

Research Article**Safety and Efficacy of High Dose Intravenous Iron Sucrose for Treating Anaemia in Pregnancy****Prasanna B¹, Naimisha M², Jhansi Ch B³, Mahaboob V Shaik^{4*}**¹Professor, Department of Obstetrics and Gynaecology, Narayana Medical College and Hospital, Nellore, Andhra Pradesh-524003, India²PG student, Department of Obstetrics and Gynaecology, Narayana Medical College and Hospital, Nellore, Andhra Pradesh-524003, India³PG student, Department of Obstetrics and Gynaecology, Narayana Medical College and Hospital, Nellore, Andhra Pradesh-524003, India⁴Scientist, Department of A.R.C, Narayana Medical College, Nellore, Andhra Pradesh-524003, India***Corresponding author**

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Abstract: Iron deficiency anaemia is the most common deficiency in women of child bearing age throughout the world and is even more common in pregnancy, as it might be expected from the increasing iron requirement. Approximately 95% cases of anaemia in pregnancy involve iron deficiency, which has deleterious effects and increases morbidity and mortality in mother as well as in the fetus. The aim of the study was to compare the safety and efficacy of high dose intravenous iron sucrose (500mg) to multiple dose intravenous iron sucrose (200mg) in treatment of anaemia in pregnancy. A prospective study was conducted in the department of Obstetrics and Gynaecology, Narayana Medical College and Hospital, Nellore. Sixty pregnant women with Hb between 6-9 gm/dl attending antenatal clinic were recruited for the study after the cause of anaemia has been evaluated by appropriate laboratory investigations. These women were divided into 2 groups, group A (30 pregnant women) were treated with high dose intravenous iron sucrose therapy (500mg) and group B (30 pregnant women) were treated with multiple intravenous iron sucrose therapy after calculating the total dose requirement. The mean haemoglobin in group A and group B raised from 6.89±0.55 to 10.53±0.79 and 6.88±0.38 to 10.61±0.71 respectively 4 weeks after treatment. There was significant rise seen in haemoglobin and reticulocyte count in both the groups. Increased tolerable side effects were seen in group A when compared to group B (40% vs 23%) and increased patient's satisfaction was seen in group A when compared to group B. Two to three hospital visits are required in group A and 6-8 visits in group B patients depending on the total dose requirement. High dose intravenous iron sucrose therapy for treatment of anaemia in pregnancy showed similar results to multiple dose intravenous iron sucrose therapy, thereby proving time saving, cost effective for the patients and decreasing the need for transfusion of blood and blood products.**Keywords:** Anaemia, Iron Sucrose, Pregnancy, Haemoglobin

INTRODUCTION

Iron deficiency anaemia (IDA) is the commonest medical disorder affecting around 87% of pregnant women in developing countries like India. With a rapidly growing economy and having established herself as a leader in information, it is surprising that India continues to report one of the highest maternal mortality figures in the world, lagging behind Sri Lanka and Botswana. Postpartum haemorrhage (PPH) is a major contributor to the high maternal mortality, estimated as contributing up to 25-30% to the figure of 401 per 100,000 live births in India. Anaemia is implicated as the direct contributor in 20% of cases [1].

Therefore anaemia is a major cause for maternal morbidity and perinatal mortality.

WHO (1972) [2] defines anaemia as Hb less than 11 g/dl during pregnancy and less than 10g/dl in the puerperium, according to US CDC(1989) as Hb less than 11g/dl during 1st and 3rd trimesters and less than 10.5g/dl during 2nd trimester, and 'as per' ICMR as Hb less than 11g/dl at any time during pregnancy [3, 4]. Of the approximate 1000 mg of iron required during pregnancy, of which 300 mg iron is actively transferred to the fetus and placenta, 500mg of iron is required for erythrocyte expansion and 200 mg is lost through various normal routes of excretion. Therefore this iron

