IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 15, Issue 4 Ver. VIII (Apr. 2016), PP 69-73
www.iosrjournals.org

"Efficacy of Intravenous versus Oral Iron for Treatment of Moderate to Severe Iron Deficiency Anemia in Pregnancy and Its Effect on Fetal Outome"

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Abstract: *The aim of this study was to compare the efficacy and safety of intravenous iron sucrose and oral iron administration for the treatment of iron deficiency anemia in pregnancy. Hundred women with established iron deficiency anemia with Haemoglobin less than 10 gm/dL (moderate to severe anemia) were randomised to receive either oral ferrous sulphate tablet 335 mg twice daily (100 mg elemental iron per tablet) or calculated dose of intravenous iron sucrose. Haemoglobin, haematocrit, mean corpuscular volume, reticulocyte count were measured at recruitment and on 4th week. Secondary outcome measures were perinatal outcome and adverse drug reactions noted in both the groups. Haemoglobin, Hematocrit, Mean corpuscular volume values varied significantly with time between the two groups at 4th week (p<0.005). There was also significant variation in Reticulocyte count between the two groups at baseline and at 10 days. When compared to iron sucrose group, oral iron group had more gastro-intestinal adverse effects while there was no significant difference between the two groups in terms of peri-natal outcome. Intravenous iron sucrose treated iron deficiency anaemia of pregnancy faster, and more effectively than oral iron therapy, with no serious adverse drug reactions.*

Keywords: *Iron Deficiency Anemia, Pregnancy, Intravenous Iron Sucrose, Oral Iron.*

I. Introduction

Child birth should be a joyous event. However, unforeseen medical problems can develop and make this time difficult. Iron deficiency anemia (IDA) continues to be a very common problem in developing countries leading to a spectrum of adverse events in pregnant women. Iron deficiency anemia continues to be the leading single nutrient deficiency in the world, affecting the lives of more than 2 billion persons, despite considerable efforts to decrease its prevalence for the past 3 decades **(1, 2).** Many of these affected individuals live in the developing world; intervention approaches that appear quiet feasible in the United States or Europe are impractical in economically poorer settings **(3)**.

The World Health Organization (WHO) defines Iron deficiency anemia in the pregnant woman as Hemoglobin (Hb) of less than 11g/dl **(4)**. According to the recommendations issued by Centre for Disease Control (CDC) based in USA, the cutoff values for anemia in pregnancy differ in different trimester. For 1st and 3rd trimester the value has been set to 11.0g/dl and for 2nd trimester the value is 10.5g/dl **(5)** due to hemodilution. It is estimated that 500 million women between 15 and 49 years of age worldwide are anemic. According to WHO estimates, up to 56% of all women living in developing countries are anemic **(6)**. As stated in the National Family Health Survey – 3 in 2004-2005, anemia is a major health problem for adults as well as children, affecting 55 percent of women and 24 percent of men. The prevalence of anemia for ever-married women has increased from 52 percent in NFHS-2 to 56 percent in NFHS-3 **(7)**.

The first choice for prophylaxis and treatment of mild iron deficiency anemia in pregnancy is oral iron therapy. But in patients with moderate and severe anemia, oral therapy takes long time and compliance is a big issue in our country. Thus, pregnant women with moderate anemia should be better treated with parenteral iron therapy and/or blood transfusion depending upon individual basis (degree of anemia, hemodynamic status, period of gestation, etc.). Different Intravenous iron formulations are available such as iron dextran and iron sucrose. They have good bioavailability and are associated with fewer side effects as compared to intramuscular iron and full dose can be delivered in a single injection. As for iron sucrose, a test dose is even not required and is at physician's discretion. Intravenous route is generally preferred for administration of parenteral iron.

Keeping in mind the above mentioned facts, it was decided to undertake a study to compare the effects of the two modes of iron administration i.e. oral and intravenous for treatment of anemia in pregnancy in terms of the effect on the hemoglobin level and other RBC indices as well as side effects of the therapy and perinatal outcome.

II. Material And Methods

This study was conducted in the Department of Obstetrics and Gynaecology at S P Medical College and Associated group of Hospitals, Bikaner. It was a prospective study. It included 50 women that were given calculated dose of intravenous iron-sucrose complex (Group A) and 50 women that were given oral iron supplement (Group B) for the treatment of their moderate to severe iron deficiency anemia. These 50 women (Group B) who received oral iron supplement were taken as control for the study.

