

Intravenous iron sucrose therapy for moderate to severe anaemia in pregnancy

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Received February 1, 2012

Background & objectives: Iron deficiency anaemia (IDA) is the most common nutritional deficiency in pregnancy. Prophylactic oral iron is recommended during pregnancy to meet the increased requirement. In India, women become pregnant with low baseline haemoglobin level resulting in high incidence of moderate to severe anaemia in pregnancy where oral iron therapy cannot meet the requirement. Pregnant women with moderate anaemia are to be treated with parenteral iron therapy. This study was undertaken to evaluate the response and effect of intravenous iron sucrose complex (ISC) given to pregnant women with IDA.

Methods: A prospective study was conducted (June 2009 to June 2011) in the department of Obstetrics & Gynecology, All India Institute of Medical Sciences, New Delhi. One hundred pregnant women with haemoglobin between 5-9 g% with diagnosed iron deficiency attending antenatal clinic were given intravenous iron sucrose complex in a dose of 200 mg twice weekly schedule after calculating the dose requirement.

Results: The mean haemoglobin raised from 7.63 ± 0.61 to 11.20 ± 0.73 g% ($P < 0.001$) after eight wk of therapy. There was significant rise in serum ferritin levels (from 11.2 ± 4.7 to 69 ± 23.1 $\mu\text{g/l}$) ($P < 0.001$). Reticulocyte count increased significantly after two wk of starting therapy (from 1.5 ± 0.6 to $4.6 \pm 0.8\%$). Other parameters including serum iron levels and red cell indices were also improved significantly. Only one woman was lost to follow up. No major side effects or anaphylactic reactions were noted during study period.

Interpretation & conclusions: Parenteral iron therapy was effective in increasing haemoglobin, serum ferritin and other haematological parameters in pregnant women with moderate anaemia. Intravenous iron sucrose can be used in hospital settings and tertiary urban hospitals where it can replace intramuscular therapy due to injection related side effects. Further, long-term comparative studies are required to recommend its use at peripheral level.

Key words Anaemia - iron deficiency - iron sucrose complex - parenteral iron therapy - serum ferritin

Iron deficiency anaemia (IDA) is the most common nutritional deficiency in pregnant women. According to WHO, the prevalence of IDA is about 18 per cent in developed countries and 35-75 per cent (average 56%) in developing countries¹. Globally, the prevalence of anaemia is 55.9 per cent with variations between developed and developing countries. In India, prevalence ranges between 33-89 per cent². About half of the global maternal deaths due to anaemia occur in South Asian countries; India contributes to about 80 per cent of this mortality ratio³. Many programmes have been introduced and implemented to reduce the burden of anaemia in the country but the decrease is lower than other South Asian countries⁴. Various surveys [National Family Health Survey (NFHS), District Level Household Survey (DLHS), Indian Council of Medical Research (ICMR) Micronutrient Survey] have been conducted to calculate the prevalence of anaemia in India. During 10th Five Year Plan (2002-2007)⁴, a study conducted by ICMR⁵ showed that the prevalence of anaemia was highest among pregnant women (50-90%) and that of moderate (<8 g%) and severe anaemia (<5 g%) was persistently high. Prevalence was high in all States of the country with considerable variations in moderate to severe anaemia⁶. Other factors responsible for high incidence of anaemia in our country include early marriage, teenage pregnancy, multiple pregnancies, less birth spacing, phytate rich Indian diet, low iron and folic acid intake and high incidence of worm infections in Indian population⁷.

WHO defines anaemia as haemoglobin (Hb) <11 g %¹ In India, the ICMR classification of iron deficiency anaemia is: 8-11 g% as mild, 5-8 g % as moderate and <5 g% as severe anaemia. In absence of interfering factors, serum ferritin <12-15 µg/l is considered as iron deficiency⁴.

The first choice for prophylaxis and treatment of mild iron deficiency anaemia in pregnancy is oral iron therapy. But in patients with moderate and severe anaemia, oral therapy takes long time and compliance is a big issue in our country. Thus, pregnant women with moderate anaemia should be better treated with parenteral iron therapy and/or blood transfusion depending upon individual basis (degree of anaemia, haemodynamic status, period of gestation, *etc.*).

