ORIGINAL ARTICLE

Parenteral Iron Therapy in the Treatment of Iron Deficiency Anemia During Pregnancy: A Randomized Controlled Trial

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Abstract

Objective: To compare the efficacy and safety profile of total dose infusion of low molecular weight iron dextran with divided doses of intravenous iron sucrose for the treatment of iron deficiency anemia during pregnancy.

Study Design: Randomized controlled trial.

Place and Duration of Study: Shifa International Hospital, Islamabad, over a period of two years from January 2008 to December 2009.

Methodology: Pregnant women at gestational age more than 12 weeks with the confirmed diagnosis of Iron Deficiency Anemia (IDA) were divided into two groups. In the group-A, intravenous iron sucrose was given in divided doses while in the group-B, total daily intake of Low Molecular Weight (LMW) of iron dextran was given. Post-infusion Hemoglobin (Hb) was checked at 4 weeks and at the time of delivery for both groups. Paired sample t-test is applied and comparison (in terms of rise in hemoglobin from pre to post) of both groups was not found to be significant.

Results: In the group-A (iron sucrose group), mean pre-infusion Hb levels was 9.09 ± 0.83 gm/dl. Mean increase in Hemoglobin (Hb) was 10.75 ± 1.097 gm/dl after 4 weeks of infusion and 11.06 ± 0.866 gm/dl at delivery ($p < 0.001$). In group-B (iron dextran group) pre-infusion haemoglobin was 8.735 ± 0.956 gm/dl and the mean increase in hemoglobin was 10.613 ± 1.22 gm/dl at 4-week while mean increase of 10.859 ± 1.11 gm/dl at the time of delivery ($p < 0.001$).

Conclusion: Both LMW iron dextran, as well as iron sucrose are equally effective in treatment of IDA during pregnancy, however, LMW iron dextran has the advantage of single visit treatment.

Key Words: *Anemia in pregnancy. Iron deficiency anemia. Parenteral iron. Iron dextran. Iron sucrose.*

INTRODUCTION

Iron deficiency is the most prevalent nutritional disorder worldwide, especially in the developing countries.[1] Increased prevalence of Iron Deficiency Anemia (IDA) in different regions of the world ranges from 12 - 43%.[2] Iron deficiency is one of the leading risk factors for disability and death worldwide, affecting an estimated two billion people.[3] Severe anemia and inability to tolerate hemorrhage are the main direct causes of maternal death worldwide.[4] Severe anemia can also increase the risk of maternal death from heart failure and augment the damage caused by antepartum or postpartum hemorrhage.[5] These women, therefore, constitute a high risk group for blood transfusions[6] as pregnancy puts these women at a risk of major peripartum blood loss.[7]

In developing countries like Pakistan, this situation is very alarming as the prevalence of anemia is very high. A study conducted on females attending Gynaecology Outpatient Department showed prevalence of iron deficiency anemia to be 43.1%.[8] IDA also affects the fetus in the form of intrauterine growth retardation, low birth weight, preterm delivery and increased perinatal morbidity and mortality. It may lead to irreversible damage to the central nervous system, with impairment of psychomotor development.[4]

In Pakistan, most of the pregnant women start gestation with significantly low iron stores, mostly due to poverty, multi-parity, dietary deficiency, poor utilization or due to compliance problems.[9] In one study, microcytic hypochromic anemia was observed in 76% women; 64% never used hematinics and no women had good dietary habits.[10]

Similarly, Ayub *et al*. reported that pregnant women belonging to all socio-economic classes were anemic.[11]

The first choice in the treatment of iron deficiency anemia for almost all patients is oral iron replacement because of its effectiveness, safety, and low cost. Routine iron supplementation during pregnancy is recommended by the World Health Organization (WHO) for the developing world.[12] Intravenous iron therapy is reserved for a small number of patients who can not tolerate oral iron therapy, are unable to adequately absorb oral iron or as is the case of majority of our population they are non-compliant.[13] Nausea and hyper emesis in early months of pregnancy and heartburns in late pregnancy makes oral iron therapy difficult to

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Received: March 18, 2011; Accepted: January 09, 2015.

tolerate in many women. In such cases treatment with intravenous iron is relatively superior to oral iron with respect to a faster increase in hemoglobin and faster replenishment of body iron stores. Intravenous iron definitely reduces the need for blood transfusions and constitutes an alternative to transfusion in profound IDA. Intravenous iron preparations comprises among others iron sucrose,[13] Low Molecular Weight (LMW) iron dextran and the recently introduced iron carboxymaltose.

