Original Article

Effect of intravenous iron sucrose on hemoglobin level, when administered in a standard-dose, to anemic pregnant women in rural Northern India

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Abstract

Introduction: To combat anemia among pregnant women, in Haryana, Northern India, administration of intravenous iron sucrose (IVIS) was initiated in 2014 as a public-health measure. We assessed the effect of IVIS on hemoglobin (Hb) levels among the pregnant anemic women. **Methods:** Pregnant women identified as moderately or severely anemic (Hb <10.0 g/dL) in the second or third trimester during routine antenatal care were prescribed IVIS in a standard-dose of 400 mg given as 100 mg on alternate days. Neither dose calculation, nor allowance for iron-store, was included in this study. We analyzed the data collected between June 2014 and December 2015, at the two primary-health-centers, on Hb level (by HemoCue method) before start of the therapy (baseline), and 4-week or more after the last infusion (endline). **Results:** A total of 990 women received IVIS. Both baseline and endline Hg-levels were available for 763 (77%), who were included in the analysis. At baseline, the proportion of moderate and severe anemia was 87.94% and 12.06%, respectively. Mean (standard deviation)-Hb increased from 7.85 g/dL (0.80) at baseline, to 9.62 g/dL (1.30) at endline, with a mean increase of 1.76 g/dL (95% confidence interval 1.67, 1.85). The mean increase in Hb-level for pregnant women who had severe and moderate anemia at baseline was 2.54 g/dL and 1.65 g/dL, respectively. Overall, 15.33% of women achieved normal Hb-level by the time of endline measurement. No serious adverse reactions were reported during the observation period. **Conclusion:** Mean increase in Hb-level was 1.76 mg/dL. Severely anemic pregnant women had larger increase in Hb-level when compared with pregnant women with moderate anemia.

Keywords: Anemia, iron deficiency, iron sucrose complex, parentral iron therapy

Introduction

More than half of the pregnant women (58%) in India suffer from anemia, defined as hemoglobin (Hb) level <11 g/dL, at any time during pregnancy.[1] The global reported range of prevalence of anemia in pregnancy is 35%–75% in developing countries.[2] The primary cause of anemia in pregnancy is iron deficiency.[3] Anemia in pregnancy could result in adverse health consequences both for mother and child.[2]

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There has been no perceptible decline in the prevalence of anemia in India, among pregnant women in the last few decades using standard supplementations with oral iron therapy formulations.[1] Iron sucrose, one of the parenteral iron preparations, has been reported to be safe and effective during pregnancy. It overcomes many of the factors linked to poor adherence. A test dose for hypersensitivity is not required.[4,5] To combat anemia among pregnant women, as a public-health measure, Haryana state in Northern India initiated the administration of intravenous iron sucrose (IVIS) in 2014.[6] As per the guidelines, all moderately anemic pregnant women were offered a total of 400 mg of iron administered as 100 mg on alternate days intravenously in the form of iron sucrose. Implementation in a primary health-care setting has challenges that could affect the overall effectiveness of the IVIS. The purpose of the present study was to assess the effectiveness of IVIS in terms of the change in Hb level among anemic pregnant women who received iron sucrose infusion at a primary care setting.

Methods

Study design and setting

We did a retrospective analysis of the routine clinical data that were recorded as part of the implementation of the program. The study sites were two primary health centres (PHCs) of rural Haryana (district Faridabad). Since July 2014, IVIS was offered to moderately anemic pregnant women (Hb level 7–9.9 g/dL) attending the antenatal care (ANC) services at these facilities. These two PHCs, namely, Chhainsa and Dayalpur, were located at 16, and 26 km away from the district hospital, respectively. The distance between district hospital and individual villages ranged from 9 to 34 km. The district hospital had the facility for blood transfusion.

Both the PHCs put together, catered to a population of nearly 96,000 spread over 28 villages.[7] This population was under continuous demographic and health surveillance by health workers, who made a fortnightly domiciliary visit. Database of every individual was managed using computerized Health Management Information System. Monthly ANC clinics were conducted in every village. Both the PHCs also provided 24 h delivery services.[8]