requirement has to be supplemented during pregnancy [5]. The National Nutritional Anaemia Control Programme (NNACP) was initiated in India in 1970 to provide free iron-folic acid tablet supplementation to pregnant women from 2nd trimester onwards and until 3 months of lactation, to eradicate IDA [6]. The reasons for failure of IFA programme were, problems with delivery system, poor compliance, inadequate dosing of iron supplementation, failure to deworm prior to taking iron, defective absorption and lack of health education. With oral iron therapy once anaemia is corrected, gastro intestinal absorption slows down and this results in failure to replenish the iron stores. To overcome the problems of oral iron, parenteral iron therapy -is an alternative as it corrects anaemia rapidly, and replenishes iron stores better than oral iron. Intravenous iron dextran was used previously to correct moderate to severe anaemia but many cases were reported with fatal anaphylactic reactions limiting its use at present. Iron sucrose has a minimal side-effects and as it is administered intravenously (IV) it overcomes the problems with oral iron, including problems of compliance. Unlike intravenous iron dextran, fatal anaphylactic reactions are rare with iron sucrose (31 Vs 0 per 1,000,000 doses) [7].

Blood transfusion is limited to those cases with moderate to severe anaemia at term and in cases of incipient or established cases of heart failure. Blood transfusion carries the risk of transfusion of mismatched blood, infections, immunological risks, and risks related to the erythrocyte damage caused by storage. With iron sucrose the maximum permissible dose to be administered at one sitting is 200 mg, and a minimum of 24 hours must elapse before next dose to be given. Thus women with very low haemoglobin require multiple visits to complete the course. Very few women will complete this course either because it is too inconvenient or expensive to travel many times to the health centre. The other disadvantage is women who present at late gestation are unlikely to have the time required to complete the treatment course.

The potential solution lies in the use of I.V. iron available as total dose infusion with preparations of ferric carboxymaltose, which is already available in the west, can be given at a dose as high as 1000mg at one sitting within 15 min [8]. Many studies are not available regarding the use of ferric carboxymaltose preparations in pregnancy but its use in postpartum anaemia has been established. Cost is the limiting factor for the use of ferric carboxymaltose in India. To overcome this issue some institutes already experimented with administration of high dose of iron sucrose (500mg) which proved as safe and effective. The safety and efficacy of high dose iron sucrose regimen (D₁ 500mg + D₂ 500mg) in patients with chronic kidney disease was proved [9, 10]. Therefore in our study, safety and efficacy of high dose iron sucrose was compared to multiple divided doses of iron sucrose.

METHODOLOGY

This is a prospective study conducted in the department of Obstetrics and Gynaecology, Narayana medical college, Nellore. Ethical clearance was obtained from the hospital ethical committee. A total of 60 women attending antenatal clinic with haemoglobin between 6- 9 gm/dl were included in the study after taking a written informed consent. After detailed history, general and physical examination patient was subjected to laboratory investigations like haemoglobin, packed cell volume (PCV), peripheral smear, complete haemogram, reticulocyte count, complete urine examination and urine culture. Reticulocyte count was checked after 10 days to know improvement while other investigations were repeated after 1 month of last dose. In all the patients recruited for the study, oral iron supplementation was not given during study period and 2 tablets with combination of Pyrantel Paomate + Mebendazole were given. Total dose for intravenous iron sucrose requirement was calculated by the formula:

$$\text{Body weight (kg)} \times [\text{normal Hb} - \text{patient Hb}] \times 2.21 + 500\text{mg} = \text{milligrams of iron needed}$$

Inclusion Criteria

- Singleton pregnancy of 16 to 34 weeks gestation with Hb between 6-9 gm/dl.

Exclusion Criteria

- Patients with history of drug sensitivity to iron preparations.
- Patients with medical problems like diabetes, hypertension, liver disorders and bronchial asthma.
- History of Acute or chronic infections.
- History of any previous blood transfusions / oral or parenteral iron administration in this pregnancy.

The patients recruited in the study were divided into 2 groups.

