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Study for Comparison of Iron Sucrose & Iron Sorbitol Citrate in Fixed Doses in Iron Deficiency Anemia during Pregnancy in a Tertiary Care Center

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Abstract
Background: *Anemia is one of the most commonly encountered medical disorders in pregnancy & Iron deficiency is the leading cause of anemia in pregnancy. Aim of the study was to assess the efficacy of Iron Sucrose and Iron Sorbitol Citric Acid & to assess the safety and tolerability of these drugs in pregnant women with moderate anemia.*
Methods: *In this study, 100 antenatal cases of gestational age 14-32 weeks with hemoglobin 7-9 gm/dl were randomly divided into two groups of 50 each, which received a fixed dose of IV Iron Sucrose (Group A) & IM Iron Sorbitol Citric Acid therapy (Group B). The efficacy of the therapy was assessed by laboratory parameters such as hemoglobin, hematocrit, MCV, MCH, MCHC and serum ferritin level after 14 and 28 days. To assess the safety, adverse drug reactions with both the therapies were recorded.*
Results: *Pretreatment hemoglobin was 7.6±0.35 gm/dl & 7.6±0.31 gm/dl in Group A & B respectively. Hemoglobin concentration increased significantly (P<0.001), increase in Hb after 4 weeks of starting therapy was 1.2 gm/dl & 0.5 gm/dl in Group A & Group B respectively. Rise in other parameters (MCV, Ferritin etc) although were minimal but more in IV Group & statistically significant (p<0.05). Adverse events were more common with Iron Sorbitol Citric Acid therapy.*
Conclusion: *Intravenous therapy appears to be safer, faster, effective & more convenient than Intramuscular therapy in treatment of Iron deficiency anemia during pregnancy.*
Keywords: *Sorbitol, Sucrose, ferritin, Anemia, Pregnancy.*

Introduction

Anemia is a condition that develops when blood lacks enough healthy red blood cells or hemoglobin[1]. Anemia is one of the most commonly encountered medical disorders in pregnancy. Anemia is a late indicator of iron deficiency, so it is estimated that the prevalence of iron deficiency is 2.5 times that of anemia. According to WHO,

the prevalence of IDA is about 18 per cent in developed countries and 35-75 per cent (average 56%) in developing countries[2]. In India, prevalence ranges from 33 to 89 per cent[3]. WHO estimates that even among the South Asian countries, India has the highest prevalence of anemia. In NHFS-4 (2015-2016) survey, total percentage of anemia in pregnancy in India ranges from 23.6-61.4%. In India estimated maternal deaths due to Iron Deficiency Anemia (IDA) is approximately 3,26,000 with an associated disability-adjusted life years (DALYs) of 12,497,000. India contributes to about 80 % of the maternal deaths due to anemia[4].

The responsible constellation of factors producing iron deficiency anemia 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. In pregnancy, iron deficiency is exaggerated because of the ability of fetus to extract its requirements in obligatory one way direction even from iron deficient mothers. Anemia is also associated with high perinatal morbidity and mortality, abortions, preterm labour, IUGR and low birth weight babies are more common in anemic women. A 2- fold increase in the risk of preterm birth has been observed in women who have anemia in mid pregnancy[5].

The first choice in the treatment of iron deficiency anemia is the oral iron replacement therapy but it has many side effects, unpredictable absorption rate and poor compliance. Therefore, parenteral iron therapy is often required in many pregnant women.

According to recent national guidelines, time tested intramuscular iron sorbitol citric acid complex is one of the first line drug for treating moderate IDA in pregnancy[6]. The major disadvantage faced by this preparation is pain and swelling at the injection site, rapid clearance requiring higher doses and need for multiple injections leading to poor compliance and high dropout rates[7]. A novel intravenous preparation, Iron sucrose promises to be more effective as it causes slow release of elemental iron from the complex, lesser renal excretion, faster replenishment of iron stores, high availability for erythropoiesis and hence rapid rise of hemoglobin (Hb) and safe due to its low allergic potential and organ toxicity[8].

We decided to give parenteral iron in a predefined fixed dose followed by oral or parenteral iron therapy according to the severity of anemia which has shown to increase the compliance in the pregnant women in rural areas.

Therefore, this study was aimed at comparing the efficacy and safety with a fixed dose of two parenteral iron preparations, iron sucrose complex (intravenous route) and iron sorbitol citric acid (intramuscular route) in iron deficiency anemia in pregnancy.