Despite the high incidence and burden of disease associated with this condition in developing world, there is a paucity of good quality trials assessing clinical maternal and neonatal effects of iron administration in pregnant women with anemia.[14] Therefore, the present study was aimed to compare the efficacy of total dose LMW iron dextran with multiple doses of iron sucrose.

METHODOLOGY

This was a randomized controlled trial, conducted at Shifa International Hospital, Islamabad, over a period from January 2008 to December 2009, after getting a formal approval of Institutional Review Board and Ethics Committee. The sample size was calculated to be 180 patients. Pregnant women with gestational age more than 12 weeks and having a confirmed diagnosis of iron deficiency anemia, who were unable to tolerate oral iron, were non-compliant or suffering from irritable bowel syndrome were included in the study. These study cohorts were randomly divided into two groups “A” and “B” by computer generated randomization. The women in group-A were given intravenous iron sucrose in divided doses and participants of group-B were given Total Daily Intake (TDI) of LMW iron dextran. Women diagnosed with anemia other than iron deficiency, hemoglobinopathies, symptomatic anemia and history of allergy to any parenteral iron preparations, allergic bronchospasm and rheumatoid arthritis were excluded from the study. Women with obstetric complications like multi-fetal pregnancy, antepartum hemorrhage and hypertensive disorders were also excluded.

Diagnosis of Iron Deficiency Anemia (IDA) during pregnancy was made on the results of all the following laboratory investigations: Hemoglobin (Hb) less than 10.5 gm/dl, Mean Corpuscular Volume (MCV) less than 76 fl, serum ferritin less than 12 µg/l and peripheral smears showing microcytic hypochromic picture. Iron deficit was calculated according to the formula {weight (kg) x (11 gm/dl-actual hemoglobin (gm/dl) x 0.24 + 500 mg} (500 mg was added for iron stores).

Patients were treated either in a daycare or in an outpatient facility fully equipped with resuscitation facilities. After a written consent from all study subjects, explaining all possible side effects, a test dose was given before administering each type of parenteral iron. In group-A, iron dextran in a dose of 0.1 ml, diluted in 20 ml of normal saline was given through a burette over 20 minutes and over a period of one hour, patients were observed for any side effects of the infusion. Patients, who developed allergic reaction to the agent were removed from the study while patients who did not develop any side effects, were then given full dose calculated LMW iron dextran. It was diluted in 1000 ml of normal saline and administered slowly over a period of 6 - 8 hours. In the group-B, calculated dose for intravenous iron sucrose was slowly infused for initial 20 minutes to observe any possible allergic reaction, followed by infusion of the total amount. After completion of infusion, all study subjects were observed for any side effects for one hour. Patients were provided with a list of expected delayed reactions and were asked to report back immediately in the week following the infusion. Post-infusion Hemoglobin (Hb) was checked at 4 weeks and at delivery for both groups.

The data was analyzed in SPSS for Windows. Beside descriptive statistics, Paired t-test was used to calculate mean differences between pre and post intervention rise in Hb at 95% confidence intervals. P-value less than 0.05 was regarded as significant.

RESULTS

In the analysis of 198 pregnant women, the mean age of 28.0 ± 4.6 years was in group-A (n=93); whereas in group-B (n=105), the mean age was 26.9 ± 5.53 years. Table I shows more demographic details of the study participants.