The inclusion criteria were all pregnant women coming to antenatal clinic with Hemoglobin (Hb) concentration less than 10 gm/dl who are willing to participate in the study. The exclusion criteria were any history of chronic illness eg. Liver or kidney disease or malabsorption syndromes which may be the cause of their anemia, multiple pregnancy or decompensated anemia. 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 investigation including liver and kidney function tests, urine (microscopy and culture), stool examination (for ova and cyst) were done. All women were given anti-helminthic therapy with tablet mebendazole 100mg twice daily for three days and encouraged to have protein rich diet to improve their general nutritional status. Folic acid tablets were given to all women.

Relevant to the study following investigations were done as baseline such as Hemoglobin level, Mean corpuscular volume (MCV), Mean corpuscular hemoglobin concentration (MCHC), Hematocrit and Reticulocyte count. These indices were assessed again at 4 weeks after the initiation of therapy. Secondary outcome measures were the side effects of the therapy and effect of therapy on perinatal outcome.

Group A included 50 pregnant women that received intravenous iron-sucrose. 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) + 500 mg [(8)].

Target Hb was taken as 11 gm/dl (as per WHO guidelines). Iron sucrose was given in a dose of 200mg intravenously on alternate day in 200ml normal saline over a period of one hour after checking sensitivity.

Group B included 50 pregnant women that received 2 tablets of 335mg ferrous sulphate (100mg elemental iron per tablet) twice daily for one month. Compliance was ensured by asking them to bring back the empty packets.

The primary outcome measures were Hemoglobin after 4 weeks. Secondary outcome were improvement in RBC indices, reticulocyte count and perinatal assessment (fetal birth weight, need for blood transfusion). These patients were followed in ante-natal clinic till delivery. Maternal and fetal outcome of these patients in terms of mode of delivery, fetal weight, APGAR score and NICU admission were noted. Any side-effects like gastro-intestinal intolerance, anaphylaxis etc. were also recorded. The results were noted and analyzed using SSPS (statistical package for social sciences).

III. Results

Baseline characteristics of the two groups are summarized in Table 1. Mean age of patients in Group A was 23.5 years and in Group B was 24.1 years. The age distribution of women in both groups was statistically comparable. The mean gestational age at the time of recruitment in both the groups was comparable (23.32 weeks in Group A and 24.5 weeks in Group B). Primiparous women comprised the maximum number of patients in both of the groups. The chief presenting complaints of patients of both the groups were edema (n=57) and breathlessness (n=58). In our study maximum patients received calculated dose of iron in the injectable iron group in the range of 1000-1299 mg and mean iron requirement was 1012 mg.

Various hematological parameters that were observed during the study are summarized in Table-2. The mean baseline hemoglobin in intravenous group was 7.22 gm% and in oral group was 7.45 gm%. It rose to 10.2gm% in the intravenous group and 9.0gm% in the oral group. The difference in rise was statistically significant (p value=0.0001) showing better hemoglobin rise with intravenous iron. The mean hematocrit was 26.85% at baseline and 32.32% at 4 weeks in the Intravenous iron group while the mean hematocrit was 24.26% at baseline and 28.09% at 4 weeks in the Oral iron group. The rise was 5.47% in the intravenous group and 3.83% in the oral group. The difference in rise of hematocrit between the two groups was statistically significant (p =0.0001). The mean MCV was 67.46fl at baseline and 79.43fl at 4 weeks in the Intravenous iron group and there was a rise of 11.97fl in MCV. The mean MCV was 68.37fl at baseline and 74.71fl at 4 weeks in the Oral iron group and there was a rise of 6.34fl. The difference in rise of MCV between the two groups was statistically significant (p value=0.0001). The mean MCHC was 28.36g/dL at baseline and 35.1g/dL at 4 weeks in the Intravenous iron group and therefore there was a rise of 6.74g/dL in MCHC. The mean MCHC was 30.3g/dL at baseline and 33.30g/dL at 4 weeks in the Oral iron group showing a rise of 3.0g/dL. The difference in rise of MCHC between the two groups was statistically significant (p value=0.0001). In our study, the mean Reticulocyte count was 1.89% at baseline and 3.4% at 10 days in the Intravenous iron group and therefore a rise of 1.51% was observed which shows erythropoeitic response to iron therapy. While the mean Reticulocyte count

was 2.1% at baseline and 2.5% at 10 days in the Oral iron group with a rise of 0.4%. The difference in rise of RC between the two groups was statistically significant (p value=0.0001) showing faster erythropoeisis with injectable iron in comparison to oral iron treatment.

