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Intravenous iron sucrose complex in the treatment of iron deficiency anemia during pregnancy

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Abstract

Objective: To evaluate the safety and efficacy of intravenous iron sucrose complex (ISC) as compared with oral ferrous sulfate in the treatment of iron deficiency anemia during pregnancy. *Study design:* prospective, open, controlled study in which pregnant women with iron deficiency anemia were sequentially selected from the antenatal clinic and assigned either to ISC (study group) or to ferrous sulfate (control group). *Methods:* Each study patient was given the total calculated amount of ICS (Hb deficit (g/l) × body weight (kg) × 0.3) in divided doses (200 mg (elemental iron) in 100 ml normal saline intravenously over 1 h daily) followed by 10 mg/kg to replenish iron stores. Each patient of the control group was given ferrous sulfate 300 mg (60 mg elemental iron) orally three times a day. All patients were monitored for adverse effects, clinical and laboratory response. *Results:* There were 52 patients and 59 controls. ISC group achieved a significantly higher Hb level (128.5 ± 6.6 g/l vs. 111.4 ± 12.4 g/l in the control group $P \leq 0.001$) in a shorter period (6.9 ± 1.8 weeks vs. 14.9 ± 3.1 weeks in the control group, $P \leq 0.001$). ISC complex group showed no major side effects while 4 (6%) of the control group could not tolerate ferrous sulfate, 18 (30%) complained of disturbing gastrointestinal symptoms and 18 (30%) had poor compliance. *Conclusion:* We conclude that ISC is safe and effective in the treatment of iron deficiency anemia during pregnancy.

Keywords: Iron deficiency anemia; Pregnancy; Iron sucrose complex; Ferrous sulfate

1. Introduction

Iron deficiency (depletion) with or without anemia has many adverse effects on nervous system, intellectual capacity, physical performance, immune response and pregnancy outcome [1–7]. These effects are exaggerated in pregnant women with iron deficiency anemia, because of the ability of the fetus to extract its iron requirement in an obligatory one way direction even from iron deficient mothers [8,9]. Unfortunately, up to 50% of women in the child bearing age are anemic or iron depleted due mainly to menstrual blood loss and inadequate iron intake or absorption [8,9]. In this age group, iron deficiency anemia ranges between 8% in Western women (where diet contains adequate iron supply) to more than 50% in developing countries (where diet is poor in iron content) [8,9]. During our study period (5 months) we tested 7253 pregnant women, of whom 5694 (78.5%) had Hb level above 110 g/l and 1559 (21.5%) had Hb level below 110 g/l (i.e. 21.5% were anemic). Severe anemia (Hb below 90 g/l) was found in 436 women (6%).

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During pregnancy, there is a great demand for iron to meet the requirement for red blood cell mass expansion in the mother, fetal and placental blood, and blood loss at delivery in addition to increased occult gastrointestinal blood loss (esophagitis, piles, etc.) [10–14]. Although iron absorption may be adequate in healthy, iron-replete women, it is far below the iron requirement of an iron depleted or deficient pregnant women [10–19]. This is aggravated by the adverse effect of pregnancy on the gastrointestinal tract which includes nausea and vomiting, motility disorder with reflux esophagitis, indigestion, constipation and tendency to develop hemorrhoids [20–23]. Therefore, parenteral iron therapy is often necessary in anemic, pregnant women.

The aim of this prospective, open-controlled, study is to evaluate the safety and efficacy of intravenous iron sucrose complex (Venofer i.v., Vifor International AG, Switzerland) as compared with oral ferrous sulphate in the treatment of iron deficiency anemia during pregnancy.

2. Materials and methods

Pregnant women (gestational age less than 32 weeks) with severe iron deficiency anemia (Hb less than 90 g/l) who gave informed consents were selected from the Antenatal Care Clinic sequentially and assigned either to iron sucrose complex (ISC) (study group) or to ferrous sulfate (control group). Patients were excluded if they had other causes of anemia such as thalassemia trait, bleeding tendency, hemolytic anemia, hypersplenism, infection, inflammation, liver or renal disease, etc. Severe Iron deficiency anemia was diagnosed if Hb is less than 90 g/l, MCV less than 78 fl, MCH less than 30, serum ferritin less than 20 μg/l with low iron and elevated total iron binding capacity (TIBC) and absence of any other cause of anemia (Table 1).

