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## Outcome of intravenous iron sucrose in treatment of anemia in pregnancy

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#### Abstract

The objective of this study was to see the efficacy, safety and tolerability of intravenous iron sucrose in iron deficiency anemia during 14 to 34 weeks of pregnancy. A clinical trial was performed involving 56 patients attending the antenatal clinic at Shri B M Patil Medical College Hospital, Bijapur from October 2011 to August 2012, with hemoglobin levels between 70-110g/L and serum ferritin of < 15 ng/ml. Iron sucrose was administered as 200 mg in 100 ml 0.9% sodium chloride per day. The primary outcome measures for the trial, haemoglobin and serum ferritin levels were measured after 4 weeks. The change in haemoglobin in women receiving intravenous iron was higher  $22 \pm 11.5$  g/L ( $p < 0.0001$ ). Similarly the change of serum ferritin was significantly higher in women receiving intravenous iron. 55% of participants had an improvement in haemoglobin more than 20 g/L. 48% of patients showed increase in ferritin level between 51 to 100 ng/ml. Intravenous iron sucrose is more effective in correction of anemia and increasing maternal iron stores.

**Keywords:** Anemia, iron sucrose, hemoglobin, ferritin

#### Introduction

Iron deficiency anemia is the most common form of anemia the world over and also the most common nutritional disorder in the world. Anemia in pregnancy, defined by the World Health Organization (WHO) as hemoglobin level of less than 11 g/dL, is a global health problem affecting 41.8% of women worldwide [1]. WHO (World Health Organisation) has estimated that prevalence of anemia in developed and developing countries in pregnant women is 14% in developed and 51% in developing countries [2]. It is projected that India has the utmost prevalence of anemia i.e., 57-96.2%, among the South Asian countries [3]. It is a direct cause of 20% of maternal mortality in India [4] and indirect cause in 20% to 40% of maternal deaths [5].

Iron deficiency anemia during pregnancy increases the risk of low birth weight (LBW), preterm birth, maternal and perinatal mortality, and poor apgar score [3].

Over the past years, various oral, intramuscular and intravenous preparations of iron have been used for correction of IDA (Iron Deficiency Anemia) in pregnant patients. The first choice in the treatment of iron deficiency anemia for almost all patients is oral iron replacement because of its effectiveness, safety, and lower cost.

Though oral iron has its place in the management of IDA, it has a major drawback of reduced compliance owing to poor tolerability and side effects. The gastrointestinal (GI) adverse effects of oral iron may further exacerbate the pregnancy associated GI disturbance which includes indigestion, constipation, nausea, vomiting, and reflux esophagitis [3].

Severe systemic adverse effects associated with iron dextran and iron gluconate limited the use of intravenous iron. Iron sucrose complex (ISC) is a relatively new drug, which is used intravenously for the correction of IDA. Iron sucrose is a widely used safe molecule with few adverse events [3]. The objective of this study is to see the efficacy, safety and tolerability of intravenous iron sucrose in iron deficiency anemia during 14 to 34 weeks of pregnancy.

#### Methods

A prospective clinical trial was performed from October 2011 to August 2012 in the department of Obstetrics and Gynecology, Shri B M Patil Medical College of B.L.D.E University, Bijapur. 56 pregnant women between 14 to 34 weeks of pregnancy were studied. The inclusion criteria were haemoglobin level between 70 to 110g/L, serum ferritin of less than 15 ng/ml, age 18 to 45 years, singleton pregnancy. The exclusion criteria were patients with history of bleeding tendency, history of blood transfusion within the prior 120 days, hemoglobinopathy or other red cell disorders, allergic conditions or asthma, acute inflammatory state.

**A total of 56 patients were studied**

The total iron sucrose dose to be administered was calculated from the following formula –Total dose required = weight in kg × (target Hb in g/L – Actual Hb in g/L) × 0.24 + 500mg. rounded up to the nearest multiple of 100mg [6].

This dose of iron sucrose complex was administered as 200mg (elemental iron) in 100ml 0.9% sodium chloride intravenously over 20 to 30 minutes daily up to the total dose. No test dose was given [7, 3]. This treatment was supplemented with 5 mg of oral folic acid daily for 4 weeks to prevent an eventual folic acid deficiency and to eliminate the influence of such a deficiency on the results. Additional oral administration of iron was excluded during the 4 weeks of study.

The patients were monitored both clinically, biologically and adverse reaction linked with it. Biologic monitoring was carried out on inclusion (day 0) in addition to the data required at the start of the study.

