The Efficacy of Intravenous Non-dextran Iron Sucrose in the Treatment of Iron-Deficiency Anemia in Pregnancy

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OBJECTIVE: Iron-deficiency anemia is the most common type of anemia in pregnancy. In our study, the efficacy of non-dextran intravenous (IV) iron sucrose complex in the treatment of iron deficiency anemia of pregnancy is investigated.
STUDY DESIGN: The study included 46 pregnant women who admitted to our hospital for routine antenatal follow-ups between January 2000 and June 2001 and had hemoglobin (Hb) value lower than 10gr/dl. Other types of anemia were discarded after diagnostic examinations including Hb electophoresis applied in each case. The IV iron sucrose therapy lasted three weeks. The first week it was given on three days in increasing doses, making a total of 350 mg/week. On the following weeks, 400mg/week was given according to the patients Hb level. The patients were hospitalized on the first week in case of an anaphylactic reaction but on the following weeks it was applied in an outpatient basis. Cases were monitorized for Hb, hemotocrit, reticulocytosis, total iron binding capacity, serum iron and ferritin values.
RESULTS: The mean age of the patients was 28±4.6 weeks. The Hb values increased at least by 0.8 gr/week in all cases. After the IV iron sucrose therapy, the most significant change was observed in the serum ferritin level ($p<0.05$). There were no side effects noted during the treatment.
CONCLUSION: The treatment with non-dextran IV iron sucrose complex is a safe alternative with fast efficacy and low rate of side effects, decreasing the need for blood transfusions in pregnancy.
(Gynecol Obstet Reprod Med 2006; 12:96-99)

Key Words: Pregnancy, Anemia, Non-dextran parenteral iron sucrose

Anemia is a very common medical problem in pregnancy. The most frequent type of anemia in pregnancy is iron-deficiency anemia. According to many researchers, a hemoglobin (Hb) value of less than 11gr./dl. and a hemotocrit (Hct) value of less than 32% is accepted as anemia. Even though it is debatable, the most common approach is to give prophylactic iron supplementation in pregnancy. Intravenous (IV) iron (Fe) is preferred only in pregnant women who can not use drugs orally because of their side effects and who present with severe anemia. Iron dextran can be administered both intramuscular (IM) and IV but since the IM administration is painful, IV administration is preferred. An important disadvantage of iron dextran is the anaphylaxis, which seems to occur as a result of the dissociation of the iron component and the carbohydrate component. The reaction is observed usually in the first minutes but sometimes it may take as long as two days.

In many studies,[1,2] anemia have been related to preterm birth, low birth weight and bad perinatal outcome. Sifakis and Pharmakides,[3] observed an increase in spontaneous abortion and fetal loss rates besides preterm birth and low birth weight in cases with Hb value less than 6 gr/dl. Iron deficiency anemia, which is an important reason of maternal morbidity and mortality especially in developing countries, has to be cured.

Intravenous non-dextran iron sucrose (Venofer®, Vifor Inc. St. Gallen, Switzerland) is Fe [III] hydroxide sucrose complex in water which is administered only intravenously. One 5 ml. vial of Venofer provides a 2-3% increase in the Hct level. After a teratment with five vials, a 1-1.5gr. increase is achieved in the Hb value. Dextran related anaphylaxis is not observed with Venofer and it does not cause toxicity since it is settled in the reticuloendothelial system of the liver. The contamination risk in blood transfusions is not in question vith Venofer and besides the incidence of other systemic adverse reactions with iron sucrose is considerably lower. Half of the iron administered IV is ready to use in erythropoiesis in three hours. Venofer, with its fast efficacy and safety in increasing the Hb value significantly, is an alternative to choose in iron-deficiency anemia of pregnancy. In our study, the efficacy of IV iron sucrose (Venofer) treatment in iron deficient pregnant women is investigated.

