IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

Study of parenteral iron sucrose in treatment of pregnancy associated iron deficiency anemia at a tertiary teaching hospital.

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INTRODUCTION

Iron deficiency anaemia is the most common and major hematological, nutritional deficiency but manageable health problem encountered among the pregnant women globally but more common in developing countries especially in tropics like India especially in under privileged population.[1]

Pregnant women with moderate anaemia should be better treated with parenteral iron therapy depending upon individual basis (degree of anaemia, haemodynamic status, period of gestation, etc.).[2] Also, oral therapy is not sufficient for treatment of moderate to severe anaemia, especially in the late second and third trimester. Parenteral therapy promises a better response in these patients and can obviate the need for blood transfusions in the antenatal and postpartum period. Modern alternative strategies call for parenteral administration of new, well-tolerated iron preparations, (e.g., iron sucrose, ferric carboxymaltose), which has been used successfully in the treatment of antenatal & postpartum anaemia.[3]

As a tertiary referral center for large area, pregnant & postpartum patients with moderate anaemia are commonly referred to us. Health care providers working in periphery do not administer iron sucrose due to many constraints such as technique of administration, serum iron studies are not available, etc. We therefore studied the efficacy and safety of intravenous iron sucrose for the treatment of iron deficiency anaemia in pregnant & postpartum women with moderate anaemia at our tertiary center, with hemoglobin level measurements at baseline & follow up. This study could help medical officers working in periphery to treat pregnant & postpartum women with moderate anaemia.

MATERIAL AND METHODS

Present study was a prospective, interventional study conducted in pregnant women & postpartum women admitted in ANC ward/PNC ward of department of obstetrics & gynaecology at Govt. Medical College & Hospital, Aurangabad. Study duration was 6 months. Institutional ethical committee approval was taken to conduct this study.

Inclusion criteria:

Pregnant women & postpartum women with moderate iron deficiency anemia (Hemoglobin levels 7-9 g/dL), admitted in ANC ward/PNC ward with more than 20 weeks period of gestation OR postpartum (delivered within 7 days), willing to participate & follow up

Exclusion criteria:

1. Anaemia due to causes other than IDA;
2. History of allergic reaction to intravenous iron infusion.
3. Known case of hemolytic anaemia, hemoglobinopathies (thalassemia, sickle cell), bleeding tendency, hypersplenism
4. Postpartum women, delivered before 48 hours, hemoglobin less than 7
5. Patients with chronic heart failure, Class II-IV heart disease, uncontrolled arterial hypertension (DBP ≥ 110 mmHg), deep vein thrombosis, thrombocytosis, chronic renal disease , severe renal failure patients (2.5 times or more higher plasma creatinine level than high limit of normal state) , with severe liver dysfunction (2.5 times or more higher AST or ALT than high limit of normal state) e.g. cirrhosis, viral hepatitis ,patients with doubled or more CK level than high limit of normal state, asthma, seizure disorder, haemochromatosis, hemosiderosis.
6. Patients not willing to participate/follow up, lost to follow up.

On enrolment, study was explained & a written informed consent was taken from patient. Detailed clinical history (menstrual, obstetric), previous treatment history including iron therapy, compliance with oral iron and chronic medical illness was taken. Detailed examination including anthropometry, general physical examination and obstetric examination was done. Routine antenatal investigations were done according to the standard departmental protocol. Investigations specific to anaemia included hemogram, reticulocyte count and peripheral blood smear, red cell indices including mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW) were done. Additional investigations such liver and kidney function tests, urine (routine microscopy and culture sensitivity), stool examination (for ova and cyst) were done. All women were administered antihelminthic therapy with tablet albendazole 400 mg single tablet and 5 mg Folic acid tablet once daily.