Various parenteral iron preparations are available in the market which can be given either intravenously or intramuscularly. Initially, iron dextran and iron sorbitol citrate was started. But test dose was required to be given before these injections as severe anaphylactic

reactions were reported with intravenous iron dextran. Iron sucrose has been reported to be safe and effective during pregnancy⁸. The injection can be given without test dose⁹.

A prospective study, therefore, was conducted in pregnant women with iron deficiency anaemia (haemoglobin between 5-9 g%) attending a tertiary care hospital in north India to evaluate the response and effect of intravenous (iv) iron sucrose complex (ISC) in terms of improvement in haemoglobin status and other parameters.

Material & Methods

The prospective study was conducted in the department of Obstetrics and Gynaecology, All India Institute of Medical Sciences (AIIMS), New Delhi, India, from January 2009 to December 2010. A total of 111 women presenting in antenatal clinic with haemoglobin between 5-9 g% were screened, consecutively. Exclusion criteria were causes other than iron deficiency anaemia, multiple pregnancy, high risk for preterm labour and recent blood transfusions, thalassaemia and other medical disorders. About 8-10 ml blood was taken from each patient.

High performance liquid chromatography (HPLC) of blood was performed, and red cell indices, peripheral blood smear and detailed serum iron studies were also conducted. Seven women with causes of anaemia other than iron deficiency (four thalassaemia, one had sickle cell disease, one was haemolytic anaemia and one had chronic renal disease) were excluded. Two women did not consent for starting injectable iron therapy. Two refused for follow up so were excluded from study. Thus, 100 women were recruited for intravenous iron sucrose therapy. Ethical clearance for the study protocol was taken from the Ethics Committee of the institute. Informed written consent was taken from all the patients before starting the therapy. Baseline investigations including liver and kidney function tests, urine (routine microscopy and culture sensitivity), stool examination (for ova and cyst) were done. All women were given antihelminthic therapy with tablet mebendazole 100 mg twice daily for three days. Folic acid tablets were given to all women during therapy.

The formula used for calculation of iron sucrose dose was as follows:

Required iron dose (mg) = (2.4 x (target Hb-actual Hb) x pre-pregnancy weight (kg)) + 1000 mg for replenishment of stores¹⁰.

The required iron dose varied depending upon index Hb level and pre-pregnancy weight. Average dose requirement was 1777 ± 168.5 mg (1400-2160 mg). Mean duration to complete total therapy was 4.5 ± 1.0 (3.5-5.5 wk).

Iron sucrose (Injection Orofer S, Emcure Pharmaceuticals Limited, India) was given in a dose of 200 mg intravenously twice weekly in 200 ml normal saline over a period of 15-20 min. First dose was given in the ward where equipment for cardiopulmonary resuscitation was available. The following doses were given on outpatient basis. Patients were observed for side effects or anaphylactic reactions. Any minor or major side effects were documented. All parameters were repeated at 2 wk interval till 8 wk.

The primary outcome measures were haemoglobin and serum ferritin levels after 4 and 8 wk. Secondary outcome measures were improvement in serum iron levels, reticulocyte count, any adverse effects and perinatal outcome [period of gestation (POG) at the time of delivery, type of birth, postpartum haemorrhage, need of blood transfusion and foetal birth weight].

Statistical analysis: The statistical analysis was done using SPSS version 15 (SPSS Inc., USA). Repeated measure analysis was done followed by post-hoc comparison by Benferroni method to see the trend of parameters with time. Confidence intervals (95%) of various proportions were also calculated. $P < 0.5$ was taken as significant.

Results

The mean age of women was 27.8 ± 3.9 (range 21-34) yr and mean parity was 1.3; mean period of gestation (PDG) at the time of diagnosis was 25.69 ± 4.82 (14-32) wk. At the beginning, mean Hb was 7.63 ± 0.61 g%. Thirty two (32%) women had mild anaemia

(>8 g%) and 68 per cent had moderate anaemia (5-7.9%). After completion of therapy, mean Hb raised to 11.20 ± 0.73 g%. Of the total women, 67 per cent achieved Hb ≥ 11 g%. The mean duration to achieve haemoglobin level more than 11 g% was 6.5 ± 2.3 wk. Table I shows the baseline haematological parameters and effect of iron sucrose therapy on all the parameters. Complete dosage schedule was done in 97 women. One woman was lost to follow up after five doses. Two delivered preterm before completion of all doses. One woman went into preterm labour and delivered at 32 wk after 6 doses and the second had preterm cesarean section because of pre-eclampsia and abruption at 33 wk (after 7 doses).

