TITLE PAGE

Original Research Article

Title: A study of effectiveness & safety of intra venous Iron sucrose therapy in antenatal women with Iron deficiency anemia

Running title: Effectiveness & safety of intra venous Iron sucrose therapy in antenatal women with Iron deficiency anemia

ABSTRACT

Aims & Objectives: To determine the effectiveness & safety of intra venous Iron sucrose therapy in antenatal women with Iron deficiency anaemia

Methodology: It is a retrospective study with secondary data analysis in which we have analyzed the data collected from January 2019 to December 2019 at the Nootan general hospital, Visnagar, Gujarat, India, of pregnant women with moderate to severe anaemia (Hb 6 to 8gm%) in the second or third trimester(20 to 34weeks of gestation) during routine antenatal care who were prescribed Intravenous Iron sucrose in a standard-dose of 1000 mg given as 200 mg on alternate days after confirming the iron deficiency anaemia. Effectiveness of the therapy has been studied by comparing the Hb level before start of the therapy (baseline)and 4 week or more after the last infusion (endline) and safety profile of the therapy has been assessed by noticing any adverse drug reaction after starting the infusion.

Results: Mean increase in Hb in cases of moderate & severe anemia was 3.7 g/dL (1.2) and 3.9(1.25) g/dL respectively. Overall rise in Hb was 3.79 g/dL (1.1)(95% CL: 3.35, 4.23). Calculated p value in our study is < 0.001 which is statistically significant.

Conclusion: The mean increase in Hb level was 3.79 g/dL when 1000 mg of IVIS was given to pregnant women with moderate and severe anemia. Pregnant women with severe anemia had larger increase in Hb level when compared with pregnant women with moderate anemia. We recommend that IVIS should be included as second choice for severely anemic pregnant women who are unable/unwilling to undergo blood transfusion.

Key words: Iron deficiency anemia, antenatal women, Iron sucrose complex, parental Iron therapy

INTRODUCTION:

Iron deficiency and its consequences continue to be prevalent in epidemic proportions despite major health reforms over the past cenury[1]. Estimates from WHO report that from 35 to 75% of pregnant women in developing countries are anemic[2]. Prevalence of anaemia among pregnant women in India is 57%[3] and Iron deficiency anaemia is responsible for 95% of anaemia during pregnancy[4]. About half of the global maternal deaths due to anaemia occur in South Asian countries; India contributes to about 80 per cent of this mortality ratio [5] . Although the adverse consequences on maternal and child health are well known, it continue to be sub-optimaly managed. In the current article we focus on management of Iron deficiency anaemia in pregnancy as it is one of the most wide spread of all nutritional deficiencies in Pregnancy.

The standard treatment in majority of the institutions is oral iron with blood transfusion reserved for severe or emergency cases. Oral iron takes long time to correct the anaemia and leads to significant gastrointestinal side effects on larger doses. Blood transfusion also has its own hazards like mismatch blood transfusion, transmission of deadly viral infections like HIV, CMV, Hepatitis and anaphylaxis. So there is a need of safe and effective alternative like injectable iron preparation which can be administered in short period with good safety profile. Iron dextran, the first parenteral iron used, lost its popularity due to anaphylaxis.

Clinical trials and the long history of the use of iron sucrose injection worldwide have established the efficacy and safety of this drug in patients with iron deficiency anaemia; it is metabolically available very quickly after administration besides being safe, convenient and more effective than intramuscular iron therapy in the treatment if iron deficiency anaemia during pregnancy[6].This study was therefore to evaluate the effectiveness and safety of intravenous Iron sucrose therapy in antenatal women with Iron deficiency anaemia.

