combination of the 2 substances increases the efficacy of anemia therapy by stimulating erythropoiesis (rhEPO) at the same time that it delivers enough iron for hemoglobin synthesis and iron stores (iron sucrose). Indeed, it is now generally accepted that rhEPO should be combined with intravenous iron, especially when iron stores are empty before therapy. In our patients functional iron deficiency was already present before therapy, and it did not worsen during the observation period. The fact that functional deficiency was still present at the end of therapy, however, shows that iron must be supplemented until the end of pregnancy in patients such as ours with empty iron stores.

Recombinant erythropoietin might be most useful in severe anemia or in cases of anemia complicated by conditions like placenta previa, in Jehovah's Witnesses[26] and hemoglobinopathy (eg, thalassemia and sickle cell disease.[27,28] Use of rhEPO could also serve as a second-line therapy if iron alone fails to increase the hematocrit within a defined interval. Because blood transfusions are a last resort, alternative strategies such as rhEPO plus parenterally administered iron are of considerable value. Our data show that adjuvant rhEPO combined with an optimized dosage schedule shortens treatment considerably while avoiding the gastrointestinal side effects and associated poor compliance found in as many as 30% of patients receiving oral iron therapy.[13]

CONCLUSION

To conclude recombinant human erythropoietin combined with intravenous iron appears to be an effective treatment for pregnancy anemia. The efficacy and safety of rhEPO during pregnancy warrants further evaluation, including cases of non-renal anemia.

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