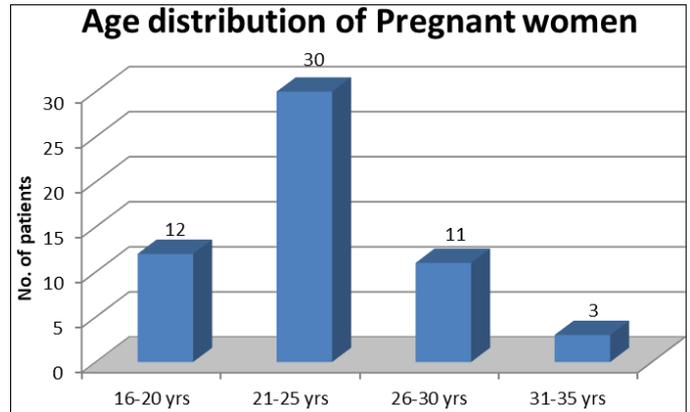
The measurements recorded were: - haemoglobin %, complete blood count, serum ferritin, urine analysis, peripheral smear for type of anemia.

After 4 weeks on day 30, haemoglobin and serum ferritin levels were repeated.

The study results were expressed as mean ± standard deviation. Student T test was used to verify the statistical significance.

**Results and discussion**

Out of 56 patients 52% of patients were between 21 to 25 years as shown in Figure 1 and most of them were multigravida between the period 31 to 34 weeks of gestation.



**Fig 1:** Age distribution of pregnant women

As depicted in Table 1 a substantial increase in Hemoglobin was observed rising from 89 ± 10.7 to 106.4 ±13 g/L(Mean ±SD) after 4 weeks with P value being < 0.0001 which was highly significant.

**Table 1:** Hemoglobin level before treatment and after 4 weeks of treatment.

Parameters	Pre treatment Hb(g / L)		Post treatment Hb(g / dl)		T-Value	P-Value
	Mean	SD	Mean	SD		
Hb (g /L)	89	10.7	106.4	13	5.62	< 0.0001

Similarly there was a highly significant difference in serum ferritin levels after 4 weeks of treatment with P value being < 0.0001 which is again highly significant as shown in Table 2.

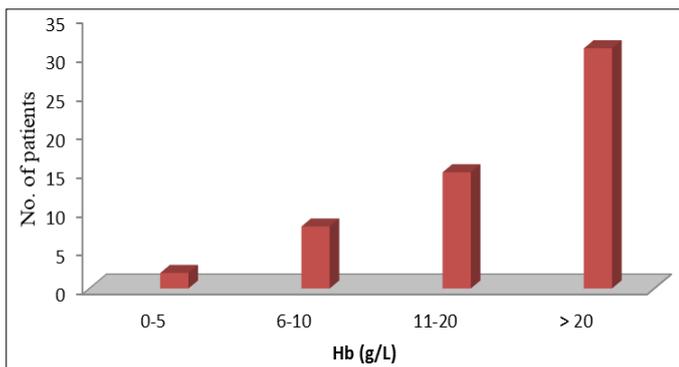
**Table 2:** Serum ferritin level before treatment and after 4 weeks of treatment.

Parameters	Pre treatment Serum ferritin (ng/ml)		Post treatment Serum ferritin (ng/ml)		T-Value	P-Value
	Mean	SD	Mean	SD		
S.Ferritin (ng/ml)	8.84	3.47	120.85	87.91	7.37	< 0.0001

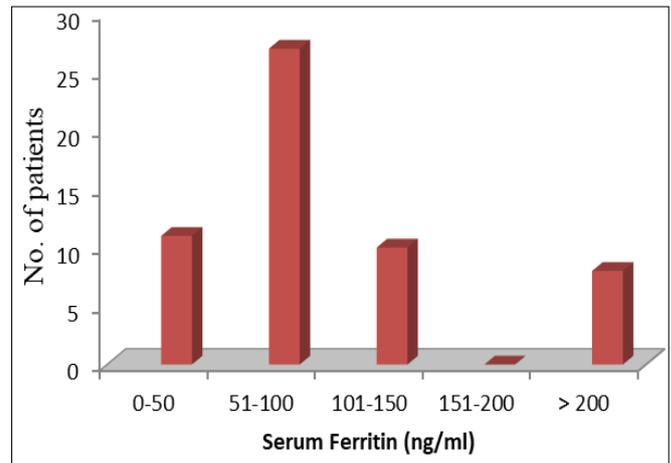
The change in Hb % was 22 ± 11.5 g /L(Mean ±SD) which was significantly higher with T value 4.67 and P value being < 0.0001 which is statistically significant. The change in serum ferritin was 112.17 ± 98.15 ng / ml (Mean ±SD) which was significantly higher with T value 5.11 and P value being < 0.0001 which is again statistically significant.

A outcomes of treatment of Intravenous iron sucrose is shown in Figure 2. 31 patients (55%) showed a greater improvement of more than 20 g/L. The differences in the responses were highly significant (p<0.0001).

As shown in Figure 3, 27 patients (48%) showed increase in serum ferritin levels between 51 to 100 ng / ml. 10 patients (18%) had increase in serum ferritin by 101 to 150 ng / ml and 8 patients (14%) had increase in serum ferritin by more than 200 ng / ml. The responses were highly significant (p<0.0001).



**Fig 2:** Outcome of treatment – degree of rise in Hb g /L.



**Fig 3:** Outcome of treatment – degree of increase in Serum Ferritin (ng / ml).

In our study 6 patients had minor side effects like burning, pain and swelling at the injection site.

