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ORIGINAL ARTICLE

COMPARISON OF ORAL IRON AND IV IRON SUCROSE FOR TREATMENT OF ANEMIA IN POSTPARTUM INDIAN WOMEN

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ABSTRACT

Objectives: To determine the efficacy of intravenous iron sucrose and oral iron in anaemic postpartum women, presenting at Institute of Kidney Disease and Research Centre.
Method: Descriptive case series. The study was carried out in the department of Obstetrics and Gynaecology at Institute of Kidney Disease and Research Centre over a period of six months from 02-02-2010 to 02-08-2010. 50 cases with proven iron deficiency with Hb ≤7gm% were included in the study. Total iron deficit was calculated using a standard formula. Target haemoglobin was 12 gm %. Iron sucrose was administered by intravenous infusion. Haemoglobin was repeated 1, 2, 3, and 4 weeks after the last dose of intravenous iron sucrose.
Results: On inclusion, the 2 groups were comparable in terms of both anthropometric and biologic data Distribution of cases by economic status showed, 21 patients (42.0%) belonged to lower class, 20 patients (40%) belonged to middle class and 09 patients (18%) were of upper class).Target hemoglobin levels were achieved in 4 weeks time in 20 (80%) patients in iron sucrose group as compared to 10 (40%) of patients in oral iron group .There was significant improvement in the various hematological parameters in iv sucrose group as compared to patients in oral iron group. There were no significant allergic reactions in IV sucrose group.
Conclusion: This study has shown a significant improvement in the iron sucrose group. Iron sucrose is safe and well tolerated.

Keywords: Iron sucrose, anaemic postpartum women, iron deficiency anemia

INTRODUCTION

The prevalence of iron-deficiency anaemia in different regions of the world ranges from 12 to 43%.The increased iron requirement in pregnancy and puerperium lead to an increased susceptibility to iron deficiency anaemia. It has been found that haemoglobin values < 11.0 g/dL in the first and third trimesters and < 10.5 g/dL in the second trimester may point to an anemic situation which should be clarified. Our departmental data indicate that iron sucrose complex therapy is a valid first-line option for the safe and rapid reversal of iron-deficiency anaemia. The haemoglobin concentration alone is insufficient to guide management. A complete work-up (ferritin, transferring saturation) is essential, preferably with hematological indices such as hypo chromic and microcytic red cells and reticulocytes, classified by degree of maturity, in particular before parenteral therapy is given. Since ferritin acts as both an iron-storage and acute-phase protein, it cannot be used to evaluate iron status in the presence of inflammation. A high ferritin level thus requires

the presence of an inflammatory process to be eliminated before it can be taken at face value. If the C-reactive protein level is also raised, the soluble transferrin receptor concentration can be used, since it is unaffected by inflammation.

Modern alternative strategies call for parenteral administration of new, well-tolerated iron preparations, (e.g., iron sucrose), which has been used successfully in the treatment of postpartum anaemia. We therefore evaluated the efficacy and safety of intravenous iron sucrose as compared with oral iron sulfate for the treatment of iron deficiency anemia in patients with anemia

METHODOLOGY

Approval of institutional ethics committee was taken before starting the trial. A randomized, retrospective, open-label, single center study was performed in 50 postpartum patients on postpartum day 2/3 >18 years old, with anemia Hb ≤ 7 gram/dl and transferrin saturation 10% and/or serum ferritin concentrations ≤15 microg/L. They were randomized into two groups.

Group A consisted of 25 women who received i.v. a total amount of iron sucrose. Iron sucrose was given by intravenous injection on alternate day according to the iron deficit calculated for each individual patient, 200mg elemental iron diluted in 100ml of 0.9% normal saline infusion, initially given at 8-12 drops/min for 15-30 minutes and patient was monitored for any sign of allergic reaction. Later rest of infusion was given at 36 drops/minute over 2 hours.