Secondary outcome measures like side-effects of the therapy and fetal outcome parameters are summarized in Table 3. Among the patients who received oral iron, gastro-intestinal side effects (gastritis/ nausea or vomiting) were observed in 7 patients in total. No patients in our study suffered anaphylactic reaction from injectable iron therapy. In our study, among the patients who received Intravenous iron the mean fetal weight at birth was 2.94 kg and among those who received Oral iron was 3.2 kg. The difference in the mean birth weight between two groups was statistically insignificant. A total of 5 patients in the Oral iron group and 3 patients in the Intravenous iron group had pre-term delivery. Remaining all pregnancies in both the groups were full term. This difference was statistically insignificant. Maximum newborns in both of the treatment groups were having APGAR score in the range of 7-10 (44 in Intravenous group and 45 in Oral group). Only 11 newborns had APGAR score less than 7 (6 in Group A and 5 in Group B). The difference was statistically insignificant. In our study, among the patients who received Intravenous iron 6 patients had Cesarean section while 7 patients in the Oral iron group had cesarean section. Remaining all patients were delivered by normal vaginal route. This difference was statistically insignificant. 8 newborns of the mothers from the Intravenous iron group and 9 newborn from the Oral iron group were admitted to NICU for critical care. This difference was statistically insignificant.

IV. Discussion

Anemia due to iron deficiency is the commonest malnutrition disorder seen throughout the world and in India. It affects 35-75% (average 56%) of pregnant women in developing countries like India and in developed countries its prevalence ranges from 25-30%. Currently there are many oral and intravenous iron preparations available. The traditional treatments, i.e., oral iron therapy and blood transfusion, involve significant drawbacks. High doses of oral iron frequently cause side effects, and noncompliance is common. Administration of oral iron supplementations is not sufficient enough to reverse anemia promptly due to the limited absorption, gastrointestinal symptoms and poor compliance for long treatment of the patients. As far as blood transfusion is concerned, because of the risk of infection (bacterial, viral, prions) and immunomodulation associated with allergenic blood products, especially in this young and otherwise healthy population, transfusions are used only in the most severe cases and particularly in life threatening situations. Therefore, intravenous iron has been considered as an alternative in the management of iron deficiency anemia.

In our study maximum patients were in age group 21-25 years in both groups (21 patients in Group A and 25 patients in Group B). The early age that came in our study may be due to the social factor of early marriage in this region of north India. The two groups in our study were comparable in respect to the mean age. The mean gestational age at the time of recruitment in the intravenous iron sucrose group (Group A) was 23.32 weeks and in the Oral iron group (Group B) was 24.5 weeks. In the studies conducted by **Kriplani et al[(9)]**, **Neeru et al[(10)]** the mean age of gestation were 25.69, 23 weeks and 22 weeks respectively which are almost comparable to the mean age of gestation of the patients in our study. In our study maximum patients were nulliparous in both of the groups (23 patients in Group A and 27 patients in Group B), remaining patients were multiparous in both of the groups. This may be due to the fact that our study is conducted on booked ante-natal patients and level of awareness and consciousness of the family as well as the patients is maximum at the time of first pregnancy so they seek regular ante-natal check-up while multiparous women generally do not get regular anti-natal check-up. Maximum patients in our study received total dose of iron in the range of 1000-1299 mg with the mean dose of 1012 mg.

At the beginning of the study, the mean baseline hemoglobin was 7.22 gm% in the intravenous iron group and 7.45 gm% in the oral iron group. After 4 weeks of the initiation of the therapy, the mean hemoglobin rose to 10.2 gm% in the intravenous group and to 9.0 gm% in the oral iron group. This shows a rise of 2.98 gm% in Group A and 1.55 gm% in group B. The difference in the rise of hemoglobin between the two groups was statistically significant with p value of 0.0001. Similar results were obtained in other various studies as **Khalfallah et al[(11)]** (mean of 19.5 g/L vs. 12 g/L; P < 0.001)**, Neeru et al[(10)]** (23.62% rise in IV group v/s 14.11% rise in oral group), **Kriplani et al[(9)]** (7.63gm% to 11.20 gm% (*P*<0.001)) and **Abhilashini et al[(12)].** The rise in hemoglobin was noted in both of the study groups as iron supplementation stimulates erythropoeisis in iron deficient states. The rise in hemoglobin of the IV iron group was significantly more as compared to the oral iron group which may be due to many factors such as better bio-availability and better compliance. So this form of supplementation is better in whom compliance can't be ensured due to social and cultural reasons. Similarly there was significant rise in Mean Corpuscular volume, Mean Corpuscular Hemoglobin concentration and Hematocrit after 4 weeks.