Eligibility for including data in analysis

Anemia in pregnancy was defined as moderate if Hb level was 7–9.9 g/dL, and severe if Hb level was <7 g/dL. The Hb level of pregnant woman was measured by HemoCue method (HemoCue AB, Ängelholm, Sweden).[9] A pregnant woman was considered eligible to receive IVIS if her Hb was between 7 and 9.9 g/dL during the second or third trimester. The eligible women were counseled by the health supervisor on the merits of the IVIS. Eligible pregnant women were prescribed a uniform total dose of 400 mg of IVIS. This dose was administered in four equally divided doses of 100 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 100 mg was given in around 30 min. Neither individual dose calculation nor an allowance for iron store repletion was included in this study. Test dose was not required for IVIS. The three subsequent doses were administered on alternate days. Women were counseled to not take any oral iron supplementation. Pregnant women with severe anemia (Hb level <7.0 g/dL) were advised to undergo blood transfusion at the district hospital. Some pregnant women rejected the advice. We had not recorded the number of women who rejected the advice or the reason(s) for rejection of the advice. These pregnant women were thereafter offered infusion of IVIS in their best interest. Those who accepted the offer were given the standard dose that was offered to moderately anemic pregnant women, i.e., 400 mg of IVIS into four divided doses. 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. We analyzed the data collected between June 2014 and December 2015, at the two primary health-care facilities, as mentioned above. The information on key variables, such as age, gestational age, education, occupation, village, dosage of IVIS received with dates, any adverse effect noticed/reported, were maintained in the registers at the ward in delivery hut of the PHCs, where the pregnant woman would come for the receiving the dosage. The administration of the dosage was done under direct supervision of respective medical officers (AKS, AS, VY, JM, AL, FA, and RR), and overall supervision of PH. Later, these data from the registered were entered into a database by the respective medical officers (AKS, AS, VY, JM, AL, FA, and RR), and checked once again for data quality by them as well as PH, SM, RK, RK, and SK.

Statistical analysis

Data were analyzed by PH and SK. Hb level before start of the therapy (baseline), and at 4-week or later after the last IVIS infusion (endline), was included in the analyses. All personal identifiers were delinked with the main dataset before the analysis so that the data could not be linked back to a specific woman. Analysis of data was done by Stata version 12 (Stata Statistical Software: Release 12. College Station, TX: StataCorp LP).[10] Descriptive analysis of the change in Hb level is presented as mean (standard deviation [SD]) and 95% confidence interval (CI). Seventeen pregnant women for whom data on time of endline Hb measurement was not available were removed from the analysis for measuring the effect of time lag on increase in Hb level. Data from one PHC (Chhainsa) were analyzed to see the distribution of pregnant women by the number of IVIS doses received. The findings were extrapolated to the other PHC (Dayalpur) for which this information was missing. We also undertook a simple linear regression with change in Hb between baseline and endline as the dependent variable and considered the ensuing duration as the independent variable. The Institute Ethics Committee of the All India Institute of Medical Sciences, New Delhi, India, approved the study.

Results

A total of 990 pregnant women received IVIS. Both baseline and endline Hb level were available for 763 (77%) pregnant women, who were included in the analysis. At baseline, the proportion of moderate and severe anemia was 87.94% and 12.06%, respectively [Table 1]. The number of pregnant women with severe anemia declined from 92 to 13, (85.9% reduction). Similarly, the reduction in moderate anemia was 32.8% [Table 1]. Overall, the mean (SD) Hb level increased from 7.85 g/dL (0.80) at baseline, to 9.62 g/dL (1.30) at endline, with a mean increase of 1.76 g/dL (95% CI: 1.67, 1.85). The mean increase in Hb level for women who had severe anemia at baseline was 1.5 times higher (2.54 g/dL), compared to the women who had moderate anemia (1.65 g/dL) [Table 1]. No serious adverse reactions were reported during the observation period.

Overall, 15.33% 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 16.39% and 5.43% for those with moderate and severe anemia at baseline, respectively. Although only 15.33% pregnant women achieved normal Hb level, a large proportion of them (85%) changed to a less severe category of anemia Tables 1 and 2].

In 81 (10.6%) pregnant women, the Hb was measured within 16 weeks of the last dose of IVIS infusion. In 665 (87.2%) pregnant women, the Hb was measured at 16 weeks or later after the last dose of IVIS infusion; while time of measurement was not available for 17 (2.2%) pregnant women. Mean (95%CI) increase in Hb level was 1.79 g/dL (1.70, 1.89) when measured at 16 weeks or later following the last dose of IVIS, while it was 1.46 g/dL (1.11, 1.81) when measured at <16 weeks (not shown in table). This difference was statistically significant ($P = 0.01$).