Perinatal outcome: Ninety nine women were followed till delivery (one lost to follow up before term). Of these, nine (9%) delivered before 37 wk POG. Table II shows the associated antenatal complications in the enrolled women. The remaining 90 women delivered after 37 wk. Of these, 28 (31.2%) underwent emergency or elective cesarean section and the remaining 62 (68.8%) delivered vaginally. Mean period of gestation at delivery was 38.5 ± 1.0 (37-41) wk. Two (2.2%) women had postpartum haemorrhage (blood loss >500ml) and required blood transfusion. Intrapartum and postpartum period of the remaining was uneventful. The mean birth weight of babies was 2762 ± 355 g.

Side effects: Five women complained of nausea and three had vomiting after first dose. One woman had diarrhoea after the second dose. One had thrombophlebitis after second dose, one had mild giddiness and restlessness at first dose which subsided spontaneously and did not recur on subsequent doses. Two women complained of mild fever after the first dose which did not recur on further dosing. One

Table I. Baseline haematological parameters and effect of iron sucrose therapy

Parameters	Baseline	2 wk	4 wk	8 wk	P value
Mean Hb (g%)	7.63 ± 0.61	7.89 ± 0.60	9.90 ± 0.80	11.20 ± 0.73	0.001
Serum iron ($\mu\text{g}/\text{dl}$)	32.72 ± 5.00	42.94 ± 9.4	59.11 ± 13.7	82.42 ± 12.5	0.001
TIBC ($\mu\text{g}/\text{dl}$)	354.2 ± 37.7	328.8 ± 14.8	320.96 ± 11.3	315.5 ± 11.6	0.001
Serum ferritin ($\mu\text{g}/\text{l}$)	11.2 ± 4.7	17.64 ± 9.3	25.60 ± 10.90	69 ± 23.1	0.001
Reticulocyte count (%)	1.50 ± 0.60	4.6 ± 0.8	4.8 ± 2.1	5.5 ± 1.8	0.001
Mean corpuscular vol. (fl)	67.24 ± 5.0	76 ± 4.5	79.3 ± 3.2	85 ± 2.3	0.001
Mean corpuscular haemoglobin (MCH) (pg)	22.3 ± 2.6	24 ± 3.2	34 ± 2.2	44 ± 3.2	0.001
Mean corpuscular haemoglobin concentration (MCHC) (g/dl)	26.5 ± 1.9	31 ± 2.3	40 ± 3.2	56 ± 2.4	0.001
Values are mean \pm SD (n= 99)					

Table II. Associated obstetrical complications in the study population (n=98)

Associated medical and obstetrical complications	Occurrence no. (%) [95% CI]
Pre-eclampsia	10 (10.2) [5.5-17.9]
Intrauterine growth restriction	12(12.2) [6.49-20.4]
Preterm labour	8 (8.16) [3.59-15.43]
Preterm premature rupture of membranes	3(3.1) [0.64-8.68]
Gestational diabetes mellitus	4(4.1) [1.12-10.12]
Intrahepatic cholestasis of pregnancy	3(3.1) [0.64-8.68]
Abruption	1(1.0) [0.03-5.5]

woman had hematemesis after first dose. She was evaluated by the gastroenterologist and no cause was found. Iron sucrose was restarted after one week and she completed the full course without any further side effects. All other women well tolerated the injections. There was no major side effects and no allergic or anaphylactic reaction.

Discussion

The total requirement of iron during pregnancy is approximately 1000 mg (500 mg for developing foetus and placenta and similar amount for red cell increment)¹¹. Usually, this iron is mobilized from iron stores. However, women with poor iron stores become iron deficient during pregnancy. Studies have shown that Hb levels <8 g% (moderate to severe anaemia) in pregnancy are associated with higher maternal morbidity^{3,11,12}. Hb less than 5 g% is associated with cardiac decompensation and pulmonary oedema. Blood loss of even 200 ml in third stage of labour can cause sudden shock and death in these women.

