International Journal of Clinical Obstetrics and Gynaecology

ISSN (P): 2522-6614
ISSN (E): 2522-6622

www.gynaecologyjournal.com
2021; 5(4): 221-224
Received: 13-05-2021
Accepted: 15-06-2021

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Comparison of intravenous iron sucrose versus oral iron for the treatment of iron deficiency anaemia in pregnancy

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DOI: https://doi.org/10.33545/gynae.2021.v5.i4d.988

Abstract
Background: Iron deficiency anemia (IDA) is the most common medical problem in pregnancy. Parenteral iron is a useful treatment, although iron dextran use decreased due to anaphylaxis. Iron sucrose is a newer agent that has overcome the shortcomings of iron dextran.
Objective: The aim of this study was to compare the safety and efficiency of intravenous iron sucrose with oral iron administration for the treatment of iron deficiency anaemia in pregnancy.
Materials and Methods: 100 women with gestational age between 14 and 35 weeks with iron deficiency anaemia & Haemoglobin between 6-8g/dL were randomised to receive either oral iron (ferrous sulphate) 200 mg thrice daily or required dose of intravenous iron sucrose. Haemoglobin, haematocrit, mean corpuscular volume, reticulocyte count were measured at recruitment and on 2nd week, 4th week and at 37 weeks of gestation. Adverse drug reactions were also noted in both these groups.
Results: Haemoglobin values varied significantly with time between the two groups at second week, 4th week and at 37 weeks. The mean difference in mean corpuscular volume from the recruitment value was not significant at 2nd week of treatment. When compared to iron sucrose group, oral iron group had significant gastro-intestinal adverse effects.
Conclusion: Intravenous iron sucrose treated iron deficiency anaemia of pregnancy faster, and more effectively than oral iron therapy, with no serious adverse drug reactions.

Keywords: MCV, PCV**,** intravenous iron sucrose, iron deficiency, anaemia, oral iron, haemoglobin (Hb)

Introduction
Iron deficiency anaemia is one of the most widespread of all nutritional deficiencies during pregnancy in India. Estimates from the World Health Organization (WHO) report that from 35% to 70% of pregnant women in developing countries are anaemic [1]. The standard treatment in majority of the institutions is oral iron, with blood transfusion reserved for severe or emergency cases. However, it is unreliable in the treatment of severe anaemia. The provision of iron supplements during pregnancy is one of the most widely practiced public health measures. The traditional treatment of iron deficiency anaemia includes oral/ parenteral iron and blood transfusion [2]. Oral iron is associated with side effects like nausea/vomiting, non- compliance and takes a long time to correct anaemia. Parenteral preparations like iron dextran, iron sorbitol are associated with anaphylactic reactions. Blood transfusion has its own hazards, including transfusion of wrong blood and deadly infections like HIV, CMV, hepatitis and anaphylaxis [3]. Thus, there is a need for a safe and effective alternative to oral iron or blood transfusion in the treatment of anaemia during pregnancy.
Recently there is increasing interest on alternative therapeutic options like intravenous iron sucrose and human recombinant erythropoietin. Iron sucrose has been shown to have several advantages like low incidence of side effects, high availability for erythropoiesis, little renal excretion and low tissue accumulation and toxicity [4]. Very few studies have been designed to measure with reasonable precision the rates with which these iron preparations can correct iron deficiency anaemia. The present study was under taken to compare the efficacy and safety of iron sucrose and oral iron for the treatment of iron deficiency anaemia during pregnancy [5].

Materials and Methods
The objectives of the study were to compare the efficacy and tolerance of intravenous iron sucrose therapy with oral iron therapy in pregnant women with iron deficiency anaemia.

This study was carried out at Santosh Medical College Ghaziabad, Department of Obstetrics & Gynaecology from August 2019 to November 2019. 100 pregnant women with gestational age between 14 to 35 weeks with established iron deficiency anaemia, confirmed with Haemoglobin 6-8 g/dL and peripheral smear features suggestive of iron deficiency anaemia were included in the study. Patients with haematological disease other than iron deficiency anaemia, hypersensitivity to iron, and history of blood transfusion in this pregnancy, liver disease and anaemia in failure were excluded from study.

This study was approved by the institutional ethical committee. Patients were recruited for the study after obtaining informed consent. Patient's symptoms such as fatigability, dyspnoea, loss of appetite, loss of weight etc. were recorded. After detailed history and examination, laboratory investigations performed were haemoglobin, packed cell volume (PCV), red cell count, red cell indices, reticulocyte count and peripheral smear. Iron deficiency anaemia was confirmed by serum iron profile consisting of serum ferritin, serum iron and total iron binding capacity.

Patients fulfilling the inclusion criteria were randomised into two groups of 50 each GROUP A: Intravenous iron sucrose 200 mg in 200 ml of normal saline was given after a test dose was administered on alternate days. Minimum 200 mg/day and upto a maximum of 600 mg / week was administered. The formula used to calculate intravenous dose of iron sucrose was:

Body weight in kg x [target Hb – initial Hb] x 2.4 plus 500 mg to calculate the iron requirement of the patient to fulfil the deficit as well as to replenish the iron stores to make it to 11g/dL.

