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Original Research Article

A randomized comparison between intravenous iron sucrose and oral iron in treatment of iron deficiency anemia in pregnancy at a rural health training centre of a teaching medical institution

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ABSTRACT

Background: Iron deficiency is a leading cause of anemia in pregnancy. 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 anemia. The aim of this study was to compare the efficacy and safety of intravenous iron sucrose and oral iron administration for the treatment of iron deficiency anaemia in pregnancy.
Methods: Hundred women with gestational age between 30 and 34 weeks with established iron deficiency anaemia with hemoglobin between 6-8g/dL were randomized to receive either oral ferrous sulphate 200 mg thrice daily or required dose of intravenous iron sucrose 200 mg in 200 ml NS on alternate days. Hemoglobin was measured at recruitment and on 2nd week, 4th week and at 37 weeks. Adverse drug reactions were also noted in both the groups. Results were analyzed by student's t-test and Chi-square test.
Results: Haemoglobin values varied significantly with time between the two groups at second week, 4th week and at term ($p<0.005$). When compared to iron sucrose group, the oral iron group had significant gastro-intestinal adverse effects.
Conclusions: Intravenous iron sucrose treated iron deficiency anaemia of pregnancy faster, and more effectively than oral iron therapy, with no serious adverse drug reactions.

Keywords: Iron deficiency anaemia, Iron sucrose, Oral iron therapy

INTRODUCTION

Nutritional iron deficiency is the most common deficiency disorder in the world, affecting more than one billion people, with pregnant women at particular risk.[1-3] World Health Organization (WHO) data show that iron deficiency anaemia (IDA) in pregnancy is a significant problem throughout the world with a prevalence ranging from 15% of pregnant women in industrialized countries to an average of 56% in developing countries (range 35-75%).[1,2] Iron deficiency anaemia has varied consequences on both maternal and fetal outcome. Maternal consequences include cardiovascular symptoms, reduced physical and mental performance, increased risk of infection, preeclampsia, postpartum haemorrhage, blood transfusions etc.

Although iron supplementation during pregnancy is one of the most widely practiced public health measures, there remain many controversial issues with this practice.[4-8] Pregnant women do not always respond adequately to oral iron therapy due to difficulties associated with ingestion of the tablets and their side effects, thereby contributing to reduced rates of compliance.[4,5] The use of injected iron has

been associated with undesirable and sometimes serious side-effects and was previously limited in clinical use.[9,10] In recent years, type II iron complexes have been developed which are better tolerated and can be used for a rapid reversal of iron deficiency anaemia.[9,10] The provision of iron supplements to pregnant women is one of the most widely practiced public health measures. The traditional treatment of iron deficiency anaemia includes oral/ parenteral iron and blood transfusion. Oral iron is associated with side effects, non-compliance and takes a long time to correct anaemia. Parenteral preparations like iron dextran, iron sorbitol is associated with anaphylactic reactions and blood transfusions are associated with cross reactions and viral infections.

The present study aimed to compare the efficacy and tolerance of oral iron therapy and intravenous iron therapy in improving iron deficiency anemia in pregnancy and evaluate the safety of intravenous iron sucrose.

METHODS

The present study is a randomized prospective study carried out in the Department of Community Medicine at the Rural Health Training Centre of Lokmanya Tilak Municipal Medical College and General Hospital, Sion, Mumbai, Maharashtra, India after approval by the institutional ethical committee conducted for a period of 6 months from November 2021 to April 2022.

For Sample size estimation, the need for 40 completed patients per treatment group were calculated based on assumptions: i) a minimum effect size detection of 4.5 g/L increase in Hb in the IV group compared to the oral only group, ii) an untreated change in Hb with SD 7 g/L and, iii) alpha value of 0.05 and power of 80%. The total numbers of patients required to demonstrate this difference would be at least 100.[11] Therefore, 100 pregnant women with gestational age between 30 to 34 weeks with established iron deficiency anaemia, confirmed with Hb 6-8 g/dL and peripheral smear features suggestive of iron deficiency anaemia were included in the study.

Patients with the following criteria were excluded from the study namely haematological disease other than iron deficiency anaemia, hypersensitivity to iron, history of blood transfusion in this pregnancy, liver disease and anaemia in failure. Patients were recruited for the study after obtaining informed consent. A detailed history was taken, including socioeconomic and dietary history, and a general physical, systemic and obstetric examination was done. Patient symptoms such as fatigability, dyspnoea, loss of appetite, loss of weight etc. were recorded. Detailed clinical examination was done and Laboratory investigations i.e., haemoglobin (Hb) was carried out prior to enrolment.