This study observed that parenterally administered iron sucrose elevates hemoglobin and restores iron stores better during the treatment of iron deficiency anemia in pregnancy. The mean changes in hemoglobin and ferritin levels throughout the treatment were significantly higher.

Oral iron is effective, safe, low cost, but there may be failure in the effectiveness due to non compliance, achlorhydria, inflammatory bowel diseases, or unrecognized bleeding. Non compliance is largely related to side effects. 10 to 40 % of patients [8] suffer adverse gastrointestinal effects - constipation, diarrhoea, epigastric discomfort, nausea, severe abdominal pain and vomiting. They can be decreased by food, but food decreases absorption by 10 to 40 %.

Iron dextran compounds are stable, strong complexes of relatively high molecular weight, long half life and relatively slow release. Life threatening anaphylactic reactions (sudden cardiovascular collapse, respiratory failure) occurred in 0.1 to 2 % of patients treated with this product. 30 % of patients suffered from adverse effects which include fever, arthritis, urticaria. 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 [9].

Intramuscular iron, iron-sorbitol citric acid complex causes metallic taste on tongue, nausea, vomiting and pain at the injection site [2]. Other parenteral iron preparations available are ferric gluconate, ferric citrate but are found to cause severe and extended liver necrosis [10].

Iron sucrose belongs to the iron complexes of medium strong type (molecular mass between 30,000 and 100,000 Da). The rate of iron delivery to the marrow is a major factor in the regulation of marrow proliferation. Iron dextran and iron sucrose have different pharmacokinetic properties. It is quickly cleared from serum with a terminal half-life of approximately 5 to 6 hours compared with iron dextran, which has a serum half-life of 3 to 4 days. It is rapidly taken by the bone marrow for erythropoiesis and the reticuloendothelial system for storage [7, 3]. Studies mostly investigating renal patients with severe Iron deficiency anemia, have shown that 70-97% of the iron is used for erythropoiesis with only 4-6% elimination [11]. Intravenous iron sucrose produces a more rapid increase in hemoglobin concentration than oral iron and intramuscular iron dextran [7].

Anaphylaxis is very rare with ISC because of its small molecular weight. Until now only one case of possible anaphylactic reaction has been described. Unlike many other parenteral 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, hence, organic toxicity (such as pancreatic, myocardial or hepatic hemosiderosis) is less likely even with iron sucrose complex overload.

In a random, prospective, open study done by Bayoumeu *et al* [6] in 2002, 24 women were given intravenous iron sucrose in 6 slow I.V injections on days 1, 4, 8, 12, 15 and 21 with a maximum of 200 mg of iron each time. An increase in hemoglobin was observed on day 30 and serum ferritin was higher in the IV group ( $P < 0.001$ ). Similarly in our study also there was highly significant difference in the serum ferritin levels after 4 weeks of treatment ( $P < 0.0001$ ).

Al Momen *et al*. [9] in the year 1996 reported findings similar to those in our study. 52 women were treated with intravenous iron sucrose 200 mg in 100 ml Normal saline daily till total dose was

met and found that intravenous treatment resulted in higher hemoglobin levels in shorter periods.

In our study, I.V ferrous sucrose was well tolerated and not associated with any serious adverse effects and was only associated with burning, pain and swelling at the injection site in 6 patients. It was reduced by thrombophobe ointment, ice pack and by injecting 5 cc of normal saline or distilled water at the end of I.V sucrose infusion. This finding is supported by previous larger studies that have investigated the safety profile of intravenous ferrous sucrose both during pregnancy and in the postpartum period [12]. Perewunskyk *et al*. [13] studied 500 women who received ferrous sucrose. Minor general adverse effect including a metallic taste, flushing of the face and burning at the injection site occurred in 0.5%, with doses up to 200 mg. The high tolerance of the drug has been partly attributed to slow release of iron from the complex and also due to low allergenicity of sucrose.

In a study by Dede *et al*. [14] in 2004, 50 patients were included and I.V iron sucrose was administered at a dose 200 mg in 100 ml normal saline daily till total dose was met. Blood samples were taken before the start of therapy and at days 7 and 28 to evaluate levels of Hb, serum ferritin, serum iron, CRP (C-Reactive Protein), MCV (Mean corpuscular volume), TIBC (Total iron binding capacity). The study showed that I.V iron therapy with an iron sucrose complex significantly increased serum ferritin levels within a short time with fewer adverse effects in women with post partum iron deficiency anemia. The results of this study were similar to our study.

Overall iron sucrose appears to be a treatment of choice with no serious side effects indicated in the rapid correction of anemia on pregnancy or restoring maternal iron stores, especially the total dose can be administered over a short period. If used in time, this treatment will certainly help the risk of homologous blood transfusion during the peripartum period.

## Conclusion

Intravenous iron Sucrose Complex (ISC) is safe and effective in the treatment of iron deficiency anemia during pregnancy. Intravenous iron sucrose is a most promising iron preparation for use in obstetrics because it is safe, effective and easy to administer.

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