In the intravenous group (i.v. group), the total iron sucrose dose to be administered was calculated from the formula: Body Weight in kilograms (before pregnancy) × (Target haemoglobin i.e12gm/dl – Actual hemoglobin) × 0.24 + 500 mg; 0.24 was a correction factor that take into account the patient's blood volume, estimated at 7% of body weight and hemoglobin iron content; 500 mg is the quantity of stored iron in adults.12 This gives amount of elemental iron needed. This dose was given in 6 slow intravenous injections (on days 1, 3, 5, 7, 9, and 10). A maximum of 200 mg of iron (2 ampules) was administered. For the first injection, 25 mg was injected very slowly and the patient was monitored during 15 minutes for signs of intolerance such as an anaphylactic reaction or hypotension. Iron was administered by slow infusion. Treatment was stopped either after administration of the calculated dose or once the haemoglobin level had reached 12 g/dL. Fifteen milligrams of folic acid was systematically associated with the treatment to prevent an eventual folic acid deficiency and to eliminate the influence of such a deficiency on the results. Additional oral or IM form of iron administration of iron was excluded during the 4 weeks of study. Haemoglobin and haematocrit was repeated1, 2, 3, 4 weeks after the last dose of intravenous iron or oral iron.

Group B consisted of 25 women, who received three 200 mg iron sulphate tablets t.d.s containing 60mg of elemental iron (i.e., a total of 180 mg of elemental iron per day for 4 weeks). The two groups were monitored both clinically and biologically. Demographic data were matched. All the caesarean sections were performed by a consultant obstetrician and were elective. The normal deliveries were all performed by senior fellows. The estimated blood loss was between 500-800 mls for the sections and not significant in all cases of normal deliveries. All women who participated were lactating postpartum and had amenorrhea during the study period. A specially designed proforma was used to collect the demographic information including name, age and gestational age. Purpose of study with beneficial effects as well as side effects of drug was explained to each eligible patient and informed consent was taken from each patient. Target Hb was 12gm/dl**.**

Inclusion Criteria- Women who are on postpartum day 2 or 3 and Hb ≤7gm%, who agree to participate in this study in writing.

Exclusion Criteria- From the study we excluded cases with a diagnosis of placenta previa, placenta abruption, pre-eclampsia and clotting disorders Patients who have participated in another clinical study in recent 3 months, or shown intolerance or hypersensitivity to iron therapy , hemolytic anemia, hemoglobinopathies (thalassemia, sickle cell) , bleeding tendency, hypersplenism , chronic heart failure, Class II-IV heart disease, uncontrolled arterial hypertension (DBP ≥ 115mmHg), 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,haemosiderosis.

Primary Outcome Measures: Proportion of patients attaining target Hb ≥ of 12gm/dl

Secondary Outcome Measures: Change of plasma hemoglobin level in 4 weeks time, target Hb achievement rate (12g/dL), transferrin saturation (%), ferritin (ng/mL), MCV (fl). On each visit, adverse reactions linked with or likely to be linked with the treatment were identified. This ensured that all incidents were noted, such as arterial hypotension during injections, tachycardia, hyperthermia, arthralgia, abdominal pain, a sensation of chest tightness, headache, vertigo, digestive problems, skin eruption, allergic reactions, and a strange taste during injection.

Statistical analysis was performed using the, Statistical Package for the Social Sciences (SPSS version 12.0). Continuous variables were compared using Mann Whitney U-test. Chi square test of Fisher exact test were used to assess the effect of change in differences in categorical variables. Data values are expressed as mean ± SD, count (%age) & $p < 0.05$ is considered to be statistically significant. The quantitative variables like age were presented by calculating Mean±SD. The qualitative variables like economic class (lower, middle, upper) and efficacy of drug (yes/no) was presented by calculating frequency and percentages Difference between the two groups for the primary end point were analyzed by using chi-square test. Student T test was applied for secondary end points.