Patients fulfilling the inclusion criteria were randomised into two groups of 50 each using computer generated random number table viz. GROUP A: Intravenous iron sucrose 200 mg in 200 ml of normal saline/day after a test dose was administered on alternate days. Minimum 200 mg/day and upto a maximum of 600 mg/week was administered. The following formula was used =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 11 g/dL. A test dose of 25 ml of iron sucrose infusion was administered and followed by a 15 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 11 g/dL. Follow-up of haematological parameters like haemoglobin was done at 2nd week, 4th week and at 37 weeks of gestation. Clinical improvement in symptoms was assessed. Pre and post treatment mean values of Haemoglobin 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. 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 analysis

Statistical analysis was carried out using unpaired t-test to compare non-nominal parameters (haemoglobin, MCV, PCV, reticulocyte count) between the two groups, for binominal variables (side effects) Chi-square test was used and P-value<0.05 was considered statistically significant.

RESULTS

Baseline characteristics are summarized in (Table 1). Baseline demographic characteristics of age, maternal weight, gestational age at booking and number of previous live births were similar in each treatment groups. 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. 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. Haemoglobin levels at recruitment, 2nd and 4th week and at term are summarized in (Tables 2, 3). The mean

difference in haemoglobin at recruitment and at 2nd week were found to be significant statistically when compared between the 2 groups. The mean differences of haemoglobin levels between the recruitment and 4th week were found to be statistically significant. Improvement of haemoglobin in iron sucrose group was much better than that of oral iron group at 2nd week, 4th week and at term.

Table 1: Baseline characteristics of pregnant women.

Characteristics	Iron sucrose (n=50) %	Oral iron (n=50) %
Age (20-29 years)	90	92
Low socio-economic status	82	86
Gestational age at recruitment (30-34 weeks)	78	74
Weight (kg) 50-52	56	50

Table 2: Measurement of haematological parameters.

Haematological parameter		At recruitment		At 2nd week		At 4th week		At term	
		Iron sucrose	Oral iron	Iron sucrose	Oral iron	Iron sucrose	Oral iron	Iron sucrose	Oral iron
Hb (g/dl)	Mean ± SD	6.89±0.6	7.16±0.6	8.15±0.6	8.22±0.7	9.48±0.7	9.15±0.7	10.84±0.9	10.09±0.7
	p-value	0.039*		0.625		0.024*		<0.001**	

*Statistically significant; ** statistically very significant.

Table 3: Differences in haemoglobin levels according to baseline values during study period.

Week	Haemoglobin levels	Group	Mean difference	SD	p-value
2nd week	Rec# Hb - 2nd week Hb	Iron sucrose	1.266	0.431	0.026*
		Oral iron	1.068	0.447	
4th week	Rec# Hb - 4th week Hb	Iron sucrose	2.594	0.718	<0.001**
		Oral iron	1.992	0.676	
Term	Rec# Hb - term Hb	Iron sucrose	3.954	0.563	<0.001**
		Oral iron	2.930	0.565	

Rec#- Recruitment; *Statistically significant; **Very significant.

Table 4: Comparison of side-effect profile between iron sucrose and oral iron.

Side-effects	Iron sucrose (n=50) %	Oral iron (n=50) %	p-value
Nausea	0	4 (8%)	0.045*
Vomiting	0	3 (6%)	0.083
Dyspepsia	0	6 (12%)	0.014*
Constipation	0	1 (2%)	0.317
Diarrhoea	0	2 (4%)	0.157
Metallic taste	0	5 (10%)	0.025*
Myalgia	1 (2%)	0	0.317
Pruritus	1 (2%)	0	0.317

* Statistically significant; ** statistically very significant.

Side effects are summarized in (Table 4). Gastrointestinal side effects were not seen in women on intravenous iron therapy. All Patients were compliant with intravenous iron therapy and oral iron. Fourty 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 3 patients in intra venous iron sucrose group and 4 women in oral iron Group were delivered by caesarean section for obstetric indications. 56% and 42% of babies in intra venous iron sucrose group and oral iron group had birth weight between 2.5-3.5 kg respectively. There was no significant difference between the birth weights in both the groups.

DISCUSSION

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 underutilized. 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. There are few studies comparing intravenous iron sucrose versus oral iron iron for the treatment of iron deficiency anaemia in pregnancy.[7-10,12] 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., in which most of the patients i.e. 62% in the iron sucrose group and 42% in the oral iron group were primigravidas.[8]

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.[7,8] The mean weight of women in our study was lesser than other data 7,8 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.[7-9,11] This is in contrast to other data which reported comparable success with both oral and intravenous iron therapy in elevating haemoglobin.[8,10] 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.[7-10,12] Poor compliance of upto 30% has been reported.[7] 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.[8,2-15] A mean higher birth weight of 250 g was noted in the intravenous group in one small study.[9] Iron sucrose seems to improve haemoglobin faster than oral iron therapy16. But there are disadvantages of intravenous iron therapy such as increased cost, need for hospitalization 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 iron sucrose, a new intravenous iron formulation promising to be more effective. Iron sucrose administration in pregnant women appears to be well tolerated and has a comparable safety profile to other intravenous iron compounds but offers the advantage of a much higher iron dosage at a time reducing the need for repeated applications and increasing patient's comfort. Three-year follow-up of a randomized 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.[17] 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 randomized clinical trial.[18]

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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