Iron requirement was calculated according to Ganzoni's formula

Iron requirement (mg) = Total iron deficit (mg)= Body Weight (kg) x target Hb (14g/dL− actual Hb) (g/dL) X 0.24 + storage iron (1000 mg)

For administration of iron sucrose women were admitted in ward where emergency cardiopulmonary resuscitation facilities were available. After calculating total iron deficit, patients were administered IV Iron Sucrose Complex as 200 mg thrice weekly till dosage was completed, not to exceed 600 mg per week. 200 mg iron sucrose was diluted in 100 ml of isotonic sodium chloride solution to be given over period of 30 minutes during each dose. First 5 ml was given slowly at a rate of 1ml/min and the women were monitored for 30 minute for any adverse symptoms and signs of anaphylactic reaction.

The general condition of the patient, blood pressure and pulse rate were noted before infusion and every five minutes during infusion and fetal heart rate monitoring was done before and after infusion. Any minor or major adverse effects were noted. All patients were followed up after 3, 6 and 12 weeks of initiation of treatment. Hb, RBC indices were done at each visit.

Outcomes such as increase in hemoglobin levels after 6 weeks of iron sucrose therapy, level of anaemia at which iron sucrose therapy was initiated, average total dose of iron sucrose administered & proportion of women developing major and/or minor adverse reaction during and after administration of iron sucrose. Statistical analysis was done applying student 't' test and Chi square test. Value of <0.05 was taken as significant and <0.001 as highly significant.

RESULTS

In present study, total 211 patients were enrolled, 200 patients completed follow up were studied. Out of 200 patients, 124 (62%) patients were antenatal & 76 (38 %) were postpartum. Mean age of antenatal women was 23.6 ± 3.3 years. 36% patients received oral iron supplements for > 100 days in present pregnancy & 18% patients had history of oral iron intolerance. 53% patients were from 28-36 weeks gestational age group, 44% patients were gravida 2/3 & 67% patients delivered vaginally.

Table 1 General characteristics of antenatal women (n=124)

Characteristics	Mean SD / number of patients (%)
Age (years)	23.6 ± 3.3
Weight (kg)	55.32 ± 10.53
Received Oral Iron Supplements for > 100 days in present pregnancy	45 (36%)
History of Oral Iron intolerance	22 (18%)
Hemoglobin level (g/dL)	7.92 ± 0.81
Gestational age on inclusion (weeks)	27.6 ± 4.6
20 – 28 Weeks	46 (37%)
28 – 36 Weeks	66 (53%)
More than 36 weeks	12 (10%)
Gravida	
Primigravida	28 (23%)
Gravida 2,3	42 (34%)
Gravida 4 or more	54 (44%)
Mode Of Delivery	
Vaginal	83 (67%)
Elective Caesarean	8 (6%)
Emergency Caesarean	28 (23%)
Instrumental	5 (48%)

Mean hemoglobin at inclusion was 7.92 ± 0.81 gm/dl. After intravenous iron sucrose, a significant rise was noted at 2 week (8.36 ± 0.64 gm/dl), 4 week (9.43 ± 0.53 gm/dl) & 6 weeks (10.68 ± 0.61 gm/dl).

Table 2- Rise in hemoglobin in antenatal women (n=124)

	Base Line	2 Week	4 Week	6 weeks	P value
Hb% (Mean± SD) gm/dl	7.92 ± 0.81	8.36 ± 0.64	9.43 ± 0.53	10.68 ± 0.61	< 0.01 (Significant)

Mean age of postpartum women was 22.6 ± 3.1 years. 45% patients received oral iron supplements for > 100 days in present pregnancy & 14% patients had history of oral iron intolerance. 59% patients delivered vaginally & mean gestational age group at delivery was 38.1 ± 2.6 weeks.

Table 3- General characteristics of postpartum women (n=76)

Variables	No. of patients (%) / Mean ± SD
Age (years)	22.6 ± 3.1
Weight (kg)	50.4 ± 8.3
Baseline Hemoglobin level (gm/dl)	7.58 ± 0.25
Received Oral Iron Supplements for > 100 days in present pregnancy	34 (45 %)
History of Oral Iron intolerance	11 (14 %)
Gestational Age At delivery (weeks)	38.1 ± 2.6
Mode Of Delivery	
Vaginal	45 (59%)
Elective Caesarean	5(7%)
Emergency Caesarean	20(26%)
Instrumental	6(8%)

Mean hemoglobin at inclusion was 7.92 ± 0.81 gm/dl. After intravenous iron sucrose, a significant rise was noted at 2 week (8.33 ± 0.57 gm/dl), 4 week (9.24 ± 0.44 gm/dl) & 6 weeks (10.7 ± 0.73 gm/dl).