RESULTS

Table 1: Anthropometric and biologic data for mothers in IV iron sucrose and Oral iron groups

Parameters	IV Sucrose (GroupA) (n=25)	Oral Iron (GroupB) (n=25)	P Value
Mean Age (Years)	28.1 ± 5.36	27.8 ± 5.28	0.838
Mean Weight (Kg)	54.5 ± 3.45	55.9 ± 2.07	0.108
Parity (Primi / Multi)	10/15 (40%/60%)	08/17 (32%/68%)	0.556
Postpartum day on inclusion	Day 2/3	Day 2/3	-
Mean Haemoglobin (gm/dl)	6.27 ± 0.48	5.95 ± 0.62	0.087
Mean PCV (%)	18.8 ± 1.46	17.8 ± 1.86	0.087
Mean Ferritin (µg/l)	9.44 ± 3.01	10 ± 1.9	0.375
Route of Delivery:			
NVD	04 (16%)	05 (20%)	0.713
NVD with episiotomy	10 (40%)	08 (32%)	0.556
Outlet Forceps	03 (12%)	05 (25%)	0.440
Vacuum	01 (4%)	00 (0%)	0.312
LSCS	07 (28%)	08 (32%)	0.758

In our prospective study, 50 postpartum women with severe iron deficiency anemia were randomized to receive i.v. iron sucrose (GroupA) or oral iron (GroupB) treatment. All patients reported regular use of iron tablets for 2 weeks before study entry. Before treatment, iron-deficiency anaemia (ferritin <15 µg/L)was confirmed in all patients. On inclusion, the 2 groups were comparable in terms of both anthropometric and biologic data (Table I). Thirty five of them had a normal vaginal delivery and the rest 15 had a caesarean section. Before the initiation of the treatment in the i.v. iron sucrose group (GroupA) the mean values of hemoglobin and ferritine blood levels were 6.27 g/dl ±0.489 and 9.44 µg/l±3.01 correspondingly (Table I). Four weeks later, the mean values of hemoglobin were 12.35±0.66gr/dl and of ferritine 295.5±45.1 µg/l (Table III). In oral iron group (GroupB) the increase in ferritine levels was significantly lower. Baseline mean hemoglobin was 5.94±0.62 gr/dl and after 4 weeks levels were 11.48±1.05 gm/dl (Table III). As for ferritin levels the mean baseline values were 10.0±1.90 µg/l and after the fourth week 160.8±33.1µg/l (Table III). The adverse effects from the iron treatment were mild but more prominent in oral iron group (GroupB) mostly constipation, diarrhoea, altered taste nausea and gastritis (Table V).

Table 2: Change in various Haematological Parameters over 4 weeks

Group name	Levels	IV Sucrose (GroupA) (n=25)	Oral Iron (GroupB) (n=25)	P-Value
Hb (gm/dl)	Baseline	6.27±0.48	5.94±0.62	0.087
	One week	7.42±0.58	6.82±0.83	0.006*
	Two week	8.62±0.60	7.64±1.21	0.002*
	Threeweek	9.9±0.66	8.6±0.79	0.000004*
	Four week	12.35±0.66	11.48±1.05	0.004*
Hematocrit (%)	Baseline	18.8±1.46	17.8±1.76	0.087
	One week	22.2±1.74	20.4±2.49	0.006*
	Two week	25.8±1.81	22.9±3.64	0.002*
	Threeweek	29.7±2.0	25.8±2.38	0.000004*
	Four week	37.06±1.99	34.45±3.17	0.004*

Hematologic response. While a comparable increase in hemoglobin was observed for both administration routes (mean increase 1.15 g/dL in the intravenous group (GroupA) vs 0.88 g/dL in the oral group (GroupB) in the first week of treatment. Both groups showed an immediate reticulocyte response and continuous increase in hematocrit. i.v. iron sucrose group(GroupA) had greater increases in hematocrit (%) from first week of treatment 22.2±1.74 as compared to 20.4±2.49 in oral iron group (GroupB) , which is statistically significant (P <0.0006) (Table-II).

