International Journal of Clinical Trials
Raja S et al. Int J Clin Trials. 2022 May;9(2):66-71
http://www.ijclinicaltrials.com
pISSN 2349-3240 | eISSN 2349-3259
DOI: https://dx.doi.org/10.18203/2349-3259.ijct20221105

Original Research Article

Efficacy and safety of intravenous iron sucrose for treatment of iron deficiency anemia in pregnancy

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Received: 11 June 2021
Revised: 13 July 2021
Accepted: 14 July 2021

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ABSTRACT

Background: Leading cause of anemia is due to thedeficiency of iron in pregnant women. The aim of the study was to evaluate the efficacy of intravenous iron sucrose for the treatment of iron deficiency anemia in pregnancy particularly for those who had unsatisfactory response to oral iron therapy.
Methods: This is an open label, observational study that was carried out in Jamal Noor Hospital, Karachi for 6 months by using non-probability consecutive sampling technique, after taking ethical approval. Seventy two pregnant women with level of Hb equivalent to or <10 g/dl, Serum ferritin level equivalent to or <10 µg/l with the age ranging from 18-40 years, Gestational age 16 weeks or above were included in the study. A two times-weekly dose of 200 mg of iron sucrose (Axifer) intravenously were infused to pregnant women. However, the dose was calculated for every patient through total iron deficit. SPSS version 22 was used to analyze the data.
Results: The study results showed that the mean age of the pregnant womenwas 25.83±5.03 years, their mean weight was 59.50±10.28 kg, and their mean gestational week was 28.88±4.09. It showed that both the haemoglobin (9.01±0.74 mg/dl versus 11.92±11.07 mg/dl), (p<0.001) and ferritin levels (9.85±12.38 ng/ml versus 50.74±59.42 ng/ml), (p<0.001)were significantly increased at term after receiving intravenous iron sucrose as compared to the baseline.
Conclusions: This study concluded that the administration of iron sucrose (Axifer) intravenously is a secure and effective choice in the management of iron deficiency anemia in pregnant women particularly for those who had inadequate response to oral iron supplementation.

Keywords: Iron deficiency anemia, intravenous iron sucrose, Efficacy, Safety

INTRODUCTION

Globally, one of the most frequent nutritional deficiency is anemia. Even though, both the genders and all the ages are affected by nutritional anemia, the dilemma is more wide spread in women that lead to maternal morbidity and death, in addition to low weight of their babies at birth.[1] In developing countries, it has been predicted that about two-third of pregnant women are affected by the nutritional anemia. Though, in developing countries mostly women were anemic at the time of conception by a projected occurrence of anemia approximately 50% amongst non-pregnant women.[1] The occurrence of anemia among married women aged 15 to 44 is estimated to be 47% in rural areas and 26% in urban areas in Pakistan.[2]

Multiple factors are involved in anemia in pregnant women in the developing countries that vary by topographical areas.[3] Globally, deficiency of iron is the major cause of anemia throughout pregnancy, while the secondary cause is the constant insufficient intake and menstruation, increased requirement of the fetus and increase volume of maternal blood in pregnancy, physiologically.[3,4] Other contributing factors are genetic

causes and poor hygiene that might initiate illness and infections.[5]

Deficiency of iron and anemia are frequently existed in pregnancy.[6,7] A little drop off in hemoglobin (Hb) level is a usual physiological effect of the raised in volume of plasma in blood throughout pregnancy. Generally, following an early raise (because of the termination of menstruation), Hb levels decline at about 20 g/l and achieve their lowest level at some stage in the second trimester, return back to pre-pregnancy levels as the pregnancy proceed to term.[6,8] The requirement of iron in pregnancy is increased because of increased requirement of volume of total blood counts needed for placenta and fetus, in labor.[7,8]