Materials & Methods

This was an open label comparative, prospective randomized study carried out from February 2016 to September 2016 in the Department of Obstetrics & Gynecology, J K Lon Hospital, Government Medical College, Kota. Ethical Clearance was taken from the Ethical Committee of the institute. A total of 100 antenatal women between 14 & 32 weeks of gestation with a haemoglobin of 7 to 9 gm/dl & who were willing to give written informed consent, attending the In & Out patient department were included in the study. Cases who were having hemoglobin levels <7 or >9 gm/dl, gestational age <14 or >32 weeks, anaemia due to other causes, known hypersens-itivity to parenteral iron preparations, recent blood transfusion, associated cardiovascular, renal or hepatic dysfunction, Infections including malaria, hook worm infestation, schistosomiasis, hereditary defects such as sickle cell anemia, thalessemia, G6PD deficiency or history of any bleeding tendency or any complication in pregnancy (APH, PIH etc) were excluded from the study.

All the 100 cases enrolled in the study were assigned into two groups. Group A including 50 cases received intravenous iron sucrose and Group B including 50 cases received intramuscular iron

sorbitol therapy. Iron was given after proper sensitivity testing in both the groups. All the selected cases were subjected to a thorough history taking, general, systemic, and obstetrical examination. Taking target hemoglobin as 11 gm/dl, the dose of iron required in both the groups was calculated by the Ganzoni Formula:

Total iron deficit (mg) = Body wt (kg) ×{Target Hb - Actual Hb(gm/dl)}×2.4+500[9]

However, the whole dose was calculated according to hemoglobin deficit by the formula but the remaining doses were continued orally after 1 month.

Group A (IV): At the start of infusion, one ampoule of 5 ml iron sucrose (100mg elemental iron) injection. was added to 100 ml of sterile normal saline and first 25ml was infused over a period of 15 minutes. This worked as a test dose in itself. Patient was closely monitored. If no adverse reactions were seen during this period, the remaining portion of the infusion was administered over next 30 minutes. Two fixed doses were given on alternate day with a total dose of 200 mg elemental iron.

Group B (IM): At every visit for therapy, a test dose of 0.5 ml of iron sorbitol citric acid was given by deep intramuscular and observed for 1 hour and if no adverse reactions were seen during this period, remaining portion was injected by Z track technique. Daily limiting dose of 75 mg (2 ml) was administered by deep intramuscular route in gluteal region for 4 consecutive days for a total of 300 mg of elemental iron. Because the iron sorbitol citric acid is highly dialyzable, 30–35% of elemental iron is excreted directly just after its administration. Therefore, practically elemental iron was similar in both the groups.

The patients were instructed to return for follow up assessment at 14th & 28th day after the completion of the treatment. All observed adverse effects and spontaneous reports from patients were recorded. Blood sample were drawn for evaluation from both groups for the measurement of efficacy parameters (Hemoglobin level, Hematocrit (PCV), Mean corpuscular volume (MCV), Mean corpuscular hemoglobin (MCH), Mean corpuscular hemoglobin concentration (MCHC), Serum Ferritin). The adverse effects were graded into two grades based on their severity[10].

Grade I- Mild to moderate reaction, which settled with antiallergic drug but not requiring discontinuation of therapy.

Grade II – Severe reaction, threatening patient life and requiring discontinuation of therapy.

The data was analyzed by using Chi Square & Student T Test. Variations of $p < 0.05$ was considered to be statistically significant.

Results

Both the groups were comparable for age, socioeconomic status, and period of gestation & laboratory investigations (Table 1). Age & gestational weeks were almost similar in both the groups with $p>0.05$. Most of the women in IM group were multigravida (74%) while only half were multigravida in IV group (50%), p value was 0.01. According to the Modified Kuppuswamy Scale, most of the women belonged to Lower middle & upper lower socioeconomic class[11]. Hemoglobin concentration, packed cell volume, mean corpuscular volume, mean corpuscular hemoglobin & serum ferritin levels of both groups were also similar before the therapy ($p>0.05$) except for mean corpuscular hemoglobin concentration ($p<0.01$).