Discussion

We aimed to measure the change in Hb level in moderately anemic pregnant women after IVIS infusion in a primary care setting in a rural area of Haryana, North India. The mean increase in Hb level was 1.76 g/dL (95% CI: 1.67, 1.85). Direct comparison of our findings with other available published information is difficult on account of differences in inclusion criteria, target Hb level, allowance made for iron store repletion, and time of endline Hb measurement.[11-18] Nonetheless, our finding is well within the range of reported increase in Hb level of 1.6 g/dL to 3.6 g/dL.[11-18]

Effect on dosage on the mean increase in Hb level is dependent on the total dose of iron prescribed, the uptake rate of prescribed dose, and the time lag between the infusion of the last dose of IVIS and measurement of Hb level. The guidelines issued by the Government of Haryana,[6] prescribed a uniform total dose of 400 mg of iron to all moderately anemic pregnant women, irrespective of the Hb level in any particular woman. 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.[14] In most of the published literature, an additional amount of 500 mg of iron was added to the calculated iron deficit for replenishing body iron reserve.[11,12,15,17,18] The maximum increase in Hb level (3.6 g/dL) was seen in a study that had added 1000 mg of iron for replenishment of iron store.[14] In our study, only 16.4% of moderately anemic pregnant women became nonanemic after receiving IVIS, and more than half (57.8%) of them remained in the same category even after receiving IVIS in recommended dose. Excess iron interacts in Fenton reaction, which produces free radicals and causes oxidative damage.[19,20] Oxidative damages could start the process that could lead to diseases such as neuropathologies, cancers, and cardiovascular diseases.[21-23] Thus, the advantages of aggressive treatment of iron deficiency anemia

Table 1: Baseline and endline hemoglobin level among pregnant women (*n*=763)

Hb levels	At baseline	At endline	Proportional change between endline and baseline (%)	Mean change in g/dL, (SD), 95% CI
Normal (Hb >11 g/dL)	-	115 (15.07)		
Mild (Hb 10-10.9 g/dL)		184 (24.12)		
Moderate (Hb 7-9.9 g/dL)	671 (87.94)	451 (59.11)	−32.8	
Severe (Hb <7 g/dL)	92 (12.06)	13 (1.70)	−85.9	
Total	763 (100)	763 (100)		
Mean change in Hb (overall)				
Mean Hb in g/dL, (SD)	7.85 (0.80)	9.62 (1.30)		1.76 (1.31)
95% CI	7.79, 7.91	9.52, 9.71		1.67, 1.85
Mean change in Hb (by initial category of anemia at baseline)				
Moderate anemia (n=671)				
Mean Hb in g/dL, (SD)	8.07 (0.53)	9.73 (1.25)		1.65 (1.25)
95% CI	8.03, 8.11	9.63, 9.82		1.56, 1.75
Severe anemia (n=92)				
Mean Hb in g/dL, (SD)	6.23 (0.59)	8.79 (1.35)		2.54 (1.43)
95% CI	6.13, 6.37	8.50, 9.07		2.24, 2.84

Hb: Hemoglobin; SD: Standard deviation; CI: Confidence interval

Table 2: Net improvement to normal hemoglobin levels of >11 g/dL (no anemia) between baseline and endline (*n*=763)

Hemoglobin levels at baseline assessment (number of pregnant women)	Hemoglobin levels at endline assessment				
	Normal (no anemia)	Mild anemia	Moderate anemia	Severe anemia	Change to normal (%)
Moderate anemia (671)	110	167	388	6	16.39
Severe anemia (92)	5	17	63	7	5.43
Total (763)	117	186	451	13	15.33

by intravenous administration of iron ought to be weighed against the potential risks arising out of excess iron administration. The IVIS dose recommended by the guidelines was even less than the amount usually added for replenishment of iron store alone. The recommended dose of 400 mg of iron was insufficient to achieve the desired nonanemic status. Therefore, we feel that the recommended dose of iron was conservative which probably avoided the adverse consequences of oxidative damages. However, the quantum of increase in Hb level could have been higher had the dose of iron been more realistic.

One of the reasons for lower increase in Hb level could be poor uptake of IVIS. We found that 70.4% of pregnant women had received all the four doses, while an additional 11.2% woman had received three of the four doses of IVIS (data not shown in table). Thus, poor uptake of IVIS was not a reason for lower increase in Hb level.