In iron deficiency in pregnancy, females are susceptible to suffer from increased tiredness and weakness, temporary loss of remembrance, reduced concentration period and less performance at work, amplified stress on the cardiovascular system because of inadequate Hb level and low levels of diffusion and infiltration of blood oxygen, poorer resistance to diseases and a decreased acceptance to considerable loss of blood due to surgical procedures in labor.[9]

The recognized risks of iron deficiency become harmful for the fetus because low level of iron increase the chances of decreased level of Hb resulting in reduction of oxygen to the uterus, placenta and the fetus that is essential for development of fetus.[9] Furthermore, neonates of iron-deficiency anemia have been revealed to have a considerable increase in both behavioral and cognitive abnormalities till the age of 10 years following repletion of iron.[10] Adverse obstetric consequences, particularly untimely and early birth, low birth weight and fetal fatality can be associated with the iron deficiency anemia, even if anemia is mild to moderate.[6,9]

Regardless of haemoglobin condition, every pregnant woman must obtain prophylactic recommended dosage of iron commencing from second trimester till the end of pregnancy. Oral or parenteral iron should be rapidly given to those who develop anemia. Oral supplementation of ferrous sulfate on daily basis is effectual in order to prevent maternal anemia and iron deficiency as well, throughout in pregnancy, and decrease the chances of low birth weight.[11,12]

A variety of parenteral iron preparations are accessible that can be administered either intramuscularly or intravenously. In the beginning, iron dextran and iron sorbitol citrate was administered. Severe adverse anaphylactic reactions were observed with intravenous iron dextran so test dose was required before these injections. Therefore, iron sucrose has been projected to be harmless and effectual throughout pregnancy.[13] The advantage of iron sucrose is that there is no need of test dose before injection.[14] Iron sucrose complex (ISC) is a comparatively innovative preparation that is given intravenously for the improvement of iron deficiency anemia. This complex increases the Hb to acceptable level particularly injected in severe iron deficiency anemia in pregnant women.[15]

With the availability of restricted resources to deal with community health troubles, awareness of the local causes of diseases responsible for anemia is critical in order to intend the suitable protection and management approaches. The aim of the study was to analyze the effects and safety of IV iron sucrose to raise the Hb and ferritin level so as to overcome the iron deficiency anaemia in pregnant women in Pakistan.

METHODS

This is an open label, observational study carried out in Jamal Noor Hospital, Karachi by using non-probability consecutive sampling technique, after taking ethical approval from the Institutional Review Board of the hospital. The duration of the study was about 6 months and it was conducted from December 2019 till June 2020 in Jamal Noor Hospital, Karachi. 72 pregnant women were enrolled for this study.

Pregnant women with Hb level equivalent to or <10 g/dl, Serum ferritin level equivalent to or <15 ng/l, with the age ranging from 18-40 years, gestational age of 16 weeks till at term were included in the study while identified allergic reaction to any active component, anemia not caused by lack of iron (such as hemolytic anemia), chronic or acute bacterial infection, pregnant women with gestational age <16 weeks, excess of iron or interruption in consumption of iron (such as haemosiderosis, haemochromatosis), liver cirrhosis and hepatitis, treated with iron products intravenously or transfusion of blood in 4 weeks were excluded from the study.

Demographic data and co-morbidities were recorded at the time of registration. A two times-weekly dose of 200 mg of iron sucrose (Axifer) intravenously were infused to pregnant women, until the aim of Hb level of patient accomplished.

The total collective dose of iron sucrose, equal to the total iron deficit (mg) can find out by the hemoglobin level (Hb) and body weight (BW).

