TITLE PAGE

Original Research Article

Title: A study of safety and effectiveness of intra venous Iron sucrose therapy in pregnant women suffering from moderate to severe Iron deficiency anaemia disease.

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

ABSTRACT

Aims & Objectives: To determine the effectiveness and safety of IV Iron sucrose therapy in antenatal women with moderate to severe Iron deficiency anaemia

Methodology: It is a retrospective study with secondary data analysis. We have analyzed the data collected from January 2019 to December 2019 at the Nootan general hospital, Visnagar, Gujarat, India. Analysis of antenatal women with moderate to severe anaemia (Hb 6 to 8gm%) in the second trimester and early third trimester(20 to 34weeks of gestation) are done during their 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 at the point baseline where start of the treatment and 4 week or more after the last treatment was given (endline). The 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 anaemia was 3.69 g/dl (1.19) and 3.91 (1.25) g/dl respectively. Overall rise of Haemoglobin 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 rise in Haemoglobin level in our study was 3.79 g/dL when 1000 mg of Intra venous iron sucrose was given to antenatal women with moderate as well as severe anaemia is concerned. The magnitude of the

anaemia difference is directly proportional rise of haemoglobin level. The amount of haemoglobin rise is seen more in severe anaemic antenatal patients compared with moderate antenatal patients. We recommend that Intravenous iron sucrose therapy should be included as second choice for severely anaemic pregnant women where situation is not supportive for blood transfusion or patient is noncompliant.

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

INTRODUCTION:

Iron deficiency and its after-effects continue to be prevalent in epidemic proportions despite major health changes over the past cenury[1]. Estimates from WHO report suggests that more than 50% of antenatal 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]. Anaemia contributes about 50 % ration in maternal mortality 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 continues to be sub-optimally managed. In the current article we focus on management of Iron deficiency anaemia in pregnancy as it is one of the most commonly spread of all nutritional deficiencies in Pregnancy.

The standard protocol for treatment of severe iron deficiency anaemia in antenatal patients came in emergency in majority of the institutions is oral iron with blood transfusion. Iron in oral route takes long time to correct the anaemia and leads to significant gastrointestinal side effects on larger doses. Transfusion of blood also has its own side effects like mismatch blood transfusion, transmission of deadly viral infections like Cytomegalo virus, HIV, Hepatitis and anaphylactic reactions. 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 for anaemia has become obsolete due to its higher side effects and anaphylactic reactions effects.

Iron sucrose injection has proved its safety and efficacy worldwide with multiple clinical trials and meta-analysis. Bio availability of Iron sucrose is very fast 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 antenatal women with moderate to severe anaemia (Hb 6 to 8gm%) in the second and early 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 at the point baseline where start of the treatment and 4 weeks or more after the last treatment was given (endline). The safety profile of the therapy has been assessed by noticing any adverse drug reaction after starting the infusion.

Counselling of the all subjects was done about pros and cons of use of injectable iron sucrose. All consented pregnant women were prescribed a total equal dose of 1000 mg of Intra venous iron sucrose. In each subjects we administer total 1000 mg of intravenous iron sucrose in five divided dosed of 200 mg in 100 ml of normal saline for the period of 30-40 mins atleast. These doses were given to antenatal patients on alternate days. To prevent any reaction or anaphylactic effects first dose was given to any patients very slowly at the speed of 60 ml/hour for initial 5 to 10 minutes. In remaining doses infusion was given at 100-125 ml/hour. There is no requirement of any test dose in intravenous iron sucrose therapy. The five doses were given continuously with one day off. Advice was given to each and every antenatal mother not to take any oral iron preparation during this therapy period. All participant antenatal women were advised to come for follow-up measurement of Haemoglobin level and other routine antenatal check up any time after 4 weeks of the last infusion of Intravenous iron sucrose.

We have used same lot and batch of IVIS for every patient so bias can be minimised. In hemocue machine, 2 lots in same batch were used.

Study Design:

Type: Retrospective analytical study

Location: Nootan General Hospital, Visnagar, Gujarat, India

Duration: 1 year.