Table 4- Rise in hemoglobin in postpartum women (n=76)

	Base Line	2 Week	4 Week	6 weeks	P value
Hb% (Mean± SD)	7.58 ± 0.25	8.33 ± 0.57	9.24 ± 0.44	10.7 ± 0.73	< 0.01 (Significant)

Local pain (4%) was noted for initial transient period, no additional treatment required. Common side effects were metallic taste (3%), constipation (2%), nausea (1%). No thrombophlebitis of vein, anaphylactic reaction were noted. No serious morbidity or mortality noted in study patients.

Table 5 – Side effects/adverse effects

	Number	Percentage
Metallic taste	6	3%
Local pain	7	4%
Constipation	3	2%
Nausea	2	1%

DISCUSSION

Anaemia in pregnancy is defined by the World Health Organization as a hemoglobin (Hb) value below 11 g/dL and a hematocrit of <0.33. The Indian Council of Medical Research (ICMR) uses further categories of anaemia depending on hemoglobin levels.[5] During pregnancy, the physiological need for absorbed iron increases from 0.8 mg/day in the first trimester to 7.5 mg/day in the third trimester. Dietary iron intake does not compensate for this strongly increased iron demand.[1]

High incidence of anaemia in India are because of low dietary intake of iron, poor bio-availability of iron, faulty food habits, phytate rich Indian diet, chronic blood loss during menses and high prevalence of infections like malaria and hookworm infestations.[2] Iron deficiency anaemia has been shown to be associated with an increased risk of premature birth and low birth weight, preeclampsia, placental abruption, and increased peripartum blood loss as well as cardiac failure and related death.[3]

Iron sucrose molecule is a type II iron complex of intermediate stability and strength. It is rapidly metabolized and readily available for erythropoiesis in the bone marrow. Complex stability and unique iron distribution profile makes iron sucrose clinically safe. Moreover, as complexes contain no biological polymers, anaphylactic reactions are unlikely and makes these preparations safe to use in pregnancy and rate of blood transfusions reduced to 1% of patients per year.[6,7]

In study by Kumari A. et al.,[8] maximum number of cases (60.86%) with increase in hemoglobin level after 4 weeks of IV iron sucrose supplementation to be 2.5–3 g/dL. Similar results were found by Perewusnyk

et al.,[6] which showed mean increase in hemoglobin of 1.9 g/dL after 7 days and 2.1–3.2 g/dL after 14 days. The maximum mean daily increase in hemoglobin was 0.23 g/dL.

Shrivastava Deepti[9] studied 256 patients with average gestational age 32.5 weeks. Mean values for Hb on day 1 was 6.9 ± 0.9 g% & administered iron sucrose parenterally. Mean rises in Hb percentage were 1.1 ± 0.2, 2.3 ± 0.8, and 3.0 ± 0.4 after 1, 2, and 3 weeks, respectively. They concluded that parenterally administered iron sucrose elevates Hb and restores iron stores earlier and also that intravenous iron administration has led to reduction in the rate of blood transfusion rate at peripartum period of 37 weeks-48 h within delivery.

Rudra S et al,[10] compared intravenous iron sucrose with oral iron in 100 pregnant women. In iron sucrose group, amount of rise in haemoglobin from baseline at 2 weeks was 0.552 ± 0.13; at 4 weeks was 1.99 ± 0.18 and at delivery was 3.67 ± 0.17. The rise in haemoglobin in iron sucrose group was statistically highly significant at each point of measurement as compared to oral iron group.