A clear increase in haemoglobin was observed in the 2 groups, rising from 6.27±0.48 g/dL to 12.35±0.66g/dl on day 28 in the IV sucrose group (GroupA) and from 5.94±0.62 g/dL to 11.48±1.05 g/dL on day 28 in the oral iron group (GroupB) .

Table 3: Change in various Haematological Parameters

Group name	Levels	IV Sucrose (GroupA) (n=25)	Oral Iron (GroupB) (n=25)	P-Value
Hb (gm/dl)	Baseline	6.27±0.48	5.94±0.62	0.087
	Four week	12.35±0.66	11.48±1.05	0.004*
Hematocrit (%)	Baseline	18.8±1.46	17.8±1.76	0.087
	Four week	37.06±1.99	34.45±3.17	0.004*
Ferritin (µg/l)	Baseline	9.44±3.01	10.0±1.90	0.375
	Four week	295.5±45.1	160.8±33.1	<0.0001 *
Trasnferrin Saturation	Baseline	7.24±1.73	8.08±1.15	0.070
(%)	Four week	29.3±4.55	22.2±1.56	<0.0001*
Reticlocyte Count (%)	Baseline	1.69±0.14	1.63±0.16	0.292
	Four week	4.27±0.18	4.2±0.19	0.209
MCHC (gm %)	Baseline	26.0±1.73	25.6±2.06	0.574
	Four week	33.1±0.97	32.08±1.41	0.009 *
MCV (fl)	Baseline	71.28±0.97	70.1±2.93	0.108
	Four week	93±1.13	85.8±3.97	<0.0001*
Hypochromasia	Baseline	46±3.82	45.6±1.35	0.357
(%)	Four week	2.37±0.14	3.01±0.95	0.001*

In 4 weeks time , at the end , mean Hb increase was more in group A(6.08±0.18g/dl) than in group B, (5.54±9.43gr/dl) Which is statistically significant (Table-III) (P <0.004) and also the increase in ferritin levels was more in group A(286.06 ±41.99)) than in group B,(150.8±31.10). Which is statistically significant (Table-III) (P <0.0001).

Twenty (80%) women in i.v. iron sucrose (GroupA) had target haemoglobin levels (>12.0 g/dL) , while 10 (40%) women in oral iron (GroupB) had achieved target haemoglobin levels in 4 weeks time , which is statistically significant (P <0.004) (Table-IV). None of the women needed additional postpartum blood transfusion.

Table 4: Change in level of Haemoglobin

Hb (gm/dl) at the end of four weeks	IV Sucrose (GroupA) (n=25) %age of patients	Oral Iron(GroupB) (n=25) %age of patients	P-Value
10-11 (gm/dl)	01(04%)	10(40%)	0.002*
11-12 (gm/dl)	04(16%)	05(20%)	0.713
>12 (gm/dl)	20(80%)	10(40%)	0004*

Data are expressed as mean ± SD. * P < 0.05 indicates Statistical significant

Iron status. Ferritin level (µg/l), transferrin saturation(%) ,MCHC (gm%), MCV(fl), Hypochromasia (%) on peripheral smear increased continuously until the end of therapy in both groups and was higher in i.v. iron sucrose (GroupA) , which is statistically significant (Table-III).

Safety- There were no serious reactions to iron sucrose(GroupA). Two patients (8%) of i.v. iron sucrose group had grade I, mild to moderate allergic reactions settled with an anti-allergic drug but not requiring discontinuation of the infusion. None of the patients had grade-II severe reaction threatening the patient's life and requiring discontinuing of infusion. Four (16%) patients reported a metallic taste, and 1(4%) reported fever. No hypotensive or hypertensive responses were seen during or after therapy. One(4%) patient developed thrombophlebitis but no thromboembolic complications were seen. Intractable gastrointestinal adverse events caused permanent study drug discontinuation in four patients (16%) (Table V) receiving oral iron(GroupB).