Sample size: Total 110 consented antenatal subjects were analysed retrospectively from the clinical data available in the medical records department of the institution 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: Microsoft excel sheet (2016) was used for entering the data and descriptive analysis was done. Statistical significance of the study has been calculated by T test (P value). Data were analysed on Haemoglobin level at pre-infusion time, and at 4-week or later after the last Intra venous iron sucrose dose post infusion time. Analysis of data was done by MedCalc version 9.2.0.1. Descriptive analysis of the change in Haemoglobin level is presented as mean (standard deviation [SD]) and 95% confidence interval (CI). The Institute Ethics Committee of the Nootan medical college & research centre, Visnagar, Gujarat, India approved the study.

RESULTS:

Intravenous iron sucrose was infused in total 110 subjects. Pre infusion Haemoglobin level and after infusion haemoglobin level for all 110 subjects were available for statistical analysis. At pre infusion level, the proportion of moderate anaemia was 80% and the proportion of severe anaemia was 20%, [Table 1]. The number of antenatal patients suffering from severe anaemia decreased from 22 to 2 (90.9% reduction). Similarly, the reduction in moderate anaemia in antenatal women was 82.9% [Table 1]. Overall, the mean (SD) Haemoglobin level rise from 7.2 g/dl (0.7) at pre infusion level, to 10.99 g/dl

(1.2) at endline, with a mean increase of 3.79 g/dl (1.1). There were no serious or major adverse reactions reported between the observation period.

Overall, 28.18 % antenatal women reached to normal haemoglobin level (Haemoglobin >11 g/dl) at the time of endline measurement. The pregnant women who achieved normal Haemoglobin level were 34.09 % in moderate anaemia. While 22.7 % antenatal women with severe anaemia achieved normal haemoglobin level. Although only 28.18 % pregnant women achieved normal Haemoglobin level, a large proportion of the moderate to severe anaemic antenatal patients (70 %) changed to a less severe category of anaemia during their current pregnancy time.

Mean increase in Hb in cases of moderate & severe anaemia was 3.69 g/dl (1.2) and 3.91 (1.25) g/dl respectively. Overall rise in Hb was 3.79 g/dl (1.1)(95% CL: 3.35, 4.23). p value which was calculated in our study is < 0.001 which is statistically significant.

DISCUSSION:

In this study, the difference in Haemoglobin level 4 week after last dose of Intravenous iron sucrose infusion was measured. The mean rise in Haemoglobin 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-exclusion criteria, allowance made for iron store repletion, target Haemoglobin level, and time of endline Haemoglobin measurement[7,8,9,10,11,12] . Nonetheless, our finding is well within the range of reported increase in Haemoglobin level [7,8,9,10,11,12] .

In this study, the percentage of patients with moderate anaemia became non-anemic after receiving Intravenous iron sucrose was 16.4%. While 15.4% of moderately anemic patients stayed in the similar category even after receiving Intravenous iron sucrose therapy in recommended dose. The total dose required of iron during pregnancy is approximately 1000 mg (500 mg for the developing foetus and placenta, and 500 mg for red blood cell rise), so the advocated dose of 1000 mg of iron was sufficient to achieve the desired haemoglobin level. It is sufficient and necessary to achieve desired level of Hb to avoid complication of anaemia in pregnancy antenatally, during delivery and during post partum period.

In India, as per FOGSI and other institutional recommendation the standard dose for prevention of anaemia in pregnancy is 100 days of supplemental oral iron at least. 100 mg of elemental iron plus 500mcg of folic acid is given daily for at least 100 days. Whereas therapeutic dose of 200 mg of elemental iron is required daily to antenatal woman with anaemia (Haemoglobin: 8 to 11 g/dl) for at least 100 days[13]. For the patients with Haemoglobin level 5-8 g/dl i.e. severe anaemia in antenatal patients , parenteral iron preparation is advocated , while transfusion of packed cell volume is advocated for antenatal patients with Haemoglobin level <5 g/dL[13] and after 35 weeks of pregnancy and patient directly come for the labour. There are oral iron and folic acid supplementation to prevent anaemia at term[14]. However, in India, prevalence of anaemia is not declined at that good level despite so many measures. Many reasons are behind the epidemic of anaemia in pregnancy in India like mainly due to poor compliance to oral iron treatment amongst the antenatal woman, linked to perceived and experienced side effects, persistent failure to remember to take iron, inadequate counselling, illogical distribution of iron tablets, 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 noted that the effect of oral iron supplementation on Haemoglobin level becomes evident in 3 months of start of supplementation[19]. The change in Haemoglobin level after infusion of Intra venous iron sucrose is therefore likely to become obvious much earlier. So in most of the previous experiences by various authors it is advocated that measurement of haemoglobin should be done when the interval between last dose of intravenous iron sucrose and measurements period is at least 4 weeks [7,8,9,10,11,12]. During the course of normal pregnancy, iron demand increases in second and third trimester partly due to hemodilution and other physiological changes and partly due to foetal and maternal growth so haemoglobin level decreases in second and third trimester if requirements do not met with increased demand [20, 21].