MATERIALS & METHODS:

It is a retrospective study with secondary data analysis in which we have analyzed the data collected from January 2019 to December 2019 at the Nootan general hospital,Visnagar, Gujarat, India, of pregnant women with moderate to severe anaemia (Hb 6 to 8gm%) in the second or third trimester(20 to 34weeks of gestation) during routine antenatal care who were prescribed Intravenous Iron sucrose in a standard-dose of 1000 mg given as 200 mg on alternate days after confirming the iron deficiency anaemia. Effectiveness of the therapy has been studied by comparing the Hb level before start of the therapy (baseline)and 4-week or more after the last infusion (endline) and safety profile of the therapy has been assessed by noticing any adverse drug reaction after starting the infusion. The eligible women were counselled on the merits of the IVIS. Eligible pregnant women were prescribed a uniform total dose of 1000 mg of IVIS. This dose was administered in five equally divided doses of 200 mg of IVIS diluted in 100 ml of normal saline as intravenous infusion over a period of 30–40 min, on alternate days. In the first dose, the rate of infusion was slow at 15–20 drops/min for first 5 min. If no adverse reaction was observed, the full dose of 200 mg was given in around 30 min. Test dose was not required for IVIS. The five subsequent doses were administered on alternate days. Women were counselled to not take any oral iron supplementation. All pregnant women were advised to come for follow-up measurement of Hb level any time after 4 weeks of the last infusion of IVIS.

Study Design:

Type: Retrospective analytical study

Location: Nootan General Hospital, Visnagar, Gujarat, India

Duration: 1 year.

Sample size: We have done a retrospective analysis of the routine clinical data that were recorded as part of hospital record after taking permission from the concerned authority.

Inclusion criteria: All the pregnant women with 20 to 34 weeks of gestation and Hb of 6 to 8gm% who received Intravenous iron sucrose therapy between January to December 2019.

Statistical analysis: Data was entered in microsoft excel sheet (2016) and discriptive analysis was done. Statatical significance of the study has been calculated by T test (P value). Data were analysed on Hb level before start of the therapy (baseline), and at 4-week or later after the last IVIS infusion (endline). Analysis of data was done by MedCalc version 9.2.0.1. Descriptive analysis of the change in Hb level is presented as mean (standard deviation [SD]) and 95% confidence interval (CI). The Institute Ethics Committee of the the Nootan medical college & research centre, Visnagar, Gujarat, India approved the study.

RESULTS:

A total of 110 pregnant women received IVIS. Both baseline and endline Hb level were available for all 110 pregnant women who were included in the analysis. At baseline, the proportion of moderate and severe anemia was 80% and 20%, respectively [Table 1]. The number of pregnant women with severe anemia declined from 22 to 20, (90.9% reduction). Similarly, the reduction in moderate anemia was 82.9% [Table 1]. Overall, the mean (SD) Hb level increased from 7.2 g/dL (0.7) at baseline, to 10.99 g/dL (1.2) at endline, with a mean increase of 3.79 g/dL (1.1). No serious adverse reactions were reported during the observation period.

Overall, 28.18 % pregnant women achieved normal Hb level (Hb >11 g/dL) at the time of endline measurement. The proportion of pregnant women who achieved normal Hb level was 34.09 % and 22.7 % for those with moderate and severe anemia at baseline, respectively. Although only 28.18 % pregnant women achieved normal Hb level, a large proportion of them (70 %) changed to a less severe category of anemia.

Mean increase in Hb in cases of moderate & severe anemia was 3.7 g/dL (1.2) and 3.9(1.25) g/dL respectively. Overall rise in Hb was 3.79 g/dL (1.1)(95% CL:

3.35, 4.23). Calculated p value in our study is < 0.001 which is statistically significant.

DISCUSSION:

In our study, the change in Hb level 4 week after last dose of IVIS infusion was measured . The mean increase in Hb level was 3.79 g/dL (95% CI: 3.35, 4.23). We could not directly compare our study results with other published studies or articles as there were differences in inclusion criteria, target Hb level, allowance made for iron store repletion, and time of endline Hb measurement[7,8,9,10,11,12] . Nonetheless, our finding is well within the range of reported increase in Hb level[7,8,9,10,11,12] .

In our study, only 16.4% of moderately anemic pregnant women became non-anemic after receiving IVIS, 15.4% of them remained in the same category even after receiving IVIS in recommended dose.The total requirement of iron during pregnancy is approximately 1000 mg (500 mg for the developing fetus and placenta, and a similar amount for red cell increment, so the recommended dose of 1000 mg of iron was sufficient to achieve the desired sufficient and necessary to achieve desired level of Hb to avoid complication of anemia in pregnancy antenataly, during delivery and during post partum period.

