Total infusion of low molecular weight iron-dextran for treating postpartum anemia

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Summary

Aim: 135 puerperal women with iron deficiency anemia participated in our prospective randomized controlled trial in order to investigate alternative treatments to blood transfusion for anemia. *Materials and methods:* The criteria for the diagnosis of anemia were Hb < 8 g/dl and ferritine < 10 μg/dl. Women were randomly separated in two groups, A and B. Women of group A (n = 109 women) received a total amount of 1000 mg low molecular weight (LMW) iron-dextran intravenously in two doses. Group B (n = 26) was the control group. They received orally 800 mg daily for 30 days of iron protein-succinylate. Three weeks later women of both groups underwent a full blood count analysis. *Results:* Hemoglobin and ferritin levels increased significantly in group A compared to group B ($p < 0.0001$). No adverse side-effects due to the treatment were noted in either group. *Conclusion:* It seems that total iron-dextran infusion is a safe and rapid therapy of iron-deficiency postpartum anemia increases the Hb level more rapidly than oral ferrous sulfate, and it also appears to replenish iron stores more rapidly.

Key words: Pregnancy; Anemia; Low molecular weight (LMW) Iron-dextran; Iron proteinsuccinylate.

Introduction

According to WHO criteria, postpartum anemia is defined as a hemoglobin level of less than 10.0 g/dl. Blood loss of up to 30% of the total blood volume is readily compensated. Blood loss of more than 1000 ml leads to increased maternal morbidity and mortality rates [1]. Iron deficiency is the principal cause of postpartum anemia. Iron deficiency during pregnancy is usually caused by the increased iron demands of the fetoplacental unit and the increased maternal red cell mass [2]. Blood loss is a contributing factor and it depends on the mode of delivery [3, 4]. A variety of symptoms such as lactation failure, lethargy, and postpartum depression can be generated by iron deficiency anemia in puerperium.

Oral iron supplementation is the first choice of treatment of mild and moderate iron-deficiency anemia. Blood transfusion remains the gold standard treatment for more severe cases. Nevertheless, there are a number of hazards due to allogenic blood transfusion, including transfusion of wrong blood, infectious diseases and anaphylaxis, any of which can be devastating for a young mother. All of these hazards, together with the national shortage of blood products, mean that transfusion should be reserved as a last resort in otherwise young and healthy women [5].

Oral iron supplementation should be prescribed at hemoglobin levels over 9.0 g/dl and 80-100 mg/day is sufficient in most cases of puerperal anemia. Iron supplementation should be continued for a period of several months to normalize iron stores. Dose-limiting gastrointestinal side-effects such as constipation, heartburn, bloating and nausea, occurring in up to 30% of patients, are a significant disadvantage of oral iron treatment [6].

Parenteral iron administration with ferrous sucrose is a quite useful alternative to the oral iron therapy. The high plasma iron concentration that occurs shortly after intravenous (IV) administration, bypasses the limited release of iron from the reticuloendothelial system and the inhibited absorption through the intestinal mucosa. Thus, sufficient quantities of iron for erythropoiesis are being delivered. The indications for parenteral administration of iron include severe anemia, need for rapid efficacy, intolerance of oral iron, insufficient absorption due to intestinal disease and no response to oral iron treatment. During the last two years low molecular weight iron-dextran (MW = 165.00 Daltons) is one of the most frequently used parenteral iron formulations. It is characterized by a strong colloidal complex of a ferric core shielded by tightly bound dextran chains. After the IV infusion low molecular weight (LMW) iron-dextran is rapidly taken up by the cells in the reticuloendothelial system in the liver and spleen from where iron is slowly released and bound to proteins [7].

Materials and Methods

One hundred and thirty-five postpartum women with severe iron deficiency postpartum anemia participated in a prospective randomized study. Ethics committee approval was obtained, and written informed consent from all the women was obtained prior to participation in this study. All women delivered at term; 91 had a normal vaginal delivery and the rest had a cesarean section (44 women). The women were divided randomly in two groups. Group A consisted of 109 women who underwent IV iron-dextran therapy and group B of 26 women who were treated by oral iron as controls. The two groups were matched for age, parity and mode of delivery. All cesarean sections were performed by a consultant obstetrician and were elective. The vaginal deliveries were all performed by senior midwives. The estimated blood loss was between 500-800 ml for the cesarean sections and was not significant in any of the normal deliveries.