Table II shows the pre and post treatment Hb% of both groups and at delivery. In the group-A (iron sucrose group), mean pre-infusion Hb levels was 9.09 ± 0.83 gm/dl. Mean increase in hemoglobin was 10.75 ± 1.097 gm/dl after 4 weeks of infusion and 11.06 ± 0.866 gm/dl at delivery.

In group-B (iron dextran group) preinfusion haemoglobin was 8.735 ± 0.956 gm/dl and the mean increase in hemoglobin was 10.613 ± 1.22 gm/dl at 4-week while

Table I: Demographic characteristics of the study participants.

	Group-A (Iron Sucrose) n=93 (47%)	Group-B (Iron Dextran) n=105 (53%)	Total 198
Gestational age weeks			
≥ 33	65 (69.89%)	59 (56.19%)	124 (62.62%)
≤ 33	28 (30.1%)	46 (43.8%)	74 (37.37%)
Parity			
Primigravida	30 (32.25%)	38 (36.19%)	69 (34.84%)
2 - 3	38 (40.86%)	31 (29.52%)	73(36.86%)
4 - 7	23 (24.73%)	34 (32.38%)	51 (25.75%)
≥ 8	2 (2.15%)	2 (1.9%)	5 (2.52%)
Serum ferritin			
≤ 6 µg/l	48 (51.61%)	51 (48.57%)	131 (66.16%)
≥ 6 µg/l	45 (48.38%)	54 (51.42%)	67 (33.83%)

Table II: Hemoglobin difference in both groups before and after treatment.

	Group-A (Iron Sucrose) n=93 (47%)	Group-B (Iron Dextran) n=105 (53%)
Pre-infusion Hb		
Mean	9.0 gm/dl	8.7 gm/dl
SD	0.83	0.95
Min - Max	6.6 - 10.4	6.1 - 10.5
Pre-infusion Hb at 4 weeks		
Mean	10.7 gm/dl	10.6 gm/dl
SD	1.04	1.22
Min - Max	8 - 14	8.5 - 14
P-value	< 0.001*	< 0.001*
Pre-infusion Hb at delivery		
Mean	11.06 gm/dl	10.8 gm/dl
SD	0.86	1.11
Min - Max	7.7 - 13	7 - 13.5
P-value	< 0.001**	< 0.001**

Min = Minimum; Max = Maximum; SD = Standard Deviation
** significant p-values pre and post 4 weeks after infusion.*
*** significant p-values pre and post-infusion at delivery calculated using paired t-test.*

Table III: Side effects of injectable iron in both groups.

Side effects	Group-A n (%)	Group-B n (%)
Palpitation	2 (1.9)	1 (1.1)
Shivering	1 (0.90)	2 (2,2)
Low blood pressure	1 (0.9)	1 (1.1)
Heat intolerance	1 (0.9)	1 (1.1)
Small joint stiffness	5 (5.7)	1 (1.1)
Adverse drug event	00	00

mean increase of 10.859 ± 1.11 gm/dl at the time of delivery.

Paired sample t-test was applied on pre and post infusion values at 4 weeks and at delivery for both groups. P-value < 0.001 was obtained, which was highly significant.

No major side effects were observed in both groups. Table III shows the percentage of minor side effects seen in the study participants.

DISCUSSION

It is highly important to prioritize the options for prevention and management of iron deficiency anemia during pregnancy because high prevalence of iron deficiency in the developing world has substantial health and economic costs, including poor pregnancy outcome, impaired school performance, and decreased productivity.[4]

Baseline characteristics of study population showed 30% of women were experiencing their first pregnancy, which reflects the poor nutritional status of women in the third world countries. This has also been documented in Cochrane Database Syst Rev. 2009 also that over 50% of the pregnant women in low- and middle-income countries suffer from iron deficiency anemia.[15]

This study population included 60% women who had gestational age > 33 weeks which reflects increased incidence of IDA as the pregnancy advances. Habib *et al*. in their study have documented that the percentage of anemic women increased from 29.6% in the first trimester to 34% in the third trimester.[16] Similarly, Ayub *et al*. have also documented progressive fall in the mean hemoglobin dropped from first trimester, to third trimester.[11] Similar trend was also found by Morasso *et al*.[17] and Dreyfuss *et al*.[18] These studies have demonstrated progressive iron depletion during pregnancy that became worse in the third trimester suggesting underlying deficient iron stores as a cause for anemia.