In India, the standard measure for prophylaxis against anemia is oral iron supplementation for 100 days, where 100 mg of elemental iron plus 500mcg of folic acid is given daily for atleast 100 days where as 200 mg of elemental iron is given daily to pregnant woman with anemia(Hb: 8 to 11 g/dL) for at least 100 days[13] . For those with Hb level 5-8 g/dL, parenteral iron administration is recommended, while transfusion of packed red cell is recommended for those with Hb level <5 g/dL[13]. Supplementation with oral iron or iron/folic acid provided either daily or weekly is effective to prevent anemia and iron deficiency at term[14] . However, in India, there has been no perceptible decline in the prevalence of anemia among pregnant women in the last few decades. The failure was attributed primarily to poor adherence to oral iron therapy among pregnant women, linked to perceived and experienced side effects, forgetfulness, inadequate counseling, logistics of tablet distribution, and beliefs about adverse effects of consumption of medications during pregnancy.

More proximal determinants included difficult access and poor utilization of prenatal health-care services[15,16,17,18]

It has been reported that the effect of oral iron supplementation on Hb level becomes apparent within 3 months of start of supplementation[19] . The change in Hb level after administration of IVIS is therefore likely to become apparent much earlier. Most of the reported studies had measured Hb level when the interval between last dose of IVIS, and Hb measurement was at least 4 weeks[7,8,9,10,11,12] . During the course of normal pregnancy, the Hb level declines and reaches nadir at 20 weeks of gestation, remains fairly constant up to 30 weeks, and rises slightly thereafter[20,21] .

We enrolled pregnant women during their second trimester of gestation when the Hb level was in naturally declining stage. Therefore, the baseline measurement of Hb was performed when the Hb level was likely to be low. The measurement of endline Hb level was done after 4 weeks of last dose of IVIS infusion. We did not have a comparator arm. Hence, we are unable to quantify the fraction of the observed 3.79 g/dL of increase in Hb level which could be apportioned to the intervention. However, we assume that the natural increase in Hb level (without intervention) would have been negligible.

Severely anemic pregnant women (Hb level <7 g/dL) in late trimester were advised blood transfusion. Those who refused to follow the advice were offered IVIS in their best interest. The mean increase in Hb level among severely anemic pregnant women was 3.9 g/dL, and the mean endline Hb was 10.2 g/dL (95% CI: 9.38, 10.42). The Hb level during pregnancy is associated with maternal and fetal outcome[2] . Literature suggests that the odds of maternal and fetal adverse outcomes are substantially higher for Hb level <9 gm/Dl[[24,25]] . Thus, though only 22.7% severely anemic pregnant women became nonanemic, but as a group, they reached a mean Hb level that was likely to protect them from the adverse consequences of anemia during pregnancy.

When a public health program is to be implemented over large and diverse geographical area through para-medical field staff, it is often advantageous to recommend a simple and uniform guideline. This could have been the rationale

for recommending uniform total dose of 1000 mg of IVIS irrespective of Hb level of an individual pregnant woman.

We compared outcomes in severely versus moderately anemic pregnant women and found that the mean increase in Hb level (3.9 vs. 3.7 g/dL), conversion to less severe category of anemia (95.45 % vs. 88.63%), and rate of increase in Hb level was higher in severely anemic pregnant women. Existing guidelines did not include administration of IVIS as a treatment option for severely anemic pregnant women. However, here, we provide evidence that not only severely anemic pregnant women benefitted, but they did so at an accelerated pace and outperformed moderately anemic pregnant women. We feel that as a public health approach, in conditions where safe blood supply is inadequate, or woman refuse to avail it for various reasons, IVIS should also be included as a second treatment option for severe anemia in pregnancy.

Measurement of Hb level was done by Hemocue. This tool is considered to be valid and reliable. The sensitivity of HemoCue method was 0.75 and specificity 1.0 considering cyanmethemoglobin method as gold standard [27]. Same tool had been used in a nationwide survey of anemia in the past as well[1]. Unfortunately, we had not instituted any quality assurance program during the course of the service delivery. Same tool was used for both baseline as well as endline measurement of Hb level.