Mean hemoglobin was 7.6, 7.8, 8.1 respectively after 0, 14 and 28 days of initiating the therapy in the intramuscular group. In the intravenous group the in mean hemoglobin level was 7.6, 8.1 and 8.8 respectively after 0, 14 and 28 days. Mean rise in hemoglobin on day 14 and 28 as compared to day 0 was 0.2 and 0.5 gm/dl respectively in the intramuscular group. While the mean rise in hemoglobin in intravenous group was 0.5 and 1.2 gm/dl on day 14 and 28 respectively. An earlier and faster rise in hemoglobin was seen in the intravenous group in comparison to the intramuscular group and the difference was apparent on day 14 of therapy itself ($p<0.01$). Serum ferritin levels in both the groups were comparable on day 0. In the intravenous group

rise in serum ferritin from mean of 10.83ng/dl on day 0 to 14.97ng/dl on day 14 and 21.74ng/dl on day 28 was observed. In the intramuscular group rise from mean of 11.42ng/dl on day 0 to 12.34ng/dl on day 14 and 13.6ng/dl on day 28 was seen ($p<0.01$). Other parameters such as PCV, MCV & MCH value also increased significantly ($p<0.01$) except for MCHC ($p=0.09$), but the rise was more in Iron Sucrose group compared to Iron Sorbitol group.

Pain at the local site and staining were the most common side effects in the intramuscular therapy group, 10% & 12% respectively. Fever, arthralgia, epigastric pain and headache were the other minor side effects noticed in 2-6% of cases in intramuscular group. Shivering and phlebitis was noticed in 4-6% of cases in intravenous group but did not warrant discontinuation of therapy. Other minor side effects like nausea and metallic taste was seen in only 1-2 % of cases (Table 2).

Table 1: Comparison of Demography & Laboratory Investigation of Cases

	Group A IV (n=50)	Group B IM (n=50)	P value
Mean Age (In Years)	24.52	25.24	0.603
Mean period of gestation (In Weeks)	28.38	28.1	0.19
Parity ≥ 2 (% of cases)	50	74	0.01
Socioeconomic Status ≤ Class IV (% of cases)	100	98	0.68
Hemoglobin (In gm/dl)	7.6±0.35	7.6±0.31	0.34
Packed Cell Volume (In %)	24.47±1.26	24.64±1.50	0.28
Mean Corpuscular Volume (In fl)	71.29±2.66	71.13±2.04	0.37
Mean Corpuscular Hemolobin (In pg)	3.56±1.32	23.75±1.36	0.24
Mean Corpuscular Hemolobin Concentration (In gm/dl)	2 7.75±1.67	29.45±1.19	<0.01
Serum Ferritin (In ng/dl)	10.83±2.88	11.42±2.36	0.13

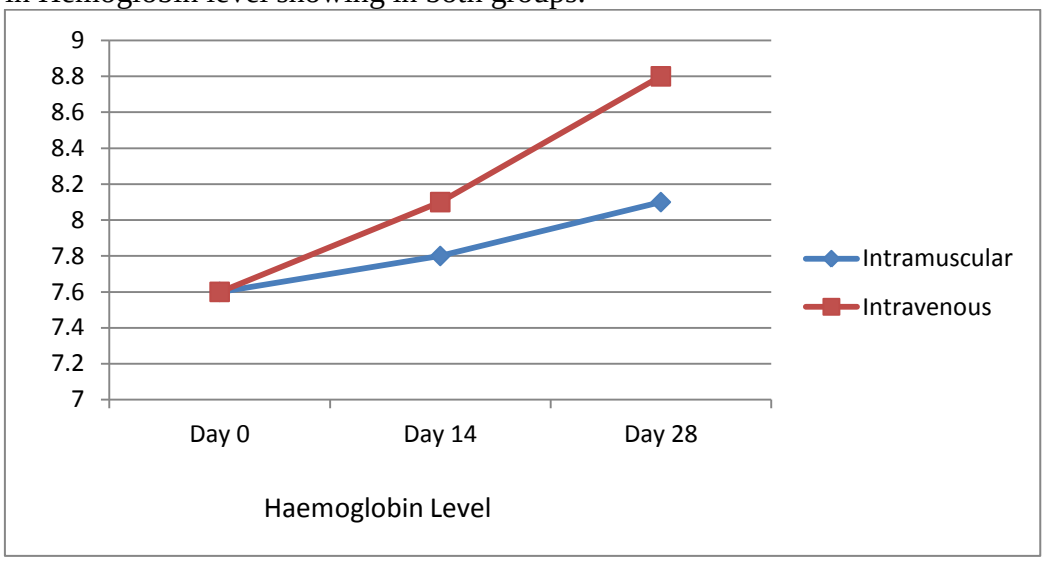
Table 2: distribution of hematological parameters according to effect of Iron therapy.