Table 1
Baseline evaluation of iron sucrose complex group (A) and control group (B)

	Iron sucrose complex group (A)	Control group (B)
Number of patients	52	59
Age (years), (mean ± S.D.)	28.4 ± 6.8	27.6 ± 7.1
Gestational age (weeks), (mean ± S.D.)	21.7 ± 6.0	21.9 ± 6.1
Hb (g/l) (normal 110–140), (mean ± S.D.)	75.8 ± 7.9	76.6 ± 7.8
MCV (fl) (normal 80–95), (mean ± S.D.)	68.6 ± 6.0	70.8 ± 5.2
Serum ferritin (μg/L) (normal 50–300), (mean ± S.D.)	11.9 ± 5.0	12.0 ± 5.3

2.1. Drug administration

2.1.1. Iron sucrose complex

The dose of iron sucrose was calculated as follows: body weight (kg) × (Hb_T-Hbi g/l) × 0.3; where Hb_T = target Hb: 130 g/l; Hbi = initial Hb G/L; 0.3 = constant

This formula was simplified from Ref. [1] (required iron to correct Hb deficit = Hb deficit (g/l) × body weight (lb) to which 1000 and 600 mg are added to males and females respectively for replenishment of Iron stores) and Ref. [24] (1 g Hb needs 3.4 mg iron, therefore iron needed = Hb deficit g/dl × body weight (kg) × 3.4 × 1.4 for replenishment of iron storage).

The amount calculated from our formula is enough to correct Hb deficit only without replenishing the iron stores. To replenish iron stores 10 mg/kg of ISC was added. ISC was administered as 200 mg (elemental iron) in 100 ml normal saline intravenously over 1 h every 1–3 days up to the total dose (most patients received the dose once daily). Thirty eight patients received the ISC doses daily as in-patients and 14 received the doses three times weekly in the short stay unit.

2.1.2. Ferrous sulfate

The control were given ferrous sulfate 300 mg tablets (each tablet contains 60 mg elemental iron) orally three times a day on an empty stomach. Ferrous sulphate was continued prophylactically at 300 mg orally once daily after the achievement of the target Hb in good responders.

2.1.3. Monitoring

Study patients and controls were seen every 2 weeks and assessed for side effects, compliance (counting tablets of ferrous sulfate), clinical and laboratory response (Hb, MCV, MCH, reticulocytes and serum ferritin).

2.1.4. Statistical analysis

Mann-Whitney test was used to compare between maximal values of Hb, MCV, serum ferritin and the time needed to reach the maximal Hb level in both ISC and control group. A difference of less than 0.05 was considered significant. By applying Kolmogorov-Smirnov (KS) statistic for normality, we found that the data do not follow normal distribution at the 0.05 level ($KS > 0.895$). This could be explained by the fact that only severely anemic patients were selected for this study.

3. Results

ISC group obtained significantly higher levels of Hb, MCV, and serum ferritin as compared with the control

Table 2
Hb, MCV, and serum ferritin in the ISC (study group) and control group after treatment

	Iron sucrose group ($n = 52$)	Control group ($n = 59$)	P-Value (2-tail)
Hb g/l (mean ± S.D.)	128.5 ± 6.6	111.4 ± 12.4	<0.001*
MCV (fl) (mean ± S.D.)	82.6 ± 5.5	74.9 ± 7.9	<0.001*
S. Ferritin g/l	95.5 ± 38.1	52.4 ± 3.1	<0.001*

* Significant at 5% level of significance.

group (Table 2). The time needed to achieve maximal Hb level was significantly shorter in the ISC group as compared with the control group (6.9 ± 1.8 weeks vs. 14.9 ± 3.1 weeks) (Fig. 1). One patient in the ISC group developed self-limited fever (38.5°C) after the fifth dose, which disappeared with paracetamol. Another patient felt tightness and discomfort in the skin of the whole body at the end of the third dose. It did not recur with the subsequent doses which were given over 4 h. Four (6%) of the control group patients could not tolerate ferrous sulfate (their laboratory results were excluded). Eighteen (30%) patients of the controlled group complained of disturbing gastrointestinal side effects (nausea, vomiting, heartburn, abdominal pain, and constipation) and 19 (32%) patients, were non-compliant (did not adhere to three tablets per day). The remaining 18 (30%) patients, adhered to the instructions but only seven of them obtained the target Hb after 12 weeks.

