

Original article:

A study on efficacy, safety & compliance of oral iron in comparison with intravenous iron sucrose in pregnancy

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ABSTRACT

Introduction: The aim of this study was to compare efficacy, safety & compliance of oral iron and intravenous iron sucrose in the treatment of iron deficiency anemia in pregnancy.

Methods: A randomized interventional study was conducted at NIMS medical college involving 140 pregnant women with iron deficiency anemia between 14 to 34 weeks. In the intravenous group calculated dose of iron sucrose infused. Target Hb was 12 g/dL. In oral group patients received 200 mg oral ferrous ascorbate daily. Haemoglobin and serum ferritin were reviewed at 4 & 6 weeks.

Results: The change in haemoglobin and ferritin levels from baseline was statistically higher in the intravenous group than the oral group at each measurement.

Conclusion: Intravenous iron sucrose elevates Hb & ferritin concentration faster than oral iron supplementations with no serious side effects.

Keywords: ferrous ascorbate , intravenous iron sucrose , iron deficiency anaemia

Introduction:

Anemia (defined by the World Health Organization as hemoglobin levels of ≤ 11 g/dl) is one of the world's leading causes of disability.¹ It is one of the most prevalent nutritional deficiency problems affecting pregnant women.² The high prevalence of iron and other micronutrient deficiencies among women during pregnancy in developing countries is of concern and maternal anemia is still a cause of considerable perinatal morbidity and mortality.³ About 70% of the pregnant women in South East Asian Region suffer from nutritional anemia which is mainly caused by Iron deficiency anemia.⁴ According to WHO-5,00,000 maternal deaths/yr and

20,000,000 morbidity cases are attributed to iron deficiency anemia and other anemia.⁵ The prevalence of Iron deficiency anemia in pregnancy in developing world is 56% (range 35-75%) and 18% in developed countries⁶. Whereas prevalence of anemia in low socio-economic group in first, second and third trimester is 9%, 14% and 37% respectively.⁷ Iron deficiency anemia (IDA) remains the commonest medical disorder in pregnancy in the developing world⁸⁻¹², Anemia is estimated to contribute to 20 percent of all maternal deaths and nine times higher risk of perinatal mortality¹³

In normal pregnancy there is 18% increase in red blood cells and 40-45% increase in plasma

volume. Because of this disproportionate increase in plasma volume, there is physiological hemodilution. Oral iron supplementation is usually enough for most of the antenatal women. But intolerance to iron, abnormalities in absorption and non-compliance may make oral iron therapy in some women inadequate and these can be benefited from parenteral iron therapy. Iron sucrose is a suitable alternative source of iron; It can be administered by intravenous infusion. It is well tolerated and safe but may cause hypotension, nausea and low back pain.^{14,15} Iron deficiency in pregnancy has varied adverse consequences on both the mother and fetus. Apart from anemia, iron deficiency is also associated with preterm labor (28.2%), pre-eclampsia (31%), sepsis, hemorrhage and low birth weight delivery¹⁶. It is also postulated that the pregnant women with iron deficiency anemia (IDA) may give birth to infants with low iron stores, which may result in abnormal child development (physical and cognitive), if the deficiencies are not corrected early.¹⁷ The aim of this study was to compare efficacy, safety and compliance of intravenous Iron sucrose compared to oral ferrous ascorbate in the treatment of iron deficiency anemia in pregnancy.

Material and method:

This randomized study (interventional study) was conducted in Department of Obstetrics and Gynaecology, National Institute Of Medical Sciences, Shobhanagar Jaipur (Rajasthan), after approval from the hospital ethical committee, over a period of 12 months (July 2012 to June 2013). 140 pregnant patients with singleton pregnancy attended the antenatal clinic of NIMS medical college who had Hb concentration 7 gm/dL to 10 gm/dL, had gestational age 14-34 weeks and proven iron

deficiency anemia. (MCV <50 fl and ferritin level <50 microgm/l) were included in the study. Anemia not attributed to iron deficiency, first trimester pregnancy, Any medical disorder complicating the pregnancy like tuberculosis, diabetes, asthma, cirrhosis, hepatitis, HIV, any obstetrical complicating factors like PIH, APH etc., patient with multiple pregnancy, acute or chronic infections, iron overload or disturbance in utilization of iron, known hypersensitivity to iron sucrose were excluded from the study.

All selected women and their attendants were explained regarding the procedure and their written informed consent was taken. All 140 patients were randomly assigned to either intravenous or oral group. 70 patients were in intravenous group and 70 patients in oral group. All women selected were clinically evaluated by a detailed history and a proper general, systemic and obstetric examination. Patients Hb estimation was done followed by peripheral smear examination, PCV, red cell count and iron deficiency anemia was confirmed by serum iron profile consisting of serum ferritin, serum iron and total iron binding capacity.