Material and Methods

The study included 46 pregnant women who were diagnosed with anemia during routine antenatal obstetric examination in the obstetric outpatient clinics of S.B. Aegean Maternity and Women's Health Teaching Hospital, İzmir. The mean age of the cases with iron-deficiency anemia was 23±3.9 (range 18-36) years.

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Submitted for Publication: 24.01.2006
Accepted for Publication: 04.02.2006

Table 1. The comparison of pretreatment and posttreatment data

	Pretreatment values	Posttreatment values	p value
Hemoglobin (gr/dl)	7.8±2.1	10.9±3.4	0.021
Hemotocrit (%)	24.6±5.8	30.3±5.9	0.041
MCV (fl)	74.5±19.3	80.0±9.4	0.178
Serum Fe^{+2} level (µg/dl)	14.6±3.9	42.7±13.9	0.001
TIBC (µg/dl)	567.8±132.8	435.9±154.1	0.324
Ferritin (ng/ml)	12.0±3.9	49.5±10.4	0.003

Cases with Hb concentration less than 10gr./dl. were diagnosed as anemic. In order to verify iron-deficiency anemia and to set a basis for the research; serum Fe level, total iron binding capacity (TIBC) and ferritin levels were determined with 20cc. blood samples of each patient. Hemoglobin electrophoresis was applied in each case to discard hemoglobinopathies. Patients with anemia other than iron-deficiency anemia were excluded from the study. Only women with normal Hb electrophoresis and serum levels compatible to iron-deficiency anemia were included in the research. Cases were also examined in detail before the study, in case of other obstetric problems and patients with potential long term problems were excluded.

Prior to IV iron sucrose treatment; whole blood count, reticulocyte count, serum Fe^{+2} level, TIBC and ferritin levels were determined. After informing the patients on the treatment and taking a written consent from each, the IV iron sucrose treatment was started according to the protocole.

The total iron sucrose dose to be given was calculated according to the formula [Hb deficiency (gr/dl.) x weight (kg.) x 0.3]. The IV iron sucrose was administered during three weeks reaching to a target dose of 400 mg/week. The first week the dose was gradually increased as; three days 50 mg/day, then 100 mg/day and 200 mg/day. Iron sucrose was infused in 100cc. isotonic solutions in 20 minutes at maximum. In the following weeks, according to the Hb deficiency, the treatment was carried out as 400 mg/week given in two days a week. The infusions were administered in an outpatient basis except the first infusion and patients were sent home after an hour of observation after the cessation of infusion.

The reticulocyte count was repeated on day 3 and whole blood counts were repeated at the end of the first week. After the first week, the patients receiving the second and third doses were checked on their whole blood count at the end of the second and third week. Serum Fe^{+2}, TIBC and ferritin levels were only repeated at the end of the third week. The pretreatment and posttreatment data were compared according to Student's t test. A p value of less than 0.05 was accepted as statistically significant.

Results

The mean age of the study patients were 23±3.9 (range 18-36) years. Three patients were excluded from the study after the second week controls because of other obstetric complications. In the study group, 22 cases were primiparous, and 24 were multiparous. The mean gestational age at diagnosis was 28±4.6 (range 16-34) gestational weeks.

The mean pretreatment Hb concentration of patients was 7.8±2.1 gr/dl.; the mean Hct value was 24.6±5.8%; mean mean corpuscular volume (MCV) value 74.5±19.3 fl.; mean serum Fe^{+2} 14.6±3.9 µg/dl.; mean TIBC 567.8±132.8 µg/dl and mean serum ferritin level was 12.0±3.9ng/ml.

All blood tests were repeated after the cases completed the treatment determined by the protocole. The posttreatment values for Hb concentration was 10.9±3.4 gr/dl; for Hct concentration 30.3±5.9%; for MCV 80.0±9.4 fl.; for serum Fe^{+2} 42.7±13.9 µg/dl.; for TIBC 435.9±154.1µg/dl and for serum ferritin it was 49.5±10.4 ng/ml. (Table 1).

According to the data during and after the treatment, the mean Hb increase was 0.5-0.8gr/dl per week. The reticulocyte crisis was observed on days 2-4.

