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ORIGINAL ARTICLE

EVALUATION OF IRON SUCROSE AND ORAL IRON IN MANAGEMENT OF IRON DEFICIENCY ANAEMIA IN PREGNANCY

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ABSTRACT

Objective: To compare intravenous iron sucrose with oral iron in treatment of severe iron deficiency anaemia in pregnant women presenting at Institute of Kidney Disease and Research Centre. 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 2-08-2010.
Methodology: 50 cases with proven iron deficiency with Hb ≤7 gm/dl were included in the study. Total iron deficit was calculated using a standard formula. Target haemoglobin was 11 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: Anthropometric and biologic data for mothers in i.v. sucrose and oral iron groups was similar. 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 haemoglobin levels were achieved in 4 weeks time in 19 (76%) patients in iron sucrose group as compared to 08 (32%) of patients in oral iron group .There was significant improvement in the various haematological 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 anaemia in the iron sucrose group. Patients achieved the target of 11 gm %. Intravenous iron therapy is safe, convenient and more effective then oral iron therapy in pregnancy and is well tolerated.

Key words: Iron sucrose, anaemic pregnant women, iron deficiency anemia

INTRODUCTION

In underdeveloped countries, anaemia is a major contributory factor to maternal morbidity and mortality[1]. According to WHO about 50 per cent of women of fertile age have iron deficiency anaemia[2]. In India National Family Health Survey -II (1998) shows that 54% women in rural and 46% women in urban areas are anemic. . Inadequate antenatal care along with lack of knowledge of dietary needs of pregnant woman, and overall poor socioeconomic conditions are all responsible for this in our country[3].

According to WHO[4] anaemia is defined as "haemoglobin less than 11gm/dl and a haematocrit of less than 0.33 . 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[5]. During pregnancy, there is a great demand for iron to meet the requirement of red cells mass expansion in the

mother fetal and placental blood and blood loss at delivery[6] . Anaemia in the most common medical disorder in pregnancy and is responsible indirectly for 40-60% of the maternal death in developing countries[7]. It affects about 18% of pregnant women in developed and 35-75% of pregnant women in developing countries[8].

Iron-deficiency anaemia is a major health problem worldwide, but responds well to iron supplementation. New approaches are leading to more effective management of this condition. The introduction of second-generation i.v. iron formulations, including iron sucrose and ferric gluconate, was clearly an improvement over i.v. iron dextran. These formulations proved to be effective in the management of IDA and are not associated with the serious allergic reactions encountered with i.v. iron dextrans. An important advantage of i.v. iron over oral iron is that it may bypass hepcidin actions by directly loading transferrin and making iron available to macrophages. Iron deficiency is usually suspected in at-risk patients with declining haemoglobin (Hb) levels and then confirmed by measuring serum ferritin levels and transferrin saturation. Patients are commonly prescribed oral iron preparations because of convenience and low cost. However, the efficacy of these agents is limited by their reduced absorption rate and gastrointestinal side-effects and compliance.

We therefore evaluated the efficacy and safety of intravenous iron sucrose as compared with oral iron sulfate for the treatment of iron deficiency anemia (IDA) 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 pregnant patients >18 years old, > 24 weeks gestation, with anemia Hb ≤7 gm/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 (IV group), the total iron sucrose dose to be administered was calculated from the formula: Body Weight in kilograms (before pregnancy) × (Target haemoglobin i.e11gm/dl – Actual hemoglobin) × 0.24 + 500 mg; target hemoglobin in grams per litre was set at 11 g/dL because of physiologic hemodilution during pregnancy; actual hemoglobin in grams per litre was the patient's hemoglobin level on inclusion; 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 using a small catheter, into a vein of sufficient caliber. 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. . 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. Iron was administered by slow infusion. Treatment was stopped either after administration of the calculated dose or once the haemoglobin level had reached 11 g/dL.In addition 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 were repeated 1, 2, 3, 4 weeks after the last dose of intravenous iron. Other hematological parameters were repeated 4 weeks after completion of treatment.