In the intravenous group, the total iron dose in mg was calculated from the following formula:

$$2.4 \times \text{weight} \times (\text{target} - \text{actual Hb}) \text{ in g/dl} + 500 \text{ mg}$$

Rounded up to nearest multiple of 100.

In the formula since the patient's pre pregnancy weight was not known, the weight at the time of the first visit was considered in kilograms. Target hemoglobin in g/dl was set at 12 g/dl.

In each infusion the maximum total dose administered was 200 mg elemental iron in 100 ml of normal saline infused over 20-30 min, given on alternate days. Each ampule was of 2.5 ml containing

50 mg of elemental iron .The ampoules were diluted with normal saline immediately before the infusion. Treatment was completed after administration of the calculated dose. Additional iron was not administered during the study.Iron sucrose is a complex of poly nuclear iron (III) hydroxide in sucrose for intravenous use .The complex is stable and does not release ionic iron under physiological conditions. Following intravenous administration , iron sucrose is dissociated by the reticuloendothelial system into iron and sucrose.Iron sucrose can be administered as intravenous injection or infusion .Iron sucrose does not contain dextran hence chances of anaphylaxis are negligible .¹⁸⁻²⁰

In the oral group , women were instructed to take two tablets (ferrous ascorbate with 100 mg of elemental iron per day with 1.1 mg of folic acid)twice daily throughout the pregnancy. Women were instructed to take the tablets on an empty stomach either 2 h before or after their meals. Ferrous ascorbate iron salt was chosen because it prevents the formation of insoluble and unabsorbable iron compounds and it causes reduction of ferric to ferrous iron which seems to be a requirement for

uptake of iron into duodenum and proximal mucosal cells of small intestine. The effect of iron absorption inhibitors which would normally bind to iron in the more alkaline pH of upper intestine is limited.²¹ Oral ferrous ascorbate has highest bioavailability in the range of 26.4-50.4 % and it acts as an antioxidant. Patients were called after 2 weeks and 1 month for repeat hemoglobin and ferritin level was assessed for improvement i.e. efficacy of the drug.

Data was analyzed using appropriate Statistical methods.

Sample Size:

Sample size was calculated at 80% study power and alpha level of 0.05 assuming standard deviation of 1(g/dl) in serum hemoglobin level over 4 weeks as per study of Shafi Deeba et al (The Journal of Obstetrics and Gynecology of India (May-June 2012) 62(3):317-321 DOI 10. 1007is 13224-012-0222-0)

For minimum detectable difference of 0.05(g/dl) in serum hemoglobin level over 4 weeks, 64 cases were required in each group which were further enhanced and rounded off to 70 cases in each group as final sample size assuming 10% drop-out/attrition/lost to follow-up

Results:

1. Actual hemoglobin levels over 4 & 6 weeks

Group	Hb _{baseline} (g/dl)	Hb _{4 weeks} (g/dl)	Hb _{6 weeks} (g/dl)
Intravenous	7.74±0.87	9.44±0.72	10.66±0.82
Oral	7.52±0.65	8.94±0.91	10.03±0.98
'p' value*	0.092	<0.001	<0.001

* Unpaired t-test

2. Serum hemoglobin levels difference from baseline

Hemoglobin levels difference from baseline	Intravenous (g/dl)	Oral (g/dl)	'p' value*
Fe _{4 weeks} - Fe _{baseline}	1.70±0.66	1.42±0.89	0.036
Fe _{6 weeks} - Fe _{baseline}	2.92±0.72	2.51±0.94	0.004

* Unpaired t-test

3. Actual ferritin levels over 4 & 6 weeks

Group	Fe _{baseline} (ng/ml)	Fe _{4 weeks} (ng/ml)	Fe _{6 weeks} (ng/ml)
Intravenous	9.25±1.34	65.24±21.08	91.08±19.54
Oral	8.82±1.52	28.62±9.71	38.52±8.92
'p' value*	0.078	<0.001	<0.001