A test dose of 20 ml of iron sucrose infusion was administered and followed by a 10 minutes window period during when no infusion was given and patient was observed for anaphylactic reactions. If no reactions occurred, the rest of the infusion was administered. GROUP B: 200 mg Ferrous sulphate oral tablets, each containing 60 mg elemental iron was given thrice daily during pregnancy as per the recommendation of World Health Organisation for the treatment of iron deficiency anaemia. The target haemoglobin was 11g/dL.

Follow-up of haematological parameters like haemoglobin and PCV were done at 2nd week, 4th week and at 37 weeks of gestation. Bone marrow response after administration of the required total dose of iron needed to correct iron deficiency anaemia was interpreted by measuring reticulocyte count. Clinical improvement in symptoms was assessed. MCV and reticulocyte count were done at 2nd week in addition to haemoglobin and PCV. Pre and post treatment mean values of Haemoglobin, PCV, MCV, reticulocyte count were compared individually and between the two groups. If the patient didn't tolerate oral or intravenous iron the dose was reduced and if still intolerant they were considered as failures in the study and were treated with blood transfusion if required. Once target level was achieved patients were advised to continue on oral iron after 4 weeks of completion of intravenous iron sucrose. Gastro-intestinal side effects (nausea, vomiting, constipation, and diarrhoea), Pruritis, fever, myalgia, hypotension, local extravasation, metallic taste, anaphylactic reactions etc were noted. Statistical package for social science (SPPS- 16) was used for statistical compilation and analysis. For statistical analysis of difference between groups, independent sample-*t* test, Chi square test or analysis of covariance were applied when appropriate. Statistical significance was accepted at $P < 0.05$.

Results

54% and 38% of women were severely anaemic in iron sucrose group and oral iron group respectively. 46% of women in iron sucrose group and 62% in oral group were moderately anaemic. Mean requirement of iron in intra venous iron sucrose group was 1057 mg and in the oral iron group it was 1059 mg. The mean requirement of iron in both the groups was almost similar and the difference was not statistically significant. All the symptoms of anaemia were comparable between the 2 groups, as in Table 1 and Figure 1.

Table 1: Comparison of Iron deficiency in Iron Sucrose group (A) and Oral iron Group (B)

Anaemic status	Iron Sucrose group (A). (n=50)	Oral iron Group (B). (n=50)	Total No of cases (n=100)
Severe	27(54%)	19(38%)	46(46%)
Moderate	23(46%)	31(62%)	54(54%)
Total	50(50%)	50(50%)	100(100%)

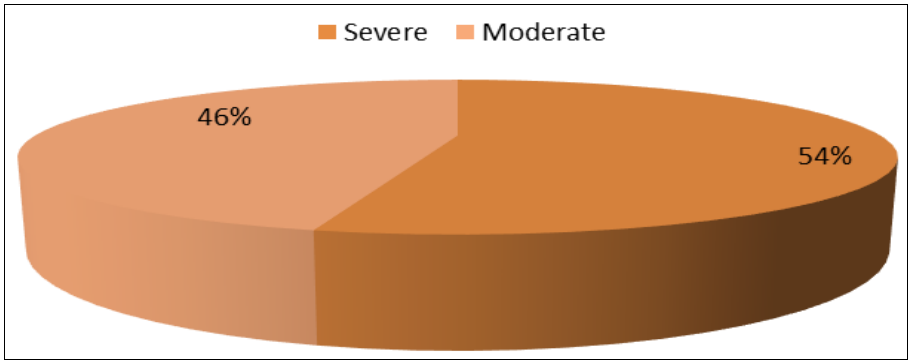

Fig 1: Iron deficiency in Iron Sucrose Group (A)and Oral iron Group (B)

Table 2: Differentiating value of, Haemoglobin (Hgb), MCV, PCV among the tested groups.

Haemoglobin Levels	Iron Sucrose group(A)	Oral iron Group(B)	P-Value
Mean Value of Haemoglobin (MVHgb)	6.89g/dL	7.16g/dL	0.039
Mean of Packed Cell Volume (PCV)	24.61%	25.52%	0.038
Mean of Mean Corpuscular Volume (MCV)	71.07fL	73.07fL	0.163
Mean Reticulocyte Count	5.08%	4.46%	0.066