Table 5: Adverse effects of iron treatment

Adverse Effects	IV Sucrose (Group A) (n=25)	Discontinuation of drug	Oral Iron (Group B) (n=25)	Discontinuation of drug
Nausea	-	-	02 (8%)	-
Headache	-	-	-	-
Diarrhoea	-	-	05 (20%)	02(8%)
Constipation		-	02 (8%)	-
Anaphylaxis Grade1	02 (8%)	-	-	-
Anaphylaxis Grade 2	-	-		-
Gastritis	-	-	03 (12%)	02(8%)
Fever	01 (4%)	-	-	-
Arthritis	01 (4%)	-	-	-
Altered Taste	04 (16%)	-	03 (12%)	-
Thrombophlebitis	01 (4%)	-	-	-

DISCUSSION

Iron-deficiency anaemia is a major health problem worldwide, but responds well to iron supplementation. The responsible constellation factors producing iron deficiency anaemia generally precedes the pregnancy, including diet poor in iron content coupled with menstrual losses and a rapid succession of pregnancies in which supplemental iron was not provided. Most women begin their pregnancy with partially or completely depleted iron reserves. Thus, the severity of the anaemia is inversely related to the amount of iron reserves[1].

In these cases the parenteral forms of administration are indicated, as well as those in which the oral treatment is ineffective[2]. The same applies to patients with inflammatory bowel diseases, many of whom are iron deficient and show digestive intolerance to ferrous salts[3].

A random, prospective, open study conducted in France by Bayomeu et al [4], involving 50 patients at 6 month of gestation to compare intravenous iron sucrose versus oral route showed an increase in haemoglobin from 9.6±0.7 g/dl to 11.11±1.3 g/dl after 4 weeks of treatment (P<0.001). The results of this study regarding the use of iron sucrose are comparable to current study. In a study conducted at Aga Khan Hospital for women and children Karachi on 60 pregnant women at 12-34 weeks gestation with

iron deficiency anaemia. I/V iron sucrose were compared to iron sorbitol. Mean increase of 2.6g/dl Hb was seen in iron sucrose group[15]. In a randomized, controlled clinical trial, Seid and colleagues (2008)[5] assessed the safety, effectiveness, and tolerability of IV ferric carboxymaltose and compared with oral ferrous sulfate in women with post-partum anemia. A total of 291 women less than 10 days after delivery with Hb 10 g/dL or less were randomized to receive ferric carboxymaltose (n = 143) 1000 mg or less intravenously over 15 minutes or less, repeated weekly to a calculated replacement dose (maximum 2500 mg) or ferrous sulfate (n = 148) 325 mg orally thrice-daily for 6 weeks. Ferric carboxymaltose-treated subjects were significantly more likely to: (i) achieve a Hb greater than 12 g/dL in a shorter time period with a sustained Hb greater than 12 g/dL at day 42, (ii) achieve Hb rise 3 g/dL or greater more quickly, and (iii) attain higher serum transferrin saturation and ferritin levels. Drug-related adverse events occurred less frequently with ferric carboxymaltose. The authors concluded that IV ferric carboxymaltose was safe and well-tolerated with an efficacy superior to oral ferrous sulfate in the treatment of post-partum iron deficiency anemia. Rare anaphylactic reactions because of the use of iron sucrose have been reported in about 0.002% of cases [6,7,8,9]. A similar study was conducted by Zubair S et al [10] to assess the safety, clinical and lab response of intravenous iron therapy in iron deficiency anaemia therapy and found favourable results.