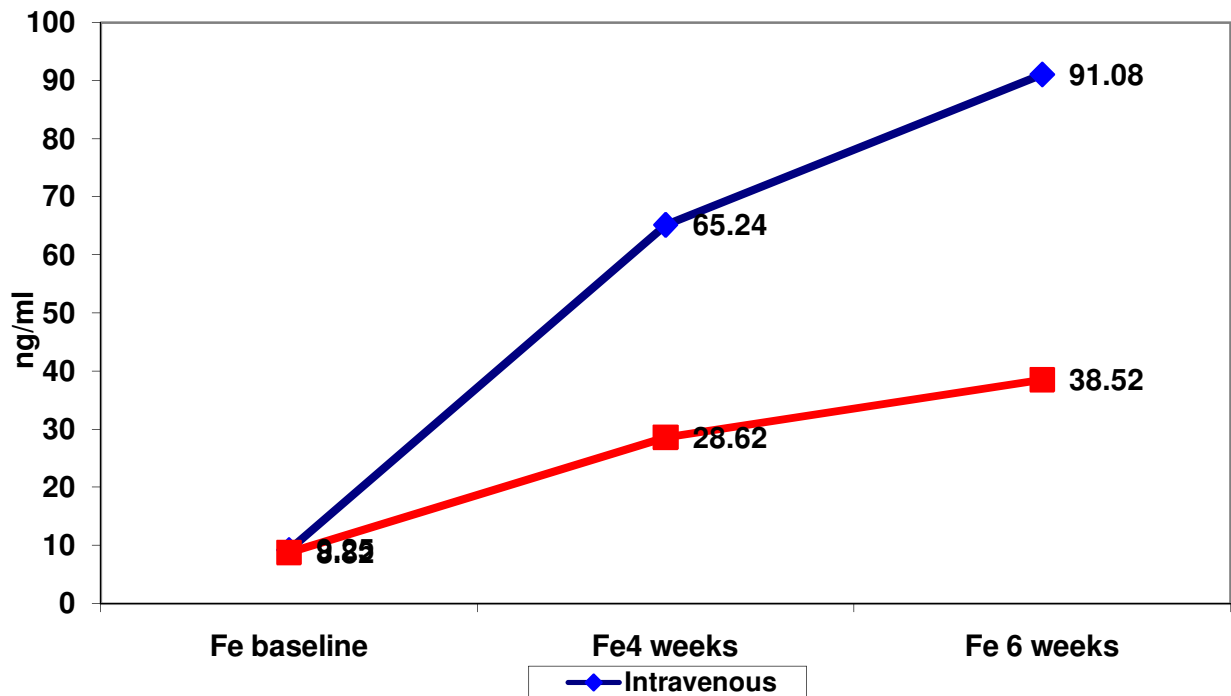
* Unpaired t-test

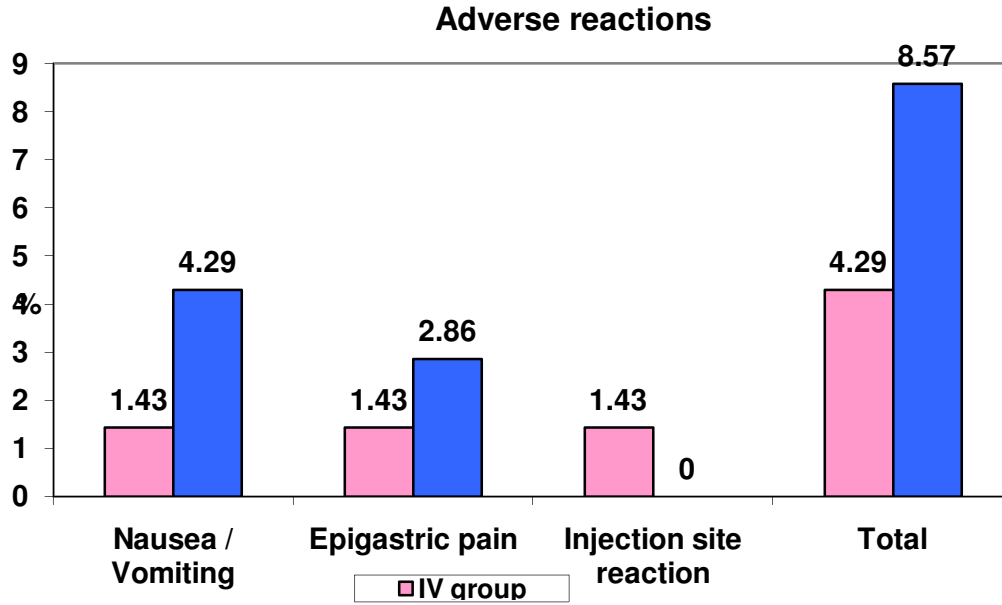
4. Serum ferritin levels difference from baseline

Serum ferritin levels difference from baseline	Intravenous (ng/ml)	Oral (ng/ml)	'p' value*
Fe _{4 weeks} - Fe _{baseline}	55.99±18.82	19.80±8.29	<0.001
Fe _{6weeks} - Fe _{baseline}	81.83±19.24	29.70±8.34	<0.001