Group B consisted of 25 women, who received three 200 mg iron sulphate tablets 1 t.d.s containing 60 mg of elemental iron (i.e., a total of 180 mg of elemental iron per day for 4 weeks)

Patients were required to carefully note treatment compliance on a calendar provided

for that purposeThe 2 groups were monitored both clinically and biologically. On each visit, adverse reactions linked with or likely to be linked with the treatment were identified

Demographic data were matched. 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 11gm/dl.**

Inclusion Criteria- Women who are >24 weeks of gestation with Hb≤7gm/dl, 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 ≥ 11gm/dl.

Secondary Outcome Measures: Change of plasma hemoglobin level, target Hb achievement rate (11g/dL), transferrin saturation (%), ferritin (ng/mL), MCV (fl) in 4 weeks time.

Statistical Analysis: 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's T test was applied for secondary end point.

RESULTS

On inclusion, the two groups were comparable in terms of both anthropometric and biologic data (Table 1, 2, and 3). All patients reported regular use of iron tablets for 2 weeks before study entry. Before treatment, iron-deficiency anemia (ferritin <15 µg/L) was confirmed in all patients. The groups did not differ in baseline hematologic characteristics, iron status, or time of treatment initiation (approximately 28 weeks gestation; Table 1).

Table 1: Anthropometric and biologic data for mothers in IV Sucrose and Oral iron groups (n=25)

Parameters	IV Sucrose	Oral Iron	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
Mean gestational age (wks)	28.2 ± 2.30	28.87 ± 2.40	0.165
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

Hematologic response: While a comparable increase in hemoglobin was observed for both administration routes (mean increase 1.15 gm/dL in the intravenous group vs 0.88 g/dL in the oral group in the first week of treatment. Both groups showed an immediate reticulocyte response and continuous increase in hematocrit. i.v. iron sucrose had greater increases in

hematocrit (%) from first week of treatment 22.2±1.74 as compared to 20.4±2.49 in oral iron, which is statistically significant (P<0.0006) (Table-2).

Table 2: Change in Haematological Parameters over 4 weeks (n=25)

Group name	Levels	IV Sucrose	Oral Iron	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*
	Three week	9.9±0.66	8.6±0.79	0.000004*
	Four week	11.3±0.70	10.26±1.077	0.0006 *
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*
	Three week	29.7±2.0	25.8±2.38	0.000004*
	Four week	33.9±2.11	30.77±3.23	0.0006 *

Target hemoglobin level of 11.0 g/dl was reached in 4 weeks time in i.v. iron sucrose. None of the patients in oral iron had target hemoglobin level of 11.0 g/dl in 4 weeks time with mean hemoglobin value of 9.73±1.23 g/dL at the end of 4 weeks, which is statistically significant (P<0.00002) (Table-4).

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 which is statistically significant(Table-3).

Table 3: Change in various Haematological Parameters (n=25)

Group name	Levels	IV Sucrose	Oral Iron	P-Value
Hb (gm/dl)	Baseline	6.27±0.48	5.94±0.62	0.087
	Four week	11.3±0.70	10.26±1.077	0.0006 *
Hematocrit (%)	Baseline	18.8±1.46	17.8±1.76	0.087
	Four week	33.9±2.11	30.77±3.23	0.0006 *
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*

Nineteen (76%) women in i.v. iron sucrose had normal antepartum hemoglobin levels (>11.0 g/dL) as compared to 8 (32%) women in oral iron, which is statistically significant (P<0.002) (Table-4).

None of the women needed additional antepartum or postpartum blood transfusion. Two i.v. iron sucrose patients (8%) 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.

Table 4: Change in level of Haemoglobin (n=25) at the end of four weeks

Hb (gm/dl)	IV Sucrose	Oral Iron	P-Value
9-10 (gm/dl)	02(08%)	12(48%)	0.002*
10-11 (gm/dl)	04(16%)	05(20%)	0.713
>11(gm/dl)	19(76%)	08(32%)	0.002*

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

Intractable gastrointestinal adverse events caused permanent study drug discontinuation in four patients (16%) (Table 5) receiving iron sulfate, whereas none patient had to be withdrawn because of side effects due to iron sucrose.