At the beginning of the study, the mean baseline reticulocyte count was 1.89% in the intravenous group and 2.1% in the oral group. After 10 days, it rose to 3.4% in the IV group and 2.5% in the oral iron group

with mean rise of 1.51% in the former and 0.4% in the later group. The difference in rise of reticulocyte count between the two groups is statistically significant with the p value of 0.0001. **Kriplani et al[(9)]** showed a rise of 3.1% after 2 weeks and **Neeru et al[(10)]** showed a rise of 1.05% after 4 weeks both of which were statistically significant. Reticulocyte count is a measure of the erytropoeitic state of bone marrow. In iron deficient states, this count is low because of low availability of iron but as iron supplementation is started there is rapid rise in this count because of the stimulation of erythropoeisis. That is why this parameter was measured after 10 days of the start of therapy to measure response of the two forms of therapy on stimulation of erythropoeisis. There was a significant rise in reticulocyte count in the IV group as compared to oral group at 10 days which may be due to better bioavailability and rapid absorption of intravenous iron showing faster erythropoeitic response to parenteral iron as compared to oral iron.

Both of the groups were similar in the terms of the side effect of therapy although gastro-intestinal side effects were slightly more in the oral iron group. No patient in the IV iron group suffered anaphylaxis. Both oral and parenteral iron therapy had nearly similar obstetric and neo-natal outcome and parenteral iron therapy was not associated with poor neo-natal or maternal outcome.

Overall, Iron Deficiency Anemia appears to be a common finding during pregnancy in developing countries, especially among the poor and the least educated population which is commonly ignored and undertreated. A calculated dose of IV iron sucrose appeared to be a safe and well tolerated form of iron supplementation in this cohort of patients. The IV arm of the study led to superior outcomes in terms of correction of anemia. Further studies are warranted to confirm these findings in different populations and to improve the estimates of the magnitude of the benefits. Examination of the effects of IV plus oral iron on postpartum psychological welfare of the mother, the quality of the bonding to her baby and the rate of developmental progress of the baby would also be worth determining in future studies. Furthermore, the current guidelines for the management of iron deficiency anemia should incorporate intravenous iron sucrose as effective and safe treatment not only in the pregnant population but also in other cohorts of patients with iron deficiency anemia. Therefore, it is crucial to adapt a viable programme with the aim to utilize the local resources effectively. Certainly, successful eradication of iron deficiency anemia will result in huge benefits for community health and productivity with a major health saving not only in the developing world but also in developed nations.

V. Conclusion

The present study revealed that intravenous iron sucrose therapy was better tolerated with higher increase in mean haemoglobin, RBC indices (MCV, MCHC and Hematocrit) and reticulocyte count when compared to oral iron therapy. There were no serious side effects with intravenous iron sucrose therapy. Intravenous iron sucrose is a good substitute to oral iron therapy in moderate to severe anaemia.

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Table 1: Showing baseline characteristics of both of the study groups.

Baseline characteristic	Group A(IV Iron)	Group B(Oral Iron)
Mean age(in years)	23.5±3.25	24.1±3
Mean gestational age at the time of recruitment(in weeks)	23.32±4.9	24.5±3.56
Mean Iron requirement(in mg)	1012	

Table 2: Variation of various hematological parameters during the course of study

Parameter	Group A		Group B		P value
	Baseline	4 weeks	Baseline	4 weeks	
Hemoglobin(gm %)	7.22±1.15	10.2±.98	7.45±.81	9.0±.83	.0001
Hematocrit(%)	26.85±7.09	32.32±2.04	24.26±2.51	28.09±2.71	.0001
Mean Corpuscular volume(femtolitre)	67.46 ±9.75	79.43 ±5.5	68.37 ±8.5	74.71 ±6.15	.0001
Mean corpuscular hemoglobin concentration(gm/dl)	28.36±3.62	35.1±.94	30.3±1.56	33.30±.92	.0001
Reticulocyte count(%)(at baseline and 10 days)	1.89±.35	3.4±.43	2.1±.31	2.5±.85	.0001

Table 3: Side-effects of the two types of therapy and fetal outcome parameters

	Group A	Group B	P value
Gastro-intestinal side effects(gastritis and nausea/vomiting)	0	7	
Chills and rigors or Thrombophlebitis	5	0	
Mean Fetal weight at birth(kg)	2.94±.44	3.2±.49	.5016
Term deliveryn (%)	47(94%)	45(90%)	.4589
Normal delivery(Vaginal)n (%)	44(88%)	43(86%)	.2584
NICU Admissionn (%)	8(16%)	9(18%)	.3569