The dose of iron sucrose was individually calculated for each patient according to the total iron deficit with this formula.

$$Total\ iron\ deficit\ (mg) = BW(kg) \times (target\ Hb - actual\ Hb\ (\frac{g}{dl}) \times 2.4 * + storage\ iron\ (mg)$$

Below 35 kg BW: target Hb= 130 g/l and storage iron= 15 mg/kg BW

35 kg BW and above: target Hb= 150 g/l and storage iron= 500 mg

*Factor 0.24=0.0034 (iron content of Hb= 0.34%)×0.07 (blood volume= 7% of BW)×1000 (conversion of g to mg)

Total Iron sucrose to be administered (in ml)= Total iron deficit (mg)/20 mg iron/ml

Data analysis

SPSS version 22 was applied to analyze the data. Frequency and percentages were calculated for categorical variables such as gender, co-morbidities and adverse effects etc. Mean±Standard deviation were calculated for numerical variables such as age, Hb and Ferritin level. Wilcoxon rank- test wasused to compare mean Hb and ferritin level at, baseline and at term. P<0.05 were taken as statistically significant level.

RESULTS

The study results showed that the mean age of the pregnant women was 25.83±5.03 years, their mean weight was 59.50±10.28 kg, their mean gestational week was 28.88±4.09, 9 (12.5%) of them had gestational diabetes, 8 (11.1%) of them had hypertension, 4 (5.6%) of them had each of the hyperthyroidism, asthma and genitourinary infection whereas 3 (4.3%) of them had chronic kidney disease (Table 1).

Table 1: Baseline profile of pregnant females (n=72).

Variables	N (%)/Mean±SD
Age (years)[1]	25.83±5.03
Maternal weight (kg)[2]	59.50±10.28
Gestational week[3]	28.88±4.09
Gestational diabetes	9 (12.5)
Hypertension	8 (11.1)
Hyperthyroidism	4 (5.6)
Asthma	4 (5.6)
Chronic kidney disease[1]	3 (4.3)
Genitourinary infection	4 (5.6)
[1]N=70	
[2]N=59	
[3]N=50	

The study results further showed that both the hemoglobin (p<0.001) and ferritin levels (p<0.001) of females were significantly increased at term after receiving intravenous iron sucrose as compared to the baseline (11.92±11.07 mg/dl verzus 9.01±0.74 mg/dl and 50.74±59.42 ng/ml versus 9.85±12.38 ng/ml respectively). Furthermore, significant difference was observed in PCV (p<0.001) and MCV as well (p<0.001) (Table 2).

Table 2: Comparison of baseline and term of hematological values.

Variables	Day-zero	at Term	P value
	Mean±SD	Mean±SD	
Hb (mg/dl)	9.01±0.74	11.92±11.06	<0.001
Ferritin (ng/ml)	9.85±12.38	50.74±59.42	<0.001
Mean corpuscular volume (fl)	74.49±12.22	77.47±13.08	<0.001
Pack cell volume (%)	28.95±5.15	38.26±40.08	<0.001

DISCUSSION

Oral iron replacement is the primary option for the treatment of Iron deficiency anemia because of its efficacy, protection and economical reason.[16-18] On the other hand, Iron therapy intravenously has been specified in severe anemic conditions in which oral iron shows intolerance or contraindication, or when iron loss cannot be controlled by oral therapy, inflammatory illness and in patients with Iron deficiency anemia planned for possiblesurgery.[18,19] Our study illustrated the efficacy of intravenous iron sucrose therapy rather than oral iron supplementation in moderate to severe anemia in pregnant women.

Roughly 1000 mg of iron is required during pregnancy for the growth of fetus and placenta and the same quantity for red cell augmentation.[20] Generally, this iron is activated from iron stores. Moreover, women with already deprived stores of iron, develop deficiency of iron during pregnancy. One of the study has revealed that Hb levels less than 8 g% (moderate to severe anemia) in pregnancy are related to higher maternal morbidity whereas Hb <5 g% is linked with cardiac de-compensation and edema of lungs. Loss of even 200 ml of blood in third phase of labor leads to abrupt shock and fatality in these women.[20] As far as our study is concerned, the mean Hb level at baseline was reported 9.01±0.74 mg/dL indicating moderate to severe anemia in pregnant women at 16 weeks of gestational age that was improved to 11.92±11.07 mg/dL at term after the IV infusion of iron sucrose. Similarly in ferritin level, it was reported that statistically significant difference was observed between baseline and at term (p<0.001).