* Unpaired t-test

Actual ferritin levels over 4 & 6 weeks





Discussion:

The study confirmed that parenterally administered iron sucrose elevated hemoglobin and restored iron stores better than oral ferrous ascorbate. It is paradoxical that while iron is one of the least expensive and most readily available medicinal substance, its deficiency particularly in the female population still presents serious problems. Patients often present themselves with severe anemia in pregnancy, this is particularly a problem in the developing countries where nutrition, mass education and availability of blood are far from satisfactory²². Low availability and poor absorption of iron and repeated and closely spaced pregnancies place a constant drain on the iron stores of pregnant women resulting in the development of IDA²³

Al Momen *et al.*, observed that the IVIS group achieved significantly higher hemoglobin level (P value ≤ 0.001) in a shorter period (P value ≤ 0.001)²⁴ In a study done by Al *et al.*, hemoglobin was different for patients in the OI and IVIS groups across time in each individual group as well as at any

given point of time. The hemoglobin level was significantly higher in the IVIS group.²⁵

Oral iron therapy is the most widely prescribed treatment for iron deficiency anaemia; however, there are many issues that may prevent oral iron supplementation from successfully managing iron deficiency anaemia. For instance, many patients do not respond adequately to oral iron therapy due to difficulties associated with ingestion of the tablets and their side effects. Side effects may play a significant role in rates of compliance.^{26,27} Furthermore, the presence of bowel disease may affect the absorption of iron and thereby minimize the benefit received from oral iron therapy.²⁸ In the past, intravenous iron had been associated with undesirable and sometimes serious side effects and was therefore limited in use.²⁹ However, in recent years, new type II and III iron complexes have been developed which are better tolerated and can be used for rapid repletion of iron stores.³⁰⁻³² Despite the increasing evidence of the safety of the newer preparations, both in pregnant and general populations, intravenous iron continues to be

underutilised because of previous concerns with tolerability of older intravenous iron preparations.^{33,34}

Iron sucrose was well tolerated with no serious adverse effects. It has a lower incidence of adverse allergic reactions, and death from anaphylactic events has not been reported yet.³⁵ Most of the symptoms in the present study were mild, and no patient discontinued the medication. Major disadvantages of intravenous treatments are cost, need for hospitalization or an outpatient setting, and the invasive nature of the procedure. However, it may be considered an alternative to oral iron in the treatment of pregnant women with severe iron deficiency anemia during the third trimester. In daily practice physicians often face poor compliance with oral therapy because of digestive side effects which can lead to worsening of anaemia. In these cases parenteral forms of administration are indicated as well as in those patients in whom oral treatment is ineffective,³⁶ like in those suffering from inflammatory bowel disease many of whom are iron deficient and show digestive intolerance to ferrous salt.³⁷ Intravenous iron therapy was found safe, convenient and more effective than intramuscular iron therapy in treatment of iron deficiency anaemia during pregnancy by Wali et al.³⁸ Oral iron supplementation is well established, effective and worldwide accepted mode of treatment in IDA. There are very few indications for blood transfusion or parenteral iron therapy. Various forms of oral iron preparations are available.^{39,40} However, patients do not always respond adequately to oral iron therapy because of non compliance due to side effects and prolonged duration of treatment.⁴¹ Duration of

treatment which plays an important role in compliance. Usually recommended period with oral treatment ranges from 3-6 months.³⁹ This is an important factor especially in our society where poverty, lack of education, long distances from health facility and false satisfaction with partial treatment compound the problems of compliance. In the present study we have tried parenteral (intramuscular iron sorbitol) route for iron supplementation. We observed very rapid and definitive rise in Hb% in very short time and target Hb% was achieved within 2 weeks only. . In our study however compliance of oral ferrous group and parenteral IS group is comparable.

Conclusion:

Iron sucrose is an effective alternative to oral ferrous ascorbate in the treatment of iron deficiency anemia of pregnancy. Intravenous iron sucrose produces a more rapid increase in hemoglobin concentration and serum ferritin levels than oral ferrous ascorbate. This study confirms that intravenous iron caused a rapid and effective improvement in the hematological parameters when compared to oral iron . In our country , with a higher incidence of iron deficiency anemia in pregnancy, specially in a rural scenario , this type of treatment may be helpful in management of these patients in a cost-effective manner. Normally blood transfusion is an option in the cases of moderate and severe anemia in the third trimester of pregnancy. The given Iron sucrose intravenously may reduce the need for blood transfusion because of its faster action . Therefore , it can be considered as an alternative to blood transfusion in the treatment of pregnant women with moderate iron deficiency anemia during the third trimester.

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