The mean value of haemoglobin at recruitment was 6.89 and 7.16 g/dL in the iron sucrose and oral iron group respectively and p value was 0.039 which was statistically significant. The mean PCV at recruitment in the intra venous iron sucrose group was 24.61% and oral iron group was 25.52% at recruitment and p value was 0.038. 52% and 42% of the patients had MCV between 61-70 in iron sucrose and oral iron group respectively. The mean MCV in intra venous iron sucrose group was 71.07 fL and in the oral iron group it was 73.07 fL and the p value was0.163 which showed no statistical significance. The mean difference in haemoglobin at recruitment and at 2nd week were found to be significant statistically when compared between the 2 groups but the mean differences of MCV and PCV were not significant. The mean differences of haemoglobin and PCV between the recruitment and 4th week were found to be statistically significant. The mean differences of haemoglobin and PCV between recruitment and at term were found to be extremely significant when compared between the 2 groups. Improvement of haemoglobin in iron sucrose group was much better than that of oral iron group at 2nd week, 4th week and at term. The difference in improvement in MCV and PCV were almost similar in both the groups at 2nd week. At the 4th week and at term the improvement in PCV was much better in iron sucrose group than in oral iron group. It was seen that the mean reticulocyte count at second week in the intra venous iron sucrose group was 5.08% and that in oral iron group was 4.46% and the p-value was 0.066 which showed that the two groups had no significant difference in reticulocyte count, as in Table 2.

Gastrointestinal side effects were not seen in women on intravenous iron therapy. All Patients were compliant with intravenous iron therapy and oral iron. Forty four percent of patients in the oral iron group had gastrointestinal side effects but they were not severe enough to affect the compliance. There were no dropouts in our study. Majority of patients delivered vaginally in both the groups. Only 2 patients in intra venous iron sucrose group and 3 women in oral iron Group were delivered by caesarean section for obstetric indications.

Discussion

In this study, the efficacy, safety and tolerability of IVIS in treating pregnancy IDA was compared with OI therapy. IVIS is safe in pregnancy. It corrects anemia at short duration and replenishes iron stores better than OI. This has been the observation in other studies too [6, 7, 8]. Comparison with other studies is difficult because of different cut-offs used for lab parameters. OI preparations used are also different. As the rate of increase in hemoglobin is faster, IVIS is suitable for treatment of IDA with lower hemoglobin in the third trimester.

Although oral iron supplementation is widely used for the treatment of IDA, not all patients respond adequately to oral iron therapy. Previously, the use of intravenous iron had been associated with undesirable and sometimes serious side effects and therefore is underutilised. However, in recent years, new type II and III iron complexes have been developed, which offer better compliance and toleration as well as high efficacy with a good safety profile [9].

There are few studies comparing intravenous iron sucrose versus oral iron iron for the treatment of iron deficiency anaemia in pregnancy. Mean age at recruitment in the present study is similar to other studies. There was no significant difference in the parity between the 2 groups which was in contrast to a study by Ragip *et al*. [10] in which most of the patients i.e. 62% in the iron sucrose group and 42% in the oral iron group were primigravidas. The mean gestational age at recruitment was 30-34 weeks in our study which is in contrast to other studies which had recruited women at 25-26 weeks of gestation. The mean weight of women in our study was lesser than other data When analyzed across time it was found that intravenously administered iron sucrose was significantly more likely to have higher haemoglobin from baseline than those patients with orally administered iron at every point at measurement (at 2nd week, 4th week and at term) during the course of the study similar to other studies [11]. This is in contrast to other data which reported comparable success with both oral and intravenous iron therapy in elevating haemoglobin. There were no serious adverse drug reactions and mild problems such as gastrointestinal symptoms in the oral iron group were seen in our study similar to other studies. Poor compliance of upto 30% has been reported. The incidence of low birth weight babies overall is similar to other studies although was no significant difference between the two groups which is in agreement with previous data [12]. A mean higher birth weight of 250 g was noted in the intravenous group in one small study. Iron sucrose seems to improve haemoglobin faster than oral iron therapy. But there are disdavantages of intravenous iron therapy such as increased cost, need for hospitalisation and the invasive nature of the procedure. However it may be considered as an alternative to oral iron to treat iron deficiency anaemia in the early third trimester especially when there is poor compliance or the patient is not able to tolerate oral iron treatment. A drawback of our study is that serum ferritin levels were not measured.

There has been a recent interest in the use of ferric carboxymaltose, a new intravenous iron formulation promising to be more effective [10]. It has been shown to have improved efficacy and iron stores when compared to oral iron and iron sucrose. Ferric carboxymaltose administration in pregnant women appears to be well tolerated and has a comparable safety profile to iron sucrose but offers the advantage of a much higher iron dosage at a time reducing the need for repeated applications and increasing patients comfort. Three-year follow-up of a randomised clinical trial of intravenous versus oral iron for anaemia in pregnancy showed that repletion of their iron stores during pregnancy improves health related quality of life after delivery. Though the evidence of the efficacy of iron sucrose in improving haemoglobin and serum ferritin is convincing, its effect on maternal and fetal outcomes are unclear. This is primarily due to lack of well-designed and larger studies powered to detect difference in clinical outcomes. Hence, there is a need to gather evidence from a well-designed large randomised clinical trial.

Conclusion

The present study revealed that intravenous iron sucrose therapy was better tolerated with higher increase in mean haemoglobin and PCV when compared to oral iron therapy. There were no serious side effects with intravenous iron sucrose therapy. Intravenous iron sucrose is a good substitute to oral iron therapy in moderate to severe anaemia.

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