As compared to western women whose iron stores are sufficient and they need 30-40 mg elemental iron per day for anaemia prophylaxis in pregnancy^{13,14}, the stores in Indian women are deficient and they need 100 mg elemental iron per day for prophylaxis. For treatment of anaemia, dose recommended is 200 mg elemental iron per day¹⁴. In the present study, 5-9 g% Hb was taken as cut-off. Intravenous iron is superior to oral iron with respect to faster increase in Hb and faster replenishment of body iron stores¹⁵. Also, it reduces the need of blood transfusions¹⁶, and it can be given at outpatient basis.

In a study to compare the clinical efficacy and safety of intravenous iron sucrose with intramuscular

iron sorbitol citrate, it was found that rise of Hb was more in intravenous group¹⁷. This study emphasized the superiority of iv iron therapy to intramuscular therapy in terms of rise of Hb and also safety profile.

Perewunskyk *et al*¹⁸ studied 400 women who received a total of 2000 ampoules of iron sucrose. Minor general adverse effects including a metallic taste, flushing of the face and burning at the injection site occurred in 0.5 per cent cases. The high tolerance of the drug has been partly attributed to slow release of iron from the complex and also due to the low allergenicity of sucrose. Till date, one death has been reported with intravenous iron sucrose injection¹⁹. The explanation given for this was because of very slow infusion (1-2 h). The cause of death may be free radicals released from the iron sucrose. The injection should be given within 15-20 min or up to 200 mg can be given as slow iv push over 2-3 min. This case has not been mentioned in the literature but is available on clinical trial registry site¹⁹. In the present study, no major side effect was reported.

Breymann²⁰ treated more than 500 antenatal women diagnosed with iron deficiency anaemia. Intravenous iron sucrose was given according to the calculated dose as either iv push over 5-10 min or iv infusion over 20-30 min. All injections were given on outpatient basis without any test dose. This study also emphasizes on the safety of iron sucrose injection. In the present study, the first dose was given in ward where facilities for emergency care were available. All subsequent doses were given on OPD basis. None of the patients required any emergency care. In other studies^{17,21}, target Hb for calculation of required dose has been taken 11 g/dl and for replenishment of stores 500 mg has been added. Keeping in mind very low iron stores in Indian women, we took 14 as index Hb and added 1000 mg for replenishment of stores. Even with this, maximum mean serum ferritin after 8 wk of starting therapy was 69 µg/l which is well within normal range. As compared to previous studies^{17,20}, ferritin levels in our study women showed a lesser increase. The reason can be due to severely depleted iron stores in Indian women.

Hookworm is one of the well established causes of anaemia in developing countries. Routine antihelminthic therapy in pregnancy is not recommended. But due to high prevalence in developing countries including India, it is advisable to give antihelminthic therapy to pregnant women presenting with anaemia²¹.

A study conducted to evaluate the safety and efficacy of iron sucrose in dialysis patients who were sensitive to iron dextran, demonstrated the safety of iv iron sucrose injections²².

In a study to assess and compare the efficacy of two and three doses of intravenous iron sucrose with oral iron therapy, there was higher frequency of responders (Hb>11g%) in intravenous group (75 vs. 80%). There was a significant difference of repleted iron stores before delivery (ferritin >50 mg/l) in the group with three intravenous iron doses in comparison to the oral iron group (49 vs. 14%; $P<0.001$). No differences were observed in maternal and perinatal outcomes. The study did not conclude any significant benefit of parenteral iron therapy over oral iron therapy²³. However, in practice, noncompliance is very common with oral iron therapy.

Drawbacks of our study was lack of control group (intramuscular iron therapy) and non-randomised trial. Large randomized controlled trials are required to compare the efficacy and safety of intravenous iron sucrose complex over intramuscular iron therapy.

In conclusion, our results showed that intravenous iron sucrose therapy was effective to treat moderate anaemia in pregnant women. Intramuscular preparations are known to be associated with local side-effects. Iron sucrose complex iv therapy was with negligible side effects. It caused rapid rise in haemoglobin level and the replacement of stores was faster. Long term comparative studies are required to assess if it can be used at peripheral level.

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