As a result, the augmentation in hemoglobin and hemotocrit levels were statistically significant ($p<0.05$). The change in mean corpuscular volume and total iron binding capacity was determined to be statistically insignificant ($p>0.05$). The most expressive change was recorded in the serum ferritin level ($p<0.05$).

Discussion

In developed countries, the pregnancy related anemia incidence is about 20%.[4] At the same time, anemia is the most frequent medical complication in pregnancy. Iron- deficiency anemia is the most common form among anemic pregnant women. The fundamental point is the evacuation of the iron stocks and inadequate dietary intake of iron. As a result, the erythrocyte volume decreases and anemia comes on the scene.[5] Especially the inadequate intake of iron via diet continues to be an important problem in developing countries.[6]

According to the World Health Organization criteria, anemia is described as a Hb concentration less than 11gr/dl6. The diagnostic criteria of iron deficiency in pregnancy is low serum Fe^{+2} level, high TIBC and low serum ferritin level. Ferritin level is frequently used to determine the decreased iron storage and is a helpful test in the early pregnancy

weeks. Mean corpuscular volume, serum Fe^{+2} value and erythrocyte distribution are nonspesific. Serum transferrin receptor level is expected to be an indicator of iron deficiency in the future.[4]

The effect of anemia on perinatal outcome and the necessity of an aggressive treatment is open to dispute.[7-10] In many studies, antenatal anemia has found to be related to intrauterine growth retardation (IUGR), preterm birth and especially postpartum infection6. Especially the correlation between first trimester anemia and negative fetal outcome seems to be stronger. Therefore diagnosis must be quick and a treatment must be provided.[10] In the postpartum period, diagnosis of anemia may be difficult and directing the treatment may become harder. The point to pay attention is that in the postpartum period, infection may falsely increase the serum ferritin level.[6] The researchers emphasize that, appropriate iron supplementation in pregnant women will have positive effect on the iron storage of the fetus in the neonatal period.[4] However, Graves[7] and Harthoorn[8] defended the uselessness of aggresive iron treatment in their studies. Harthoorn[8] and colleagues evaluated the serum erythrocyte zinc protoporhyrine level in diagnosis of iron deficiency to determine the correlation between maternal anemia degree and fetal state. There was no difference observed in the fetuses of anemic and non-anemic mothers. However, studies like this are limited in literature.

In the treatment of anemia, oral or parenteral route may be used. The advantage of the oral route is easy application and probably less adverse reactions. The disadvantages are variable biological benefit and low patient compliance because of gastrointestinal side-effects. The intravenous iron have been used widespread with success. Many studies in literature compare the efficacy of different therapeutic iron forms but the results are debatable.[11-14]

Most of the studies involve the treatment of iron deficiency anemia with iron dextran. The biggest disadvantage of iron dextran compounds are the serious side-effects.[12] In their study, Singh[5] and colleagues determined that iron dextran was more effective than ferrous fumarate. There was no adverse reaction during the study but the probability of anaphylaxis always existed. This important risk have brought about the usage of more improved drugs with less side-effects. Al-momen[14] compared IV iron-sucrose-complex with ferrous sulphate in terms of efficacy and safety. In his prospective controlled study of 107 cases he declared that IV administration was more effective and faster in efficacy than the oral route. He also stressed on the low patient corcordance in case of the oral drug intake. Johnson[11] and Kosch[15] agreed that the IV treatment was more influential and faster effective. In studies comparing IV iron dextran and sucrose complexes, there was no significant difference in terms of treatment efficacy. However, the fundamental difference between the two is the incidence of side-effects. Fischbane[16] and colleagues examined iron-dextran and iron-sucrose-complexes in the wide metaanalysis. Among the 74 side-effects reported in literature about iron-gluconate-sucrose complexes, no mortality was recorded. On the other hand, 196 cases of allergy-anaphylaxis were reported on iron-dextran-complexes, 31 cases of which resulted in mortality. Other than this pruritus, dyspnea (1.5%), chest pain (1.0%) emesis (0.5%), hypotension (0.5%) and flushing (0.3%) were observed. Consequently, iron-sucrose complexes are clearly superior to iron-dextran-complexes. Van Wyck[13] et al. reported no adverse effects in their study of 223 cases receiving iron-sucrose-complex treatment for dialysis-associated anemia. The authors claimed that there was no significant decrease in blood pressures during the dialysis, and there was a significant increase in ferritin, transferrin level with no significant change in TIBC. After the administration of iron-sucrose-complexes Hb level increased 0.4-0.5 gr/dl. weekly and made a plateau at the fourth week; ferritin level made its peak at the second week.