Multiple studies have proposed that IV iron sucrose is harmless and effective substitute to oral iron in the management of Iron deficiency anemia.[21-23] Our study also proved that successful outcomes were achieved after administration of IV iron sucrose in iron deficiency anemia. Another study demonstrated that administration of iron sucrose intravenously is well accepted with a

safety profile and efficiently increases the Hb levels and brings back the body iron to the normal level in anemic patients. The mean rising of Hb level was 3.29 g/dl in women while 4.58 g/dl in men; above 80% of women and 90% of men gave a positive outcome to IV iron therapy and improvement of anemia was achieved in approximately 70% of thepatients.[22] Our study was inconsistent with the above mentioned study, that showed average increase of 2.91 mg/dl of Hb level at term in pregnant women after administration of IV iron sucrose with the significant difference ($p<0.001$) between baseline and term.

A randomized control assessment reported by Neeru et al, utilized iron sucrose intravenously in contrast with oral iron for management of iron deficiency anemia and observed that efficacy of iron sucrose was more in raising hemoglobin level significantly (23.62% vs 14.11% in oral iron) ($p<0.05$).[24] Our study findings were consistent with the above mentioned study revealed that intravenous iron sucrose increased the Hb level from the baseline to term (9.01±0.74 mg/dl versus 11.92±11.07 mg/dl) with significant difference ($p<0.001$).

A retrospective study by Haldar et al on 990 pregnant women who were injected with 400 mg of iron sucrose intravenously at two primary health care centers in country side of India, observed that average rise of Hb level was 1.76 g%.[25] Our study results were contradictory with the above-cited study that revealed that after a dose of 200 mg of IV iron sucrose twice weekly, it was observed that mean increase of Hb level was 11.92±11.07 mg/dl at term after receiving intravenous iron sucrose.

In another randomized study by Dubey et al after administration of iron sucrose intravenously or oral iron in 200 pregnant women, it was observed that iron sucrose augmented hemoglobin level and iron stores more rapidly as compared to oral iron significantly ($p<0.001$).[26] Our study showed consistency with the above research, indicated that IV iron sucrose than the oral iron supplementation significantly increased the hemoglobin ($p<0.001$) as well as ferritin level ($p<0.001$) between baseline and term. Hence improves the iron deficiency anemia in pregnant women more rapidly as compared to oral iron supplementation.

Another researcher Perewunsnyk et al analyzed 400 pregnant women receiving 2000 ampoules of iron sucrose in which only 0.5% cases were reported the side effects such as metallic taste, reddening of the face and inflammatory reaction at the site of injection.

The high acceptance of the drug has been partially accredited to sluggish discharge of iron from the iron sucrose complex and also because of low tendency to cause allergic reaction of sucrose.[27] The finding of the above study is contradictory to present study, where no major side effect was reported.

Interestingly, three marketable formulations; Iron dextran, sodium ferric gluconate complex and iron sucrose are presently existing for intravenous iron treatment. All existing parenteral iron preparations can cause side-effects temporarily, like metallic taste, backache, vomiting, diarrhea, pain in abdomen, low blood pressure and allergic or even anaphylactic reactions.[28] Symptoms of anaphylaxis such as difficulty in breathing, pain in chest, angioedema, urticaria with low blood pressure, are usually abrupt, rapid, and severe, generally happening in concurrence with the initial dose of parenteral iron.[29] However, the present study does not reported any side effects related with the iron sucrose therapy.

Regarding cost effectiveness, an open label randomized controlled trial (RCT) was carried out in India across four government medical colleges, comparing cost efficiency of intravenous (IV) iron sucrose and oral iron for the remedy of anemia in pregnant women. IV iron sucrose was estimated to be more expensive but more effectual as compared to the oral therapy for treatment of severe anemia. On the other hand, IV iron sucrose decreases the chances of blood transfusion among pregnant women with severe anaemia.[30] As far as present study is concerned, IV iron sucrose (Axifer) was economical but more effective than IV iron therapy (Venofer), which reduces the probability of blood transfusion during pregnancy with iron deficiency anemia.