Parameters	Group A (IV)		Group B (IM)	
	Before	After	Before	After
Hemoglobin (In gm/dl)	7.6±0.35	8.8±0.39	7.6±0.31	8.1±0.35
Packed Cell Volume (In %)	24.47±1.26	26.50±1.20	24.64±1.50	25.19±1.42
Mean Corpuscular Volume (In fl)	71.29±2.66	74.01±2.86	71.13±2.04	71.87±2.09
Mean Corpuscular Hemoglobin (In pg)	23.56±1.32	25.2±1.40	23.75±1.36	24.37±1.33
Mean Corpuscular Hemoglobin Concentration (In gm/dl)	27.75±1.67	29.98±1.42	29.45±1.19	30.3±1.14
Serum Ferritin (In ng/dl)	10.83±2.88	21.74±6.03	11.42±2.36	13.6±2.36

Table 3: distribution of side Effects in both the groups of patients

Side effect	Group A (I.V)		Group B (I.M)	
	NO.	%	NO.	%
Arthragia	-	-	1	2
Fever	-	-	2	4
Headache	-	-	2	4
Epigastric pain	-	-	3	6
Local pain	-	-	5	10
Staining	-	-	6	12
Metallic taste	1	2	-	-
Nausea	1	2	-	-
Shivering	2	4	-	-
Phlebitis	3	6	-	-
Total	7	14	19	38

Figure 1 Rise in Hemoglobin level showing in both groups.



Discussion

Our study was undertaken to evaluate the efficacy and safety of intravenous iron sucrose therapy and compare it with intramuscular iron sorbitol therapy for anemia during pregnancy in fixed doses.

As seen in Table 2 & Figure 1, Mean rise in hemoglobin on day 14 and 28 as compared to day 0 was 0.2 & 0.5 gm/dl respectively in the intramuscular group while the mean rise in hemoglobin in intravenous group was 0.5 & 1.2 gm/dl on day 14 and 28 respectively. The normal rise in the hemoglobin level usually starts after three days of the starting of iron therapy, and the rate in rise of the hemoglobin level in pregnant women is 0.8 gm/dl per week as compared to non-pregnant women of 1.0-1.2 gm/dl per week[12]. The daily iron requirement in pregnancy is 4 mg/day (2.5 mg/day in early pregnancy, increasing up to 6 mg/day after 32 weeks) [13] and so for 1 month 120 mg to maximum of 150 mg iron is required. The rise could not be compared to other studies as they gave complete doses of drugs according to iron deficit rather than fixed dose as was used in this study.

The rise in IV group was comparable to Dhanani et al[7] but the rise in IM group was half as compared to IV group, exact reason could not be identified. One of the probable reason could be increased absorption of iron sorbitol citrate in the fat. However, study by S Singh et al[14] showed a rise of 3.52gm/dl in IV group & 2.33gm/dl in IM group & Suguna V et al[15] showed a rise of 4.1gm/dl in IV group & 2.93gm/dl in IM group after 1 month after giving full calculated dose, shows that the initial rise was comparable to these studies.

Both the groups had statistically significant increase in serum PCV, MCV, MCH, MCHC as seen in Table 2. However rise was more in the intravenous group. Rise in our study, although achieved by fixed doses, was comparable to Dhanani et al[7].

Only 14% (7 cases) had adverse effects which were of grade I type with IV iron sucrose therapy while 38% (19 cases) had grade I adverse effects with IM iron sorbitol citrate therapy as seen in Table 3. There were no grade II adverse effects in both the groups. Results were comparable to Singh S [14]et al & Suguna V [15]et al.

Conclusion

This study showed that the rise & rate of rise of hemoglobin in intravenous iron sucrose therapy was much higher compared to intramuscular iron sorbitol citrate group albeit with least side effects. Hence, intravenous iron sucrose therapy was found to be much more efficacious & with a better safety profile than intramuscular iron sorbitol citrate therapy for treating moderate anemia in pregnancy

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