

# Intravenous Iron Sucrose and Oral Iron for the Treatment of Iron Deficiency Anaemia in Pregnancy

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## ABSTRACT

**Purpose:** 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.

**Materials and Methods:** Hundred women with gestational age between 30 and 34 weeks with established iron deficiency anaemia with Haemoglobin-6-8g/dL were randomised 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. Haemoglobin, haematocrit, mean corpuscular volume, reticulocyte count were measured at recruitment and on 2<sup>nd</sup> week, 4<sup>th</sup> 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, 4<sup>th</sup> week and at term ( $p < 0.005$ ). The mean difference in mean corpuscular volume from the recruitment value was not significant at 2<sup>nd</sup> week. 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:** Iron deficiency anaemia, Iron sucrose, Oral iron therapy

## INTRODUCTION

Anaemia is estimated to affect 20-50% of the world's population and pregnancy [1,2] is one of the most important risk factors. The Centre for Disease Control and Prevention defines anaemia when haemoglobin and haematocrit values are less than 11g/dL and 33% in the first and third trimester and 10.5 g/dL and 32% in the second trimester. Estimates of the world-wide prevalence of iron deficiency anaemia in pregnancy are much higher than estimates in the developed world, due to malnutrition and lack of pre-natal iron supplement programmes in underdeveloped countries [3]. More than two third of pregnant women in the developing countries are affected from anaemia of which 95% is due to iron deficiency [4]. Iron deficiency anaemia has varied consequences on both maternal and fetal outcome [5]. Maternal consequences include cardiovascular symptoms, reduced physical and mental performance, increased risk of infection, preeclampsia, postpartum haemorrhage, blood transfusions etc. Anaemia is responsible for 40-60% of maternal deaths in non-industrialised countries. Fetal consequences are increased risk of growth retardation, prematurity, intra-uterine death, prelabour rupture of membranes and infection [4].

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 are associated with anaphylactic reactions and blood transfusions are associated with cross reactions and viral infections.

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 [5]. Very few studies have been designed to measure with reasonable precision the rates with which these iron preparations can correct iron deficiency anaemia [6]. 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 in pregnancy.

## MATERIALS AND METHODS

This study was carried out at JIPMER in the Department of Obstetrics and Gynaecology from August 2009 to July 2011. 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.

This study was approved by the institutional ethical committee and with the Helsinki declaration of 1975 (revised in 2000). Patients were recruited for the study after obtaining informed consent. Patients symptoms such as fatigability, dyspnoea, loss of appetite, loss of weight etc were recorded. Detailed clinical examination was done and Laboratory investigations (haemoglobin (Hb), packed cell volume (PCV), mean corpuscular volume (MCV) and peripheral smear, urine routine and culture and sensitivity, stool for ova/ cyst) were carried out prior to enrollment.

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 fulfill the deficit as well as to replenish the iron stores to make it to 11g/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 11g/dL.

Follow-up of haematological parameters like haemoglobin and PCV were done at 2<sup>nd</sup> week, 4<sup>th</sup> 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 2<sup>nd</sup> 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. 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 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/Fig-1]. 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. 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

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

[Table/Fig-1]: Baseline characteristics

Hematological Parameters		At Recruitment		At 2 <sup>nd</sup> Week		At 4 <sup>th</sup> 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**	
PCV%	Mean±SD	24.61+2.3	25.52+2.0	28.70+2.4	28.88+2.6	32.55+2.9	32.17+2.6	36.28+2.7	35.56+2.4
	p-value	0.038*		0.726		0.504		0.180	
MCV(Fl)	Mean±SD	71.07+7.8	73.07+6.3	83.32+6.3	84.09+6.5	-	-	-	-
	p-value	0.163		0.553		-		1	

[Table/Fig-2]: Hematological parameters measured serially. \* statistically significant \*\* statistically very significant

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 was 0.163 which showed no statistical significance [Table/Fig-2].

Haemoglobin levels, MCV and PCV at recruitment, 2<sup>nd</sup> and 4<sup>th</sup> week and at term are summarised in [Tables/Fig-2,3]. The mean difference in haemoglobin at recruitment and at 2<sup>nd</sup> 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 4<sup>th</sup> 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 2<sup>nd</sup> week, 4<sup>th</sup> week and at term. The difference in improvement in MCV and PCV were almost similar in both the groups at 2<sup>nd</sup> week. At the 4<sup>th</sup> 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.

Side effects are summarised in [Table/Fig-4]. 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 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 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.

There are few studies comparing intravenous iron sucrose versus oral iron iron for the treatment of iron deficiency anaemia in pregnancy [7-11]. 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., [8] 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 [7,8] which had recruited

Week	Mean Difference	Group	Mean Difference	SD	p-value
2 <sup>nd</sup> Week	Rec <sup>#</sup> Hb-2 <sup>nd</sup> week Hb	Iron Sucrose	1.266	0.431	0.026*
		Oral Iron	1.068	0.447	
	Rec PCV-2 <sup>nd</sup> Week PCV	Iron Sucrose	4.090	1.985	0.051
		Oral Iron	3.356	1.718	
	Rec MCV-2 <sup>nd</sup> week MCV	Iron Sucrose	12.25	6.821	0.317
		Oral Iron	11.02	5.381	
4 <sup>th</sup> Week	Rec Hb-4 <sup>th</sup> Week Hb	Iron Sucrose	2.594	0.718	<0.001**
		Oral Iron	1.992	0.676	
	Rec PCV-4 <sup>th</sup> Week PCV	Iron Sucrose	7.938	3.334	0.026*
		Oral Iron	6.644	2.300	
Term	Rec Hb-Term Hb	Iron Sucrose	3.954	0.563	<0.001**
		Oral Iron	2.930	0.565	
	Rec PCV-Term PCV	Iron Sucrose	11.666	2.470	<0.001**
		Oral Iron	10.040	1.685	

**[Table/Fig-3]:** Differences in hematological parameters according to baseline values during the study period  
<sup>#</sup>Rec-recruitment \* statistically significant \*\* statistically very significant

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
Pruritis	1(2%)	0	0.317

**[Table/Fig-4]:** Comparison of side effect profile between iron sucrose and oral iron group. \*significant

women at 25-26 weeks of gestation. 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 2<sup>nd</sup> week, 4<sup>th</sup> week and at term) during the course of the study similar to other studies [7,8,9,11]. This is in contrast to other data [8,10] 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 [7-11]. Poor compliance of upto 30% has been reported [7].

The incidence of low birth weight babies overall is similar to other studies [12-14] although was no significant difference between the two groups which is in agreement with previous data [8,11]. 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 therapy [15]. But there are disadvantages 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. It has been shown to have improved efficacy and iron stores when compared to oral iron [16] and iron sucrose [17]. 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 [18] 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 [19].

## 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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