CONCLUSION:

The mean increase in Hb level was 3.79 g/dL when 1000 mg of IVIS was given to pregnant women with moderate and severe anemia. Pregnant women with severe anemia had larger increase in Hb level when compared with pregnant women with moderate anemia. IVIS should be included as second choice for severely anemic pregnant women who are unable/unwilling to undergo blood transfusion.

REFERENCES:

1. Stevens GA, Finucane MM, De-Regil LM, et al. Global, regional, and national trends in haemoglobin concentration and prevalence of total and severe anaemia in children and pregnant and non-pregnant women for 1995-2011: a systematic analysis of population-representative

data. Lancet Glob Health. 2013;1(1):e16–e25. [PMC free article] [PubMed] [Google Scholar]
2. The prevalence of anaemia in women: A tabulation of available information. 2nd ed. Geneva: World Health Organization; 1992. World Health Organization. [Google Scholar]
3. Malhotra J. Iron deficiency anemia in India. FOGSI Focus 2009; 9–11.
4. Raja KS, Janjua NB, Khokhar N. Intravenous iron sucrose complex therapy in iron deficiency anemia in the pregnant women. Rawal Med J. 2003;28: 40–3.
5. 5.Toteja GS, Singh P, Dhillon BS, et al. Prevalence of anemia among pregnant women and adolescent girls in 16 districts of India. Food Nutr Bull 2006; 27 : 311-5. Back to cited text no. 3[PUBMED]
6. Wali A, Mushtaq A, Nilofer Comparative study: efficacy, safety and compliance of intravenous iron sucrose and intramuscular iron sorbitol in iron deficiency anemia of pregnancy. J Pak Med Assoc. 2002;52:392–395. [PubMed] [Google Scholar]
7. Gupta A, Rathore AM, Manaktala U, Gupta A, Gupta S. Role of intravenous iron sucrose in correction of anemia in antenatal women with advanced pregnancy. Indian J Hematol Blood Transfus. 2015;31:251–4. [PMC free article] [PubMed] [Google Scholar]
8. Thakor N, Bhagora S, Asari U, Kharadi A, Pandor J, Prajapati D. Effect of intravenous iron sucrose therapy for moderate-to-severe anemia in pregnancy: A longitudinal study. Int J Med Sci Public Health. 2015;4:11–4. [Google Scholar]
9. Patel S, Goyal A, Shrivastava A, Verma R. Safety and efficacy of parenteral iron sucrose complex therapy in iron deficiency anemia in antenatal and postnatal women. Int J Med Sci Public Health. 2013;2:360–3. [Google Scholar]
10. Shrivastava D, Inamdar S, Bhute S, Singh A. Effectiveness of intravenous iron sucrose in management of iron-deficient anemia of pregnancy at rural hospital set up. J Obstet Gynaecol India. 2012;62:154–7. [PMC free article] [PubMed] [Google Scholar]
11. Dewan B, Philipose N, Balasubramanian A. Assessment of intravenous iron sucrose in the management of anemia in gynecological and obstetrical practice. J Obstet Gynaecol India. 2012;62:281–5. [PMC free article] [PubMed] [Google Scholar]