In our study, the Hb concentrations of patients receiving iron-sucrose-complex treatment shoved a statistically significant increase while the MCV and TIBC did not reveal a significant change. The most statistically significant increase was observed in the ferritin level. There were no adverse effects observed in our cases and no problems in compliance to treatment. Intravenous iron-sucrose-complex treatment is a fast effective and highly safe alternative in the treatment of iron deficiency anemia in pregnancy. Higher compliance to treatment than the oral route and having no serious side-effects unlike other iron preparations are the major advantages of this treatment.

References

1. Scholl TO, Hediger ML. Anemia and iron-deficiency anemia: compilation of data on pregnancy outcome. Am J Clin Nutr 1994; 59:4925.
2. Yip R. Significance of abnormally low or high hemoglobin concentration during pregnancy: special consideration of iron nutrition. Am J Clin Nutr 2000; 72:272S.
3. Sifakis S, Pharmakides G. Anemia in pregnancy. Ann N Y Acad Sci 2000; 900:125.
4. Haram K, Nilsen ST, Ulvik RJ. Iron supplementation in pregnancy-evidence and controversies. Acta Obstet Gynecol Scand 2001; 80:683-8.
5. Singh K, Fong YF, Kuperan F. A comparison between intravenous iron polymaltose complex and oral ferrous fumarate in the treatment of iron deficiency anemia in pregnancy. Eur J Haematol 2000; 64:27-34.
6. Hurch R. Anemia in pregnancy. Schweiz Rundsch Med Prax 1999; 88:157-63.
7. Graves BW, Bareger MK. A conservative approach to iron supplementation during pregnancy. J Midwifery Womens Health 2001; 46:159-66.

8. Harthoorn-Lasthuizen EJ, Lindenmans J, Langenhuijsen MM. Does iron-deficient erythropoiesis in pregnancy influence fetal iron supply? Acta Obstet Gynecol Scand 2001; 80:392-6.
9. Kumpf VJ. Parenteral iron supplementation. Nutr Clin Pract 1996; 11:139-46.
10. Schwartz WJ. Iron deficient aneamia in pregnanncy. Clin Obstet Gynecol 1995; 38:443-54.
11. Johnson CA, Mason NA, Bailie GR. Intravenous iron products. ANNA J 1999; 268:522-4.
12. Buglanov AA, Saiapina EV ,Turaev AT. A comparative study of the effectiveness of iron preparations in the treatment of iron deficient anemias in pregnant women. Akush Ginekol (Mosk) 1994; 6:16-8.
13. Van Wyck DB, Cavallo G, Spinowitz BS. Safety and efficacy of iron sucrose in patients sensitive to iron dextran: North American clinical trial. Am J Kidney Dis 2000; 36:88-97.
14. Al-Momen AK, al-Meshari A, al-Nuaim L. Intravenous iron sucrose complex in the treatment of iron deficiency anemia during pregnancy, Eur J Obstet Gynecol Repr Biol 1996; 69:121-4.
15. Kosch M. Iron deficiency: When parenteral substitution? MMW Fortsch Med 2001; 143:38.
16. Fischbane S, Unguraenaue VD. The safety of intravenous iron dextran in hemodialysis patients. Am J Kidney Dis 2000; 35:360-1.