- In **group A (study group)** – 30 patients received the total dose requirement in a gap of 2-3 days with a maximum of 500mg as a single dose per day, diluted in 250 ml of 0.9% NaCl, over a period of 3 hrs. Patients were monitored during infusion and for 1 hour after infusion
- In **group B (control group)** – 30 patients received the total iron requirement intravenously given in divided doses as maximum of 200mg on alternate days. Clinical safety was evaluated based upon the nature and severity of adverse effects if any, were recorded during and at the end of 1 hour of infusion.

Haemoglobin and Reticulocyte count were estimated at baseline, 10 days and 4 weeks after treatment. This rise in haemoglobin levels after 4 weeks of therapy was analysed on coulter cell counter.

The patient’s satisfaction to therapy was recorded on a global assessment of response (Likert’s scale) to therapy on a 5 - point rating scale of “1- Excellent, 2- Good, 3- Average, 4- Poor and 5- Very poor “ at the end of study period [11]. This rating was done

independently by the patients and the physicians with respect to efficacy and tolerability.

Statistics

Results were analyzed by SPSS using Students paired ‘t’ test. Student’s sample T-test performed to analyse the reticulocyte count, hemoglobin levels and gestational periods etc. *p* value less than 0.01 was considered significant.

RESULTS

Table 1: Various parameters before and after treatment in the two groups

Parameters	Group	Number	Mean ± S.D.	<i>p</i> -value
AGE	GROUP-A	30	23.47±3.048	0.120
	GROUP-B	30	24.23±3.866	
POG1	GROUP-A	30	24.20±3.458	**
	GROUP-B	30	26.30±4.070	
POG2	GROUP-A	30	28.20±3.458	0.000
	GROUP-B	30	30.23±3.989	
Hb1	GROUP-A	30	6.897± 0.5530	0.000
	GROUP-B	30	6.880±0.3845	
Hb2	GROUP-A	30	10.5333±0.79278	0.000
	GROUP-B	30	10.6133±0.71232	
Ret1	GROUP-A	30	0.7133±0.21129	0.000
	GROUP-B	30	0.6963±0.22148	
Ret2	GROUP-A	30	3.2900±0.41219	0.000
	GROUP-B	30	3.2767±0.37202	

Group A: single dose group (500mg); Group B: multiple dose group (200mg); **The correlation and *t* cannot be computed because the standard error of the difference is 0. POG 1& 2: Period of gestation baseline and after treatment; Hb 1& 2: Haemoglobin levels baseline and after treatment; Ret 1& 2: Reticulocyte count baseline and after treatment.

Among 60 enrolled patients there were no drop outs in the study. Out of 30 women in group- A and 30 women in group B mean age was 23.47 and 24.23 respectively. Mean period of gestation in group A was

24.20 and in group B was 26.30 at the initiation of the treatment. Mean period of gestation 4 weeks after initial treatment in group A was 28.20 and in group B was 30.23. Mean hemoglobin levels before treatment in group A was 6.897 and in group B was 6.880. Mean hemoglobin levels 4 weeks after treatment in group A was 10.53 and in group B was 10.61. Mean reticulocyte count before treatment in group A was 0.713 and in group B was 0.696. Mean reticulocyte count 4 weeks after treatment in group A was 3.29 and in group B was 3.27 (Table 1).

Table 2: Percentage increase in laboratory parameters after the treatment

Paired differences	Group	Mean ± Std. Deviation	<i>p</i> - value
Hb 2 – Hb 1	Group A	3.63667 ± 0.78805	.000
	Group B	3.73333± 0.64505	.000
Ret 2 – Ret 1	Group A	2.57667± 0.39730	.000
	Group B	2.58033± 0.37432	.000

The rise in hemoglobin and reticulocyte count was seen in both group A and group B and was found to be statistically significant (*P* value < 0.01) (Table 2 &

Fig. 1A, B). There was no influence of body weight, initial haemoglobin and reticulocyte counts on percentage increase in haemoglobin in both the groups.

