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Serum ferritin changes on administration of intravenous iron in iron deficiency anemia in pregnancy

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Abstract
The objective of this study was to see the changes in the serum ferritin levels on administration 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 serum ferritin of < 15 ng/ml and hemoglobin levels between 70-110g/L. Iron sucrose was administered as 200 mg in 100 ml 0.9% sodium chloride per day. The primary outcome measures, serum ferritin and haemoglobin levels were measured after 4 weeks. 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. 48% of patients showed increase in ferritin level between 51 to 100 ng/ml. Serum ferritin levels increase with intravenous iron sucrose administration thus making it effective in increasing maternal iron stores along with correction of anemia.

Keywords: Serum ferritin, anemia; iron sucrose; hemoglobin

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]. an adequate iron balance during pregnancy implies body iron reserves of > or = 500 mg at conception.
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 ie. 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].
The physiologic iron requirement in the second half of gestation cannot be fulfilled solely through dietary iron. Iron supplements during gestation consistently increase serum ferritin and hemoglobin and reduce the prevalence of iron deficiency anemia.
In humans, mothers with low levels of ferritin had cord blood ferritins 30% to 60% below those with better iron stores [6, 7]. Ferritin in cord blood usually correlates with maternal ferritin or hemoglobin measured at delivery [8].The smaller iron stores associated with low birth weight interact with anemia in the mother to increase the offspring's anemia risk nearly 4-fold.Thus follow up studies of infants born to anemic women suggest that the infant's iron endowment mirrors that of the mother [9].
In the setting of anemia, low serum ferritin is the most specific laboratory test for iron deficiency anemia. However it is less sensitive, since its levels are increased in the blood by infection or any type of chronic inflammation, and these conditions may convert what would otherwise be a low level of ferritin from lack of iron into a value in the normal range. For this reason, low ferritin levels carry more information than those in the normal range.
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 was to see the changes in the serum ferritin levels on administration of intravenous iron sucrose in iron deficiency anemia during 14 to 34 weeks of pregnancy.

Material and 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 serum ferritin of less than 15 ng/ml, hemoglobin level between 70 to 110g/L, 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 [10].

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 [11, 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: - serum ferritin, hemoglobin%, complete blood count, urine analysis, peripheral smear for type of anemia.

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

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

Result

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.

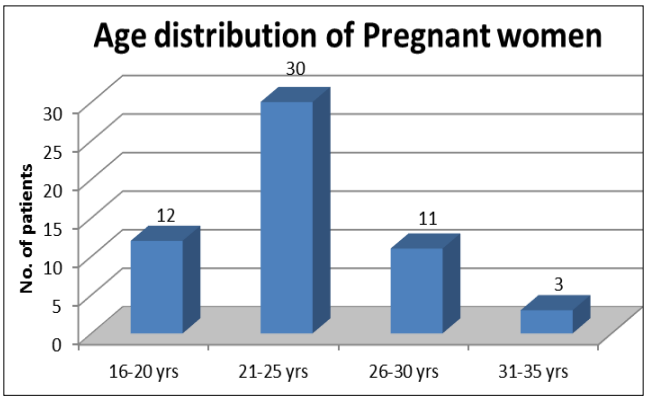

Fig 1: Age distribution of pregnant women

There was a highly significant difference in serum ferritin levels from 8.84 ± 3.47 to 120.85 ± 87.91 ng/ml (Mean ± SD) after 4 weeks of treatment with P value being < 0.0001 which is again highly significant as shown in Table 1.

Table 1: Serum ferritin level before treatment and after 4 weeks of treatment

Parameters	Pretreatment 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

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 as depicted in Table 2 which was highly significant.

Table 2: Hemoglobin level before treatment and after 4 weeks of treatment.

Parameters	Pretreatment 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

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. 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.

As shown in Figure 2, 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 with administration of intravenous iron sucrose. The responses were highly significant (p< 0.0001).

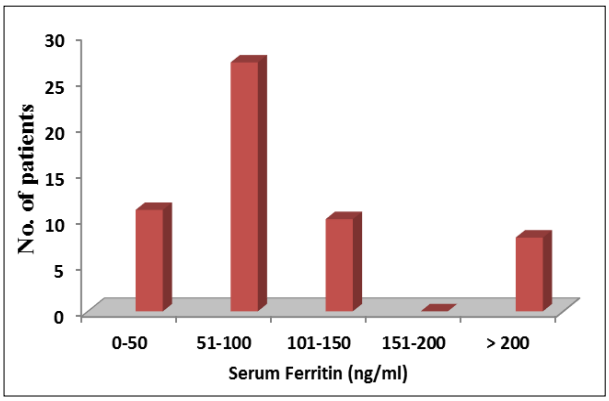

Fig 2: Outcome of treatment-degree of increase in Serum Ferritin (ng / ml).

As shown in Figure 3. 31 patients (55%) showed a greater improvement of more than 20 g/L. The differences in the responses were highly significant (p< 0.0001).

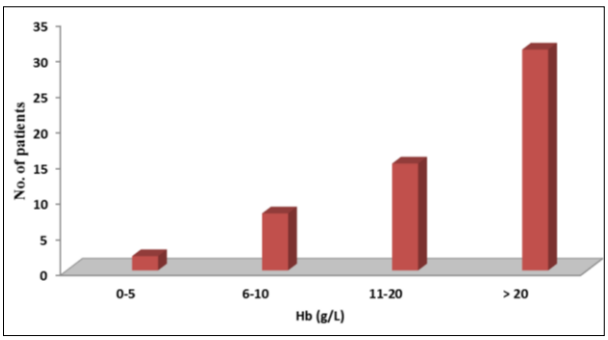

Fig 3: Outcome of treatment – degree of rise in Hb g /L.

Discussion

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.

Ferritin is a ubiquitous intracellular protein that stores iron and releases it in a controlled fashion. The amount of ferritin stored reflects the amount of iron stored. Ferritin stores iron in a non-toxic form to deposit it in a safe form, and to transport it to areas where it is required. Thus, the serum ferritin is the most convenient test to estimate iron stores.

If the ferritin level is low, there is a risk for lack of iron, which could lead to anemia.

Oral iron is effective, safe, low cost, but there may be failure in the effectiveness due to noncompliance, achlorhydria, inflammatory bowel diseases, or unrecognized bleeding. Non-compliance is largely related to side effects. 10 to 40% of patients [12] 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 [13].

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 [14].

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 [15]. Intravenous iron sucrose produces a more rapid increase in hemoglobin concentration than oral iron and intramuscular iron dextran [11].

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* [10] 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. Serum ferritin was higher in the IV group ($P < 0.001$). An increase in hemoglobin was observed on day 30.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* [13] 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 thrombophob 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 [16]. Perewunsnyk *et al* [17] 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* [18] 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 restoration of maternal iron stores along with correction of anemia in pregnancy, 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 per partum period.

Conclusion

Serum ferritin levels markedly rise with administration of intravenous iron sucrose thus making it effective in increasing maternal iron stores along with correction of anemia. 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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