4. Discussion

Our study illustrates clearly that intravenous iron sucrose complex is safe, convenient and effective in pregnant women with iron deficiency anemia as compared with ferrous sulfate (or probably any other oral iron preparation). This rapid and profound response was directly related to the high amount of iron that could be delivered directly to the hemopoietic tissues. It has been recognized for decades that oral iron therapy is not adequate for pregnant women with iron deficiency anemia, mainly because of the augmented demand for iron to meet the requirement of maternal anemia (500–1000 mg), maternal red cell mass expansion (400–600 mg), placenta (250 mg), umbilical cord (50 mg), fetus (200 mg) and the expected blood loss at delivery (200–500 mg). Even patients who respond well to oral iron therapy require a long time (months) to reach target Hb. This means that they have to suffer from the iron deficiency for extended periods unnecessarily.

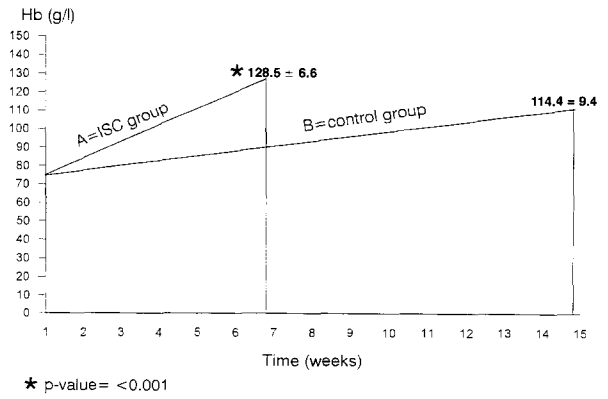

Fig. 1. X-axis, Hb level (g/l); Y-axis, time (week); A, ISC group; B, control group; * P-value ≤ 0.001.

Therefore, a pregnant woman without anemia may require at least 1000 mg of elemental iron to be delivered to the hemopoietic organs while an anemic one may need more than 2600 mg. This requirement cannot be met by oral root in the majority of patients because of limited absorption, bioavailability and compliance. In addition, oral iron therapy is further complicated by the adverse effects of pregnancy on the gastrointestinal tract [20–23].

Intramuscular iron therapy is to be discouraged because of its adverse effects which include pain, irregular absorption, staining, and malignancy [24–26]. Intramuscular ISC in particular is contraindicated because of poor absorption. There are several intravenous iron preparations beside iron sucrose complex such as iron dextran which has been used extensively over the last 30 years. Up to 30% of patients who are given iron dextran suffer from adverse effects which include arthritis, fever, urticaria and anaphylaxis [24–30]. It is contraindicated in rheumatoid arthritis because of its association with arthritis flare-up. ISC, on the other hand, seems to be safe with fewer and milder side effects even in patients with rheumatoid arthritis [31–34].

Anaphylaxis is very rare with ISC because of its small molecular weight. Until now only one case of possible anaphylactic reaction has been described (vifor international file). Unlike many other parenteral iron preparations, ISC is taken up mainly by the reticuloendothelial system and it is unlikely that it would be taken up by the parenchymal cells of liver, kidney, adrenal gland or other organs [32], hence, organic toxicity (such as pancreatic, myocardial or hepatic hemosiderosis) is less likely even with iron sucrose complex overload.

Unlike other parenteral iron preparations, intravenous ISC is safe, with infrequent, self-limited side effects (fever, skin discomfort). The side effects of ISC can be completely avoided by dividing the total dose into smaller doses (100–200 mg/day) and by slow administration (infusion over 1–4 h) [32–34].

It should be emphasized that iron deficiency even without anemia should be prevented before its development [4–7]. In other words, to treat patients when they become anemic is too late.

Although ISC therapy may appear invasive, expensive and time consuming, it is highly and rapidly effective without major side effects. This makes it convenient and cost effective in pregnant, iron deficient women who are unable to obtain an adequate amount of iron rapidly by the oral root.

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