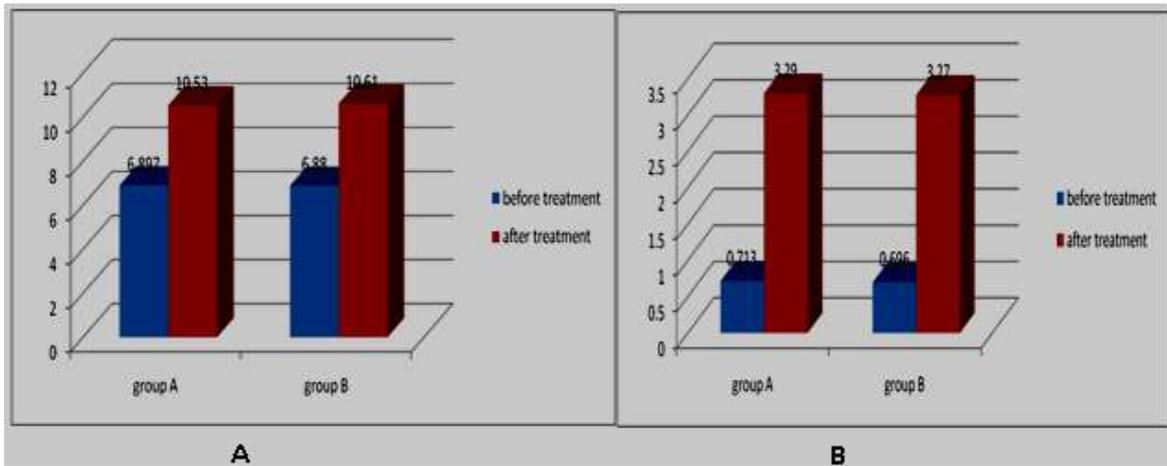


Fig. 1: A: Haemoglobin levels in two groups before and after treatment, B: Reticulocyte count changes in two groups before and after treatment

The adverse effects in group A and group B was 40% Vs 23%. In group A gastrointestinal symptoms like nausea, vomiting, heart burn was seen in 23%, dizziness was seen 6.6% muscle cramps was seen in 3.3% and pruritus was seen in 6.6% of patients.

In group B gastrointestinal symptoms was seen in 13.3%, dizziness was seen in 3.3% and pruritus was seen in 6.6% of patients (Fig. 2). Intravenous iron sucrose therapy was therefore well tolerated by majority of the patients without any anaphylactic reactions in either of the groups.

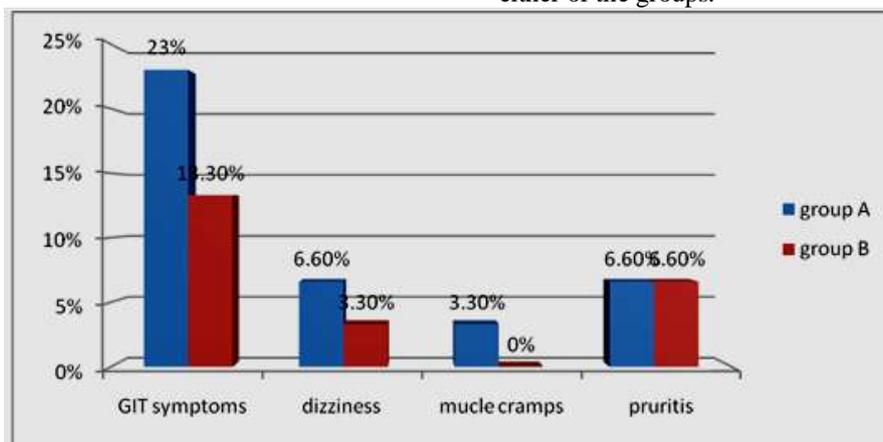


Fig. 2: Comparison of adverse effects during transfusion in both groups

Patients satisfaction analyzed on Likert's scale in group A showed excellent in 53% patients, good in 20% patients, average in 7% patients and poor in 20% patients.

patients whereas group B showed excellent in 40% patients, good in 27% patients, average in 20% patients and poor in 13% patients (Fig. 3).