12. Bayoumeu F, Subiran-Buisset C, Baka NE, et al. Iron therapy in iron deficiency anaemia in pregnancy: intravenous route versus oral route. *Am J Obstet Gynaecol.* 2002;186:518–522. doi: 10.1067/mob.2002.121894. [PubMed] [CrossRef] [Google Scholar]
13. Guidelines for Control of Iron Deficiency Anaemia. National Iron-plus Initiative. Ministry of Health and Family Welfare. Government of India. 2013. [Last accessed on 2016 Dec 12]. Available from: http://www.nrhm.gov.in/images/pdf/programmes/child-health/guidelines/Control-of-Iron-Deficiency-Anaemia.pdf .
14. Peña-Rosas JP, Viteri FE. Effects and safety of preventive oral iron or iron+folic acid supplementation for women during pregnancy. Cochrane Database Syst Rev. 2009 Oct;7(4):CD004736. [PubMed] [Google Scholar]
15. Mithra P, Unnikrishnan B, Rekha T, Nithin K, Mohan K, Kulkarni V, et al. Compliance with iron-folic acid (IFA) therapy among pregnant women in an urban area of South India. Afr Health Sci. 2013;13:880–5. [PMC free article] [PubMed] [Google Scholar]
16. Galloway R, McGuire J. Determinants of compliance with iron supplementation: Supplies, side effects, or psychology? Soc Sci Med. 1994;39:381–90. [PubMed] [Google Scholar]
17. 28. Galloway R, Dusch E, Elder L, Achadi E, Grajeda R, Hurtado E, et al. Women's perceptions of iron deficiency and anemia prevention and control in eight developing countries. Soc Sci Med. 2002;55:529–44. [PubMed] [Google Scholar]
18. Malagi U, Reddy M, Naik R. Evaluation of national nutritional anaemia control programme in Dharwad (Karnataka) J Hum Ecol. 2006;20:279–81. [Google Scholar]
19. Puolakka J, Jänne O, Pakarinen A, Järvinen PA, Vihko R. Serum ferritin as a measure of iron stores during and after normal pregnancy with and without iron supplements. Acta Obstet Gynecol Scand Suppl. 1980;95:43–51. [PubMed] [Google Scholar]
20. Paintin DB, Thomson AM, Hytten FE. Iron and the haemoglobin level in pregnancy. J Obstet Gynecol Br Commonw. 1966;73:181–90. [Google Scholar]

21. Lu ZM, Goldenberg RL, Cliver SP, Cutter G, Blankson M. The relationship between maternal hematocrit and pregnancy outcome. Obstet Gynecol. 1991;77:190–4. [PubMed] [Google Scholar]
22. Gonzales GF, Steenland K, Tapia V. Maternal hemoglobin level and fetal outcome at low and high altitudes. Am J Physiol Regul Integr Comp Physiol. 2009;297:R1477–85. [PMC free article] [PubMed] [Google Scholar]
23. Butler NR, Bonham DG. Perinatal mortality. First Report of the 1958 British Perinatal Mortality Survey. Edinburgh: E & S Livingstone; 1963. [Google Scholar]
24. Cançado RD, de Figueiredo PO, Olivato MC, Chiattone CS. Efficacy and safety of intravenous iron sucrose in treating adults with iron deficiency anemia. Rev Bras Hematol Hemoter. 2011;33:439–43. [PMC free article] [PubMed] [Google Scholar]
25. Cançado R, Lobo C, Friedrich JR. Iron deficiency anemia treatment with parenteral iron. Rev Bras Hematol Hemoter. 2010;32(Suppl 2):121–8. [Google Scholar]
26. Sharma DC. India still struggles with rural doctor shortages. Lancet. 2015;386:2381–2. [PubMed] [Google Scholar]
27. Bhaskaram P, Balakrishna N, Radhakrishna KV, Krishnaswamy K. Validation of hemoglobin estimation using Hemocue. Indian J Pediatr. 2003;70:25–8. [PubMed] [Google Scholar]

Table 1

Baseline and endline hemoglobin level among pregnant women (n=110)

Hb levels	At baseline	At endline
Normal (> 11 g/dL)		31
Mild (10 – 10.9 g/dL)		62

Moderate (Hb 7-9.9 g/dL)	88	15
Severe (Hb < 7g/dL)	22	2
Total (n)	110	110

Table 2

Mean change in Hb among pregnant women after IVIS therapy (n=110)

Hb levels	At baseline	At endline	Mean change in g/dL (SD), 95% CI
Moderate anemia (n=88) Mean Hb in g/dL(SD) 95% CI	7.5 (0.8) 7.33, 7.67	11.2 (1.15) 10.95, 11.44	3.7 (1.2) 3.48, 3.92
Severe anemia (n=22) Mean Hb in g/dL(SD) 95% CI	6.3 (0.6) 6.04, 6.55	10.2 (1.25) 9.38, 10.42	3.9 (1.25) 3.37, 4.42
Mean change in Hb (overall) Mean Hb in g/dL(SD) 95% CI	7.2 (0.7) 7.07, 7.33	10.99 (1.2) 10.77, 11.21	3.79 (1.1) 3.35, 4.23
P value - 0.0001			