Thus, it has been proved that iron sucrose is well accepted as a parenteral iron preparation and has better and rapid results to raise hemoglobin levels following 3 weeks after treatment and at term with a considerable increase in serum ferritin levels as well, which is more imperative to compensate the probable loss of blood at the stage of delivery and lactational requirement. However, the study might not be immune from selection bias due to the non-probability sampling technique. Furthermore, it was a single center study so the results cannot be generalized to larger population.

CONCLUSION

This study concluded that the administration of iron sucrose intravenously (Axifer) is a secure and effective choice in the management of iron deficiency anemia in pregnant women particularly for those who had inadequate response to oral iron supplementation. Intravenous iron sucrose is well accepted along with controllable safety profile clinically and enhanced Hemoglobin and ferritin level both and thus decrease complications during pregnancy due to iron deficiency anemia.

ACKNOWLEDGEMENTS

We are thankful to Mr. Faraz Alam for providing logistic support of this research project.

Funding: Pharm Evo Private Limited
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. WHO. Maternal Health and Safe Motherhood Programme & World Health Organization. Nutrition Programme. The prevalence of anaemia in women : a tabulation of available information, 2021. Available at: https://apps.who.int/iris/handle/10665/5. Accessed on 20 November 2021.
2. Ansari NB, Badruddin SH, Goldenberg RL. Anemia prevalence and risk factors in pregnant women in an urban area of Pakistan. FoodNutr Bull. 2008;29(2):132-9.
3. van den Broek N. Anaemia in pregnancy in developing countries. Br J ObstetGynaecol. 1998;105(4):385-90.
4. Gopalan C. Current food and nutrition situation in south Asian and south-east Asian countries. Biomed Environ Sci. 1996;9(2-3):102-16.
5. Seshadri S. Prevalence of micronutrient deficiency particularly of iron, zinc and folic acid in pregnant women in South East Asia. Br J Nutr. 2001;85(suppl 2):S87-92.
6. Cao C, O'Brien KO. Pregnancy and iron homeostasis: an update. Nutr Rev. 2013;71(1):35-51.
7. Burke RM, Leon JS, Suchdev PS. Identification, prevention and treatment of iron deficiency during the first 1000 days. Nutrients. 2014;6(10):4093-114.
8. Scholl TO. Iron status during pregnancy: setting the stage for mother and infant. Am. J. Clin. Nutr. 2005;81(5):S1218-22.
9. Zimmermann MB, Hurrell RF. Nutritional iron deficiency. Lancet. 2007;370(9586):511-20.
10. Congdon EL, Westerlund A, Algarin CR. Iron deficiency in infancy is associated with altered neural correlates of recognition memory at 10 years. J. Pediatr. 2012;160(6):1027-33.
11. Peña-Rosas JP, De-Regil LM, Dowswell T, Viteri FE. Daily oral iron supplementation during pregnancy. Cochrane Database Syst Rev. 2012;12:CD004736.
12. Haider BA, Olofin I, Wang M, Spiegelman D, Ezzati M, Fawzi WW. Nutrition Impact Model Study Group (anaemia). Anaemia, prenatal iron use, and risk of adverse pregnancy outcomes: systematic review and meta-analysis. BMJ. 2013;346.
13. Silverstein SB, Rodgers GM. Parenteral iron therapy options. Am J Hematol. 2004;76(1):74-8.