There is a great concern regarding the possible consequences for these women, when left untreated and allowed to go into labor. These women potentially can increase maternal and neonatal morbidity and mortality.[4,5] In countries like Pakistan where healthcare resources are already scarce, and maternal and neonatal services are poor; correction of iron deficiency anemia during pregnancy becomes more vital. In this study, around 66% women in both groups had serum feritin below 6 µg/l, reflecting severely depleted iron stores. This again is an indicator of poor nutritional status of these women. A study conducted at Military Hospital, Rawalpindi, documents that high prevalence of iron-deficiency anemia exists in pregnancy despite routine use of iron prophylaxis.[19]

Table II shows that effectiveness of both parenteral iron preparations, however, the iron dextran group showed more significant rise in patients who were more iron depleted. Ayub *et al*. showed similar result where marked rise was seen in those women whose iron stores were more deficient at the beginning of the study.[20]

Anemia correction was achieved in both groups before delivery effectively as is also documented by Perewusnyk *et al*., in this study, none of the study participants required blood transfusion, as also reported by Perewusnyk *et al*.[10] This is especially important in women who oppose blood transfusions for various reasons and facilities for properly screened blood transfusion are very limited and inaccessible. Comparing the cost effectiveness and convenience TDI infusion of iron dextran seems to be cost effective as it involves single visit and a single time expense for infusion, compared with multiple doses of iron sucrose. This becomes important for low-income countries putting fewer burdens on healthcare system. Compliance is also a big issue in Pakistan. The reasons for this non-compliance are many varying from undesirable gastro-intestinal symptoms to non-availability of healthcare facilities, medications or at times even inability to reach a healthcare facility. In view

of less availability or poor access to healthcare system, poor compliance, poverty and cultural and religious issues all contributing to less than adequate quality of healthcare during pregnancy, the concept of total dose infusion, seems cost effective and convenient for the patient. This would also save precious resources of the local healthcare system.

In order to ensure safety of parenteral iron, infusion of iron should be given in a daycare or outpatient setting where equipment for cardiopulmonary resuscitation is available. Infusion should be given in peripheral veins and care should be taken to avoid chemical phlebitis at the infusion site. Most importantly slow intravenous administration of either iron dextran or iron sucrose during the infusion not associated with increase in the markers of oxidation/ inflammation.[21]

There was no anaphylaxis encountered during administration of either of the parenteral iron therapies. Ayub *et al*. in their study have also reported similar findings and have recommended it as safe and effective alternative to oral iron in the treatment of IDA during pregnancy.[20] Similarly, Sinha *et al*. concluded in their comparative study that TDI of LMW iron dextran is safe and is not associated with any increase in adverse events compared to iron sucrose.[22] Plasma half life of LMW is 3 - 4 days, this stability and slow release of iron results in less oxidative stress, however, these are seen more with non-dextran iron.[23]

In this study, hypotension was reported to be 0.9% with iron dextran while 1.1% with iron sucrose. This corresponds to the information provided by both the product manufacturers according to which LMW iron dextran is less prone to produce hypotension(< 0.1%) than iron sucrose (< 1%),[1] while the frequency of serious adverse events appears to be the same.

CONCLUSION

TDI of LMW iron dextran, as well as divided doses of intravenous iron sucrose is safe and effective option for treatment of moderate to severe IDA during pregnancy.

Acknowledgement: The authors feel greatly indebted to Dr. Osama Ishtiaq, Endocrinologist, Shifa International Hospital, Islamabad, for his valuable contribution to statistical evaluation of this article.

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