Table 5: Adverse effects of iron treatment (n=25)

Adverse Effects	IV Sucrose	Discontinuation of drug	Oral Iron	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%)	-	-	-

Safety: There were no serious reactions to iron sucrose. 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. A clear increase in hemoglobin was observed in the 2 groups, rising from 6.27±0.48 g/dL to 11.3±0.70 /dl on day 28 in the i.v. sucrose group and from 5.94±0.62 g/dL to 10.26±1.077 g/dL on day 28 in the oral iron group.

In 4 weeks time , at the end , mean haemoglobin increase was more in the i.v. sucrose group (5.03±0.22g/dl) than in oral iron group, (4.32±9.45gr/dl) Which is statistically significant (Table-IV) (P <0.0006) and also the increase in ferritin levels was more in i.v. sucrose group (286.06 ±41.99)) than in oral iron group ,(150.8±31.10). Which is statistically significant (Table4) (P <0.0001).

DISCUSSION

Iron-deficiency anaemia is a major health problem worldwide, but responds well to iron supplementation. New approaches are leading to more effective management of this condition. Iron deficiency is usually suspected in at-risk patients with declining haemoglobin levels and then confirmed by measuring serum ferritin levels and transferrin saturation. Iron deficiency anemia during pregnancy is common and deserves special attention because of its potential consequences. In practice, physicians are often faced with poor compliance, justified by digestive side effects that can lead to worsening anemia. In these cases the parenteral forms of administration are indicated, as well as those in which the oral treatment is ineffective. Except for bone marrow biopsy, serum ferritin is best indicator for assessment of iron stores in the non-pregnant women[2, 9]. Treatment of iron-deficiency anemia has included oral iron, intramuscular iron, iron dextran, recombinant erythropoietin and blood transfusion[10, 11]. However, most of these have their disadvantages. Even patients who respond well to oral iron therapy require a long time (months) to reach target Hb compared with weeks required in case of treatment with parenteral iron.. The use of intramuscular iron preparations is discouraged because of pain, irregular absorption and staining.

Blood transfusion may improve symptomatic anemia quickly but there is a risk of transfusion reaction and blood born infection transmission[12].

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. A random, prospective, open study conducted in France by Bayomeu et al[13] 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±1.3g/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[14] 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 another study carried out by Raja et a[1] at Rawalpindi on intravenous iron sucrose complex therapy in iron deficiency anaemia in pregnant women. Fifty pregnant women between 16-32 weeks of gestation with haemoglobin of 8 gm/dl were included. Results showed mean Hb level increased from 7.5 to 11gm/dl [11]. In present study mean Hb before therapy was 6.27±0.48 in iron sucrose group and after therapy 11.3±0.70 (P<0.00002) in 4 weeks time. Our results are consistent with the study of Raja et al.

This indicates that as the severity of anaemia increase the response to iron sucrose therapy becomes excellent. Because as soon as tissues iron deficiency is established, the serum Transferrin concentration increases in direct proportion to degree of iron deficiency [3]. Like most of the other studies there were no major adverse reactions noted in any patient in our study.

Present study shows that of i.v iron sucrose significantly (P<0.00002) increase haemoglobin levels within 4 weeks. There were no major adverse reactions.

Intravenous iron is effective in achieving target Hb of 11g/dl in 80% of patients. For iron defined patients, intravenous iron is incorporated into hemoglobin within 3 to 4 weeks by erythropoiesis [16]. Intravenous iron treated iron deficiency anemia of pregnancy and restored iron stores faster and more effectively than oral iron, with no serious adverse reaction [7].

Conclusion: Intravenous iron therapy is safe, convenient and more effective then oral iron therapy in treatment of iron deficiency anemia during pregnancy. Limitations with intravenous iron replacement include the need for medical supervision in the setting of limited healthcare resources; the need for patients to take multiple days off work and the cost of IV iron.

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