In an open, randomized controlled trial, Westad et al (2008) [11] analyzed the effect of IV ferrous sucrose compared with oral ferrous sulphate on hematological parameters and quality of life in women with post-partum anemia. A total of 128 post-partum women with hemorrhagic anemia (Hb between 6.5 g/100 ml and 8.5 g/100 ml) were included in this study. The intervention group (n = 59) received 600 mg iron sucrose intravenously followed by 200 mg iron sulphate daily from week 5. The control group (n = 70) were given 200 mg iron sulphate daily. Randomization and start of treatment occurred within 48 hours of the delivery. Participants were followed-up at 4, 8 and 12 weeks. Main outcome measures included Hb, ferritin and quality of life assessed with the Medical Outcomes Study Short Form 36 (SF-36) and the Fatigue Scale. After 4 weeks, the mean Hb values in both groups were similar (11.9 g/100 ml versus 12.3 g/100 ml, p = 0.89). The mean serum ferritin value after 4 weeks was significantly higher in the intervention group with 13.7 microg/L versus 4.2 microg/L in the control group ($p < 0.001$). At 8 and 12 weeks, the hematological parameters were similar. The total fatigue score was significantly improved in the intervention group at week 4, 8 and 12, whereas SF-36 scores did not differ. The authors concluded that women who received 600 mg IV iron sucrose followed by standard oral iron after 4 weeks, replenished their iron stores more rapidly and had a more favorable development of the fatigue score indicating improved quality of life.

Guidelines from the American College of Obstetricians and Gynecologists on anemia of pregnancy (ACOG, 2008) [12] stated that parenteral iron is useful in the rare patient who cannot tolerate or will not take modest doses or oral iron. Patients with malabsorption syndrome and severe iron deficiency anemia may benefit from parenteral therapy. The guidelines note that anaphylactic reactions have been reported in 1 percent of patients receiving parenteral iron dextran. In comparison with patients who take iron dextran, patients who take ferrous sucrose have fewer allergic reactions (8.7 versus 3.3 allergic events per 1 million doses) and a significantly lower fatality rate 31 versus 0, $p < 0.001$). The ACOG guidelines concluded that, in most circumstances, oral iron preparations are appropriate and sufficient total dose of ISC was administered at intervals and it was given in diluted form and slowly. High doses of oral iron frequently cause side effects, and noncompliance is common.

Intravenous iron treated iron deficiency anaemia of pregnancy and restored iron stores faster and more effectively than oral iron, with no serious adverse reaction[13]. The guidelines cited a randomized controlled clinical study by Bhandal & Russell (2006) [14] comparing oral versus intravenous iron sucrose for postpartum anemia, finding that women treated with intravenous iron had higher hemoglobin levels in the short term (on days 5 and 14) but that by day 40, there was no significant difference in the hemoglobin levels of the two groups.

Intravenous iron sucrose is effective in achieving target Hb of 11g/dl in 80% of patients[7]. For iron defined patients, intravenous iron is incorporated into haemoglobin within 3 to 4 weeks by erythropoiesis[8]. Indications for the use

of iron sucrose complex are: preexisting (moderate–severe) anemia; no effect of oral iron; side effects of oral iron; limited time until delivery; coexisting risks (e.g., bowel disease, renal disease); pre- and postoperative period and postpartum anemia.

Intravenous iron sucrose tolerance seems to be excellent in our study without adverse effect, in accordance with the literature. Overall; iron sucrose appears to be a treatment of choice with no serious side effects indicated in the rapid correction of anemia. Oral iron preparations are efficacious but poorly tolerated due to non-absorbed iron-mediated GI side effects.Parenteral iron therapy replenishes iron stores quicker and is better tolerated than oral therapy. The dose to be administered should take into account the ideal weight, the quantity required to restore iron reserves as evaluated by the ferritin level.

CONCLUSION

Intravenous iron therapy is safe, convenient and more effective then oral iron therapy in treatment of iron deficiency anemia and when compliance is the problem. Limitations with intravenous iron replacement include the need for medical supervision in the setting of limited healthcare resources; and the cost of i.v. iron new intravenous preparations.

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