14. Van Wyck DB, Cavallo G, Spinowitz BS, Adhikarla R, Gagnon S, Charytan C et al. Safety and efficacy of iron sucrose in patients sensitive to iron dextran: North American clinical trial. Am J Kidney Dis. 2000;36(1):88-97.
15. Kriplani A, Mahey R, Dash BB, Kulshreshta V, Agarwal N, Bhatla N. Intravenous iron sucrose therapy for moderate to severe anaemia in pregnancy. Indian J Med Res. 2013;138(1):78-82.
16. Auerbach M, Ballard H. Clinical use of intravenous iron: administration, efficacy, and safety. Hematology Am SocHematolEduc Program. 2010;2010:338-47.
17. Cançado RD, Lobo C, Friedrich JR. Tratamento da anemia ferropriva com ferro via parenteral. Rev Bras HematolHemoter. 2010;32(2):121-8.
18. Muñoz M, Breymann C, García-Erce JA, Gómez-Ramírez S, Comin J, Bisbe E. Efficacy and safety of intravenous iron therapy as an alternative/adjunct to allogeneic blood transfusion. Vox Sang. 2008;94(3):172-83.
19. Lindgren S, Wikman O, Befrits R, Blom H, Eriksson A, Granno C et al. Intravenous iron sucrose is superior to oral iron sulphate for correcting anaemia and restoring iron stores in IBD patients: A randomized, controlled, evaluator-blind, multicentre study. Scand J Gastroenterol. 2009;44(7):838-45.
20. Toteja GS, Singh P, Dhillon BS, Saxena BN, Ahmed FU, Singh RP et al. Prevalence of anemia among pregnant women and adolescent girls in 16 districts of India. Food Nutr Bull. 2006;27(4):311-5.
21. Al RA, Unlubilgin E, Kandemir O, Yalvac S, Cakir L, Haberal A. Intravenous versus oral iron for treatment of anemia in pregnancy. Obstet Gynecol. 2005;106(6):1135-40.
22. Cançado RD, Novis de Figueiredo PO, AlbeOlivatoMS,Chiattone CS. Efficacy and safety of intravenous iron sucrose in treating adults with iron deficiency anemia. Rev Bras HematolHemoter. 2011;33(6):439-43.
23. Bhandal N, Russell R. Intravenous versus oral iron therapy for postpartum anaemia. BJOG. 2006;113(11)1248-52.
24. Neeru S, Nair NS, Rai L. Iron sucrose versus oral iron therapy in pregnancy anemia. Indian J Comm Med. 2012;37(4):214-8.
25. Haldar P, Kant S, Yadav V, Majhi J, Malhotra S, Kaur R et al. Effect of intravenous iron sucrose on hemoglobin level, when administered in a standard-dose, to anemic pregnant women in rural Northern India. J Family Med Prim Care. 2018;7(4):762.
26. Dubey S, Suri V, Aggarawal N, Das R. Is it safe to use intravenous iron sucrose during pregnancy? a randomized controlled trial. Int J ReprodContraceptObstet Gynecol. 2013;2(4):544-9.
27. Perewusnyk G, Huch R, Huch A, Breymann C. Parenteral iron therapy in obstetrics: 8 years experience with iron-sucrose complex. Br J Nutr. 2002;88(1):3-10.
28. Chandler G, Harchowal J, Macdougall IC. Intravenous iron sucrose: establishing a safe dose. Am J Kidney Dis. 2001;38(5):988-91.
29. National Kidney Foundation. KDOQI Clinical Practice Guidelines and Clinical Practice

Recommendations for Anemia in Chronic Kidney Disease. Am J Kidney Dis. 2006;47(3):S1-146.
30. Ray S, Neogi SB, Singh R, Devasenapathy N, Zodpey S. Is IV iron sucrose a cost-effective option for treatment of severe anemia in pregnancy as compared with oral iron? Health Policy and Planning. 2020;35(10):23-34.

Cite this article as: Raja S, Saleem E, Sohail S, Shams H. Efficacy and safety of intravenous iron sucrose for treatment of iron deficiency anemia in pregnancy. Int J Clin Trials 2022;9(2):66-71.