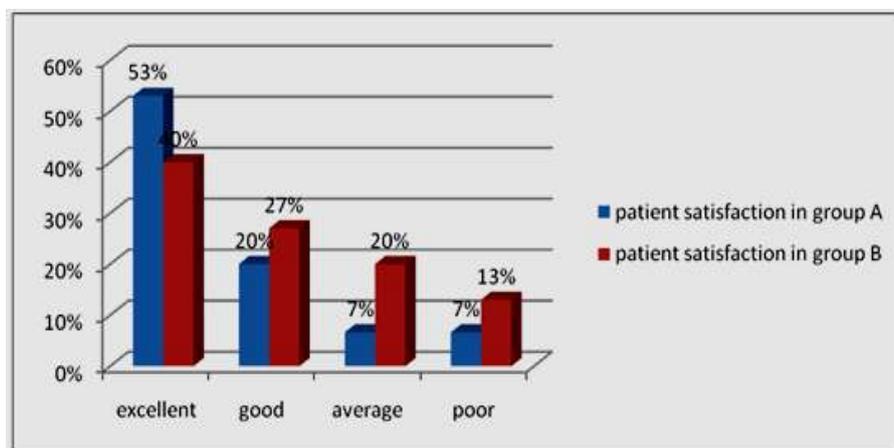


Fig. 3: Patient satisfaction levels in both groups

DISCUSSION

The prevalence of IDA in both rural and urban India is static, although there are indications that it might be rising. In a study conducted by district level house hold survey (DLHS 2) in 2006, 70% of pregnant women and adolescent girls in the country were anemic. Although in pregnant women iron supplementation programme was started in 1970, still there is high incidence of IDA and related complications. There is need for fresh thinking in managing IDA.

Anaemia during pregnancy causes risk of hemorrhage and other related complications of IDA resulting in increased in mortality and morbidity in these women. The newborns of anemic women are at a significant risk of non-hematological consequences like lower scores on IQ tests and cognitive performance. Iron is essential for hemoglobin synthesis. Its balance in the body depends on GIT absorption and bioavailability of iron in the food which is low. Intravenous iron sucrose is safe in pregnancy, corrects anaemia in short duration and replenishes iron stores better than oral iron. To avoid the inconvenience and to reduce the cost with multiple iron sucrose injections, we studied the safety and efficacy of high dose infusion (500 mg at each sitting) of iron sucrose. This high dose iron infusion efficacy was studied in patients with chronic kidney disease and proved safe and effective in correcting anaemia [9, 10].

The high dose iron sucrose therapy in pregnant women (Jehovah's witness) was proved safe and effective in study done by Elliot Main [12]. In this study, the efficacy, safety and tolerability of high dose intravenous iron sucrose in treating pregnant women with iron deficiency anaemia was compared with multiple dose intravenous iron sucrose therapy. There was significant improvement in hemoglobin levels in both group A (single dose; 500mg) and group B (multiple dose: 200mg) 4 weeks after initial treatment.

There is increase in the tolerable side effects in group A when compared to group B (40% VS 23%) though no serious side effects were seen in both the groups during study. In this study the increased patient's satisfaction was seen in group A when compared to group B because of less number of visits and is cost effective. In rural setup it is effective way of treating anaemia since very few women will complete multiple visits needed for total dose of iron sucrose. Hence it may be considered as an alternative to multiple dose treatment in correcting anaemia.

CONCLUSION

In conclusion, an accelerated regimen of high dose intravenous iron sucrose therapy in pregnant women is

safe and effective way of improving hemoglobin and may potentially save time and improve satisfaction of the patient. Even after forty years of IFA prophylaxis programme for pregnant women, there is no much difference in reducing the incidence of iron deficiency anaemia and its related complications. Hence fresh thinking is required in the management of iron deficiency anaemia in pregnancy. Therefore high dose regimen may be considered as one of the alternative to manage anaemia in pregnancy especially in developing countries like ours, where it is more practical. Further research is required to prove this as one of the alternative treatment in pregnancy to manage anaemia.

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