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Cases of placenta previa, placenta abruption, preeclampsia, signs of infection or evidence of renal or hepatic dysfunction and clotting disorders were excluded from our study. All other types of hereditary or acquired anemia were also excluded.

The main criteria to administer intravenous iron were hemoglobin levels < 8 g/dl and ferritin levels < 10 g/dl. In group A intravenous infusion of 500 mg iron-dextran daily was used diluted in NaCl 0.9% for two days. The administration was performed slowly within five hours to avoid any cross reactions. In group B, the control group, oral supplementation of iron proteinsuccinylate (800 mg) was used daily for six weeks. Women of both groups were asked to document treatment compliance and symptoms on a diary chart provided for that purpose. Compliance was further emphasized by regular contact with one of the investigators. Blood samples were taken at recruitment into the study (day 0) and one week and four weeks after the start of treatment. We measured hemoglobin, ferritin, SGOT, SGPT blood levels and proteinuria in both groups. The incidence and severity of adverse events were recorded. In accordance with recommendations, the intravenous treatment was administered under close monitoring of vital signs.

Results

Data was available from 99 out of 109 women from group A (89%) one week later and from 91 women of the same group (83%) four weeks later. One case was excluded from the study because of a secondary postpartum hemorrhage and she was readmitted to our hospital for blood transfusion. All study results can be seen in Tables 1 and 2.

Table 1. — *Group A; mean values of blood results before and after parenteral iron treatment.*

	Before treatment n = 109	1 week after n = 98	4 weeks after n = 91
Hemoglobin (g/dl)	< 8	8.8	12.6
Ferritin (μg/l), mean values	10	48	115
SGOT, SGPT (U/l) mean values	09	11	14
Urine protein (g/l)	0	0.3	0.2

Table 2. — *Group B; mean values of blood results before and after oral iron treatment.*

	Before treatment n = 26	1 week after n = 20	4 weeks after n = 20
Hemoglobin (g/dl)	< 8	8.4	10.3
Ferritin (μg/l), mean values	10	26	68
SGOT, SGPT (U/l) mean values	09	12	13
Urine protein (g/l)	0.2	0.1	0.2

Statistical analysis of the results was performed with the Graph Pad Mann Whitney unpaired non parametric t-test and with the Wilcoxon matched pairs signed-rank test. The two-tailed p value is for both tests < 0.0001 which was considered significant. Thus there was significant difference between the two groups regarding hemoglobin increase four weeks post treatment (Figure 1).

No serious adverse events were reported in either group. Side-effects were detected in six cases of group A. In two of them, due to heartburn or facial flushing (transient symptoms which resolved immediately after the infusion was interrupted), the therapy was replaced by oral iron therapy for the next four weeks. Although the symptoms were described by the women as a fairly unpleasant warm sensation, the replacement of the therapy was due to our concern less than the actual severity of the symptoms. Constipation and dyspepsia were the main side-effects in the oral iron therapy group (Table 3). These were all gastrointestinal in nature and 100% compliance was reported and confirmed at the pill counts.

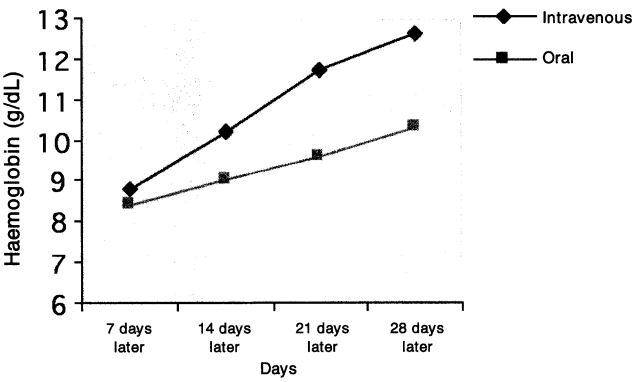

Figure 1. — Response of Hb to intravenous and oral therapies.