Enrolment of the antenatal subjects was done in second trimester when the Haemoglobin level was in physiologically decreasing phase. Therefore, measurement of haemoglobin was done at pre infusion level and it was expected to be low. Post infusion end point haemoglobin measurement was

done after 4 weeks of last intravenous iron sucrose infusion. There is no control arm in our study. So, we are unable to attribute the fraction of the observed 3.79 g/dl of increase in Haemoglobin level which could be due to the intervention. But, considering the facts from the previous studies, haemoglobin rise without intervention is expected to be minimal.

Blood transfusion was being advised to severely anaemic antenatal patients (Haemoglobin level <7 g/dl) in late trimester. And intra venous iron sucrose was given to those who have not consented for blood transfusion. The average rise in haemoglobin level was 3.9 g/dl and mean post infusion end point haemoglobin was 10.2 g/dl (95% CI: 9.38, 10.42) in antenatal subjects with severe anaemia. As per clinical data low haemoglobin level (<9 gm/dl) is linked with adverse maternal and foetal outcome[2]. Thus, even though proportion of severely anaemic antenatal patients to become non anaemic was only 22.7%, but mean Haemoglobin level achieved post infusion was expected to improve maternal and foetal outcome many fold.

It is recommended to have uniform guideline for public health programme as it has to be implemented over large and diverse geographical area through semi skilled staff. So a uniform dose of 1000 mg intravenous iron sucrose total is recommended for therapeutic usage in antenatal patients with moderate to severe anaemia.

We compared outcomes i.e. rise in haemoglobin level in severely anaemic subjects against antenatal patients with moderate anaemia. The mean rise in Haemoglobin level (3.9 vs. 3.7 g/dl), improvement in category of anaemia (95.45 % vs. 88.63%), and rate of increase in Haemoglobin level was higher in antenatal patients with severe anaemia in comparison with moderately anaemic antenatal patients. Current guidelines do not support administration of Intravenous iron sucrose in antenatal patients with severe anaemia. But we conclude here that antenatal patients with severe anaemia got more benefit in terms of haemoglobin rise than antenatal patient with moderate anaemia. The former also get benefit of haemoglobin rise at faster pace. As a public health approach, in conditions where there is scarcity of blood and its products or any non compliance from the patient side there would be safe and faster option of

intravenous iron sucrose therapy should be considered in antenatal patients with severe anaemia.

HemoCue machine was used to measure haemoglobin level in all patients. This machine is valid and technique is reliable. With sensitivity of 0.75, HemoCue method was gold standard and it has also a very good specificity of 1.0 [27]. In the past when nationwide survey of haemoglobin measurement was done this technique was being used by scientist[1.] Same technique was used for both pre infusion and at least 4 weeks after last infusion measurement of Haemoglobin level.

Possibility of thalassemia had been ruled out by use of Mantzer Index in all patient and Hb electrophoresis in selected patient if required.
There was history of previous blood transfusion in 6 patients in previous pregnancy.
All the patients were on vegetarian diet.

CONCLUSION:

In antenatal women with moderate to severe anaemia the mean rise in Hb level was 3.79 g/dl after IV iron sucrose was given. The difference of amount of haemoglobin rise is seen more in pregnant women with severe anaemia than antenatal women with moderate anaemia. Intravenous iron sucrose should be given in moderate to severe anaemic antenatal patients as second choice where blood transfusion found difficult or any non compliance from the patient side.

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Table 1

Pre-infusion and post infusion haemoglobin level among pregnant women (n=110)

Hb levels	At pre infusion	At post infusion
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			

Table 3

	Mild	Moderate	Severe	Total
Primi	0	34	6	40
2nd Para	0	25	7	32
Multipara	0	29	9	38
Total	0	88	22	110

Table 4

	Average Hb before IVIS	Mean Hb after IVIS	Rise in HB	Total patients

Primi	8.1	11.79	3.69	40
2nd Para	7.9	11.68	3.78	32
Multipara	7.2	11.11	3.91	38
Total				110