In a systematic review of six trials by Shi Q et al,[11] significant increases in haemoglobin concentration (0·85 g/dL, 95% CI 0·31–1·39) was observed in the intravenous group compared with the oral iron group. There were fewer mild adverse events in the intravenous group than in the oral iron group (risk ratio 0·50, 95% CI 0·34–0·73).

In a multicenter, open-label, randomised, controlled trial, 2018 patients were enrolled & randomly assigned to the intravenous iron sucrose group (999 patients) and to the standard therapy group (1019 patients). The difference in change in haemoglobin concentration was significantly higher at each timepoint in the intravenous iron sucrose group than in the standard therapy group, with highest mean difference (0·95 g/dL,95% CI 0·80–1·10) noted at 6 weeks post-randomisation.[12]

In a study done by Agarwal Rohina S et al,[13] they noted baseline Hb 6.2 g% and 5.95 g%, Haematocrit 18.8 and 17.8 %, MCV 71.28 and 70.1 fl in IV iron sucrose and oral group respectively. After 4 wks., Hb% increased to 11.3 and 10.26 g%, Haematocrit increased to 33.9 and 30.77% and MCV increased to 93 and 85.8 fl in IV iron sucrose and oral group respectively. Vundi VR et al,[14] treated antenatal women with intravenous iron sucrose & noted mean baseline haemoglobin as 8.16 g/dl & post-treatment haemoglobin after 4 weeks showed a mean value of 10.66gm/dl, which was statistically significant & the average rise of haemoglobin was 2.5g/dl. Similar to present study above two studies measured iron sucrose response in terms of rise in hemoglobin only, results were comparable to present study.

In a study conducted by Gadappa et al[15] in same institute, intravenous ferric carboxymaltose (FCM) was given to postpartum women with moderate anemia, hemoglobin rise was noted from baseline 7.58 ± 0.75 gm/dl to 9.15 ± 1.23 gm/dl at 6 weeks after therapy, difference was statistically significant.

Intravenous iron treated iron deficiency anaemia of pregnancy and restored iron stores faster and more effectively than oral iron, with no serious adverse reaction.[16] Bashiri et al.[17] reported the common side effects of intravenous iron sucrose are fever, shivering, nausea, change in test and hypotension in less than 1% cases and anaphylactoid reaction rarely occurred. Similar results were noted in present study. The risk of allergic reactions is extremely low, it is also cost effective as it is an alternative to blood transfusion except for acute hemorrhagic emergencies, and it enables to shorten hospitalization time, as there is faster clinical recovery than with oral iron therapy in IDA.[9]

Of all the pregnant women with severe anaemia (haemoglobin concentration <7 g/dL), 47.7% are treated at health facilities and out of total obstetric complications, 33.3% are treated with blood transfusion.[18] Because of the safety issues associated with blood transfusion, it is recommended that blood transfusion be considered as a last resort or when the patient is unresponsive to intravenous iron supplementation in severe anaemia.[19]

Clinical trials and the long history of the use of iron sucrose injection worldwide have established the efficacy and safety of this drug in patients with IDA; it is metabolically available very quickly after administration besides being safe, convenient, and more effective than intramuscular iron therapy in the treatment of IDA during pregnancy.[9] The intravenous iron therapy can replace blood transfusion in antenatal period for moderate IDA, as there are numerous hazards of blood transfusion including transfusion of wrong blood, infection, anaphylaxis, and lung injury any of which would be devastating for

mother.

CONCLUSION

Iron deficiency anaemia in antenatal & postpartum women treated with intravenous iron sucrose had effective rise in hemoglobin, restoration of iron stores with no serious adverse reaction. The intravenous iron sucrose therapy can replace blood transfusion in antenatal & postpartum women with moderate iron deficiency anaemia. Antenatal women receiving iron sucrose also had more antenatal visits & surveillance by virtue of iron sucrose treatment. Use of iron sucrose in antenatal & postpartum women with moderate anemia by medical officers at peripheral health centers can reduce complications of anaemia as well as morbidity & mortality related to anaemia.

Conflict of Interest: None to declare
Source of funding: NIL

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