Table 3. — *Adverse effects of iron treatment.*

Adverse effects	Group A	Group B
Headache	1	–
Nausea	3	1
Heartburn, facial flushing	2	–
Constipation	–	5
Dyspepsia	–	4

Discussion

Young, healthy women can compensate for heavy blood loss better than a puerperal woman with a heart defect who may decompensate even after less severe loss. Additionally, blood loss needs to be viewed in relation to the body mass and the estimated total blood volume. It is a fact that blood loss is frequently underestimated [8].

Blood loss during the delivery is the main cause of postpartum anemia in young women. About 30% of anemic women have iron deficiency anemia with hemoglobin levels below 10 g/dl, and about 10% of anemic women have hemoglobin levels below 8 g/dl [9]. In about 5% of all deliveries postpartum hemorrhage is significantly high, more than 1000 ml [10]. Blood transfusion and oral iron therapy are the most common methods to treat iron deficiency anemia. Blood transfusion is a rapid method with excellent results in the treatment of anemia but also with a high risk for transmission of viral infections (HIV, HCV, HBs, CMV) and serious transfusion cross reactions [11].

Administration of oral iron supplementations is not sufficient enough to reverse anemia promptly due to the limited absorption, the gastrointestinal symptoms, and the poor compliance for long-term treatment of the patients [12]. Oral iron treatment should be prescribed at hemoglobin levels of over 9.5 g/dl. In such cases administration of 80-100 mg daily is sufficient enough. Such iron supple-

mentation should be continued for a period of several months to normalize not only the hemoglobin levels but also the ferritin stores. It has been shown that a puerperal woman with iron deficiency, but not anemia, can replenish the iron stores through iron supplementation alone [13]. Treatments with recombinant human erythropoietin could be useful in some cases of chronic inflammation when erythropoiesis is reduced. In cases of iron deficiency anemia the combination of iron supplementations and erythropoietin does not prevent iron loss nor increase the endogenous erythropoiesis [14]. On the contrary, high iron levels in plasma circulation after simultaneous intravenous administration of iron and erythropoietin is essential for stimulation of erythropoiesis [15].

One alternative is parenteral administration of iron sucrose. The high plasma iron concentrations that occur shortly after parenteral administration, bypass the limited release of iron from the reticuloendothelial system and the inhibited absorption through the intestinal mucosa. This whole process provides sufficient quantities of iron for erythropoiesis for puerperal women. Intravenous iron treatment is indicated for patients with poor compliance to oral supplementations, in cases with poor iron absorption (bowel operations or diseases), in patients with severe renal impairment, and in postpartum hemorrhage [16]. Iron-dextran contains iron in a stable aqueous iron (III)-hydroxide dextran complex, which is analogous to the physiological form of the ferric hydroxide phosphate protein complex. The formulation is characterized by a strong colloidal complex of a ferric core shielded by tightly bound dextran chains. Four hours after a total IV infusion approximately 1-1.2% of the iron was available for direct exchange to transfer [17]. Following the IV infusion LMW iron-dextran is rapidly taken up by the cells in the reticuloendothelial system particularly in the liver and spleen. The plasma half-life is five hours for circulating iron and 20 hours for total iron binding [18].

After four weeks of the study, with a total dose of 1000 mg of iron-dextran, there was complete reversal of anemic status in all women in group A. In group B there was improvement of anemia which was not as significant as in group A, though. We have reached these results according to the levels of hemoglobin and ferritin levels of the women who participated in the study. It is already known that intravenous administration of excessive doses of iron might cause liver necrosis, renal, suprarenal and pulmonary damage. The presence of iron-dextran in the plasma circulation is associated with absence of any undesirable effects to the patients. Iron-dextran is quite safe in daily doses of 500 mg for the liver, in comparison with other iron supplementations. There are some reports for rare anaphylactic reactions with the use of iron-dextran in about 2% of cases [19]. Similar anaphylactic reactions were also detected in our study.

In conclusion, it seems that iron-dextran could be a reliable and safe solution for treating postpartum iron deficiency anemia, without any presentation of toxic effects and minimal anaphylactic reactions. In our study, the parenteral ferrous treatment appeared to provide a rapid resolution of both iron stores and hemoglobin levels for women with postpartum iron deficiency anemia. However a larger study is needed to examine the future risks of the infusion and the accompanying clinical benefits this may provide.

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