In India, the standard measure for prophylaxis against anemia is oral iron supplementation for 100 days, where 100 mg of elemental iron is given daily to nonanemic pregnant woman, while 200 mg of elemental iron is given daily to anemic pregnant woman with Hb level between 9 and 11 g/dL for at least 100 days.[24] For those with Hb level 5–7 g/dL, parenteral iron administration is recommended, while transfusion of packed red cell is recommended for those with Hb level <5 g/dL.[24] Supplementation with oral iron or iron/folic acid provided either daily or weekly is effective to prevent anemia and iron deficiency at term.[25] However, in India, there has been no perceptible decline in the prevalence of anemia among pregnant women in the last few decades.[1] 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.[26-29]

It has been reported that the effect of oral iron supplementation on Hb level becomes apparent within 3 months of start of supplementation.[30] 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.[11,12,14,15,17,18] We also found that mean increase in Hb level was statistically higher when measured at 16 weeks or later, postlast dose of IVIS infusion as compared to when measured earlier. In an overwhelming majority (86.8%) of the pregnant women, the Hb was measured more than 16 weeks postlast dose of IVIS infusion. In rural India, pregnant women who received at least one antenatal checkup, 37% received it in the first trimester.[1] Thus, it is unlikely that the pregnant women in rural area would be registered at a primary care facility at a gestational stage where the interval between last dose of IVIS and the time to delivery would be significantly larger than 16 weeks. Thus, our findings about increase in Hb level probably reflect the best-case scenario for rural population. Moreover, we feel that sufficient time was provided for effect of IVIS, in the form of increase in Hb level, to become manifest. Therefore, the observed increase in Hb level could not have been an underestimate on account of insufficient time interval between the last dose of IVIS infusion and measurement of Hb level.

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.[31,32]

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 in vast majority (86.8%) was done after an interval of 16 weeks or more postlast dose of IVIS infusion. These pregnant women were likely to be at a gestational stage where there would have been slight increase in the Hb level even without any intervention. We did not have a comparator arm. Hence, we are unable to quantify the fraction of the observed 1.76 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) were advised blood transfusion. Those who refused to follow the advice were offered IVIS in their best interest. A total of 92 such pregnant women received IVIS. The mean increase in Hb level among severely anemic pregnant women was 2.54 g/dL, and the mean endline Hb was 8.79 g/dL (95% CI: 8.50, 9.07). 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.[33,34] We found that the mean endline Hb level in our study was very close to the cutoff value. Thus, though only 5.53% 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. We again revert back to the moot question

as to whether total iron dose calculation based on Ganzoni`s formula[35] and consequent administration of much higher dose of IVIS would have resulted in much improved endline Hb status, particularly among severely anemic pregnant women?[35,36] Intuitively, it does appear to be so but would require further careful exploration.

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 400 mg of IVIS irrespective of Hb level of an individual pregnant woman. However, IVIS is expected to be administered at PHC under the supervision of a medical officer. We have shown that the administration of 400 mg of IVIS did not achieve the desired result of converting large proportion of pregnant women to nonanemic status. As of March 31, 2015, more than 90% of 25,300 PHCs in India had a medical doctor.[37] Therefore, we feel that there is a merit in advocating customized iron dose administration based of Hb level and prepregnancy weight of the pregnant women. One could also develop a nomogram that could be used as a ready reckoner at primary care facilities for easy calculation of the required dose of IVIS thus reducing the chances of miscalculation.

We compared outcomes in severely versus moderately anemic pregnant women and found that the mean increase in Hb level (2.54 vs. 1.65 g/dL), conversion to less severe category of anemia (85.9% vs. 32.8%), and rate of increase in Hb level (coefficient of 0.03 vs. 0.02) 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.[38] 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. If the tool was systematically and consistently making a biased measurement, it could have led to misclassification of category of anemia. However, if the error were consistent, the quantum of increase in Hb would still be valid and reliable. Thus, the main finding of the study, i.e., the quantum of increase in Hb level would have remained unaffected.

Anemic pregnant women were identified during antenatal clinics held at village level. Therefore, identification of eligible anemic pregnant women was near universal. We did not have the number of eligible women who refused the offer of IVIS. We tried to estimate this number by assuming that the prevalence rate of anemia in pregnant women would be no different than what has been reported for the state as a whole. The prevalence of moderate and severe anemia in Haryana in 2005–2006 was 41.1% and 1.9%, respectively.[1] The total number of pregnancies registered during the period June 2014 to December 2015 was 3,500 (as per Ballabgarh Health and Demographic Surveillance data). Two-thirds of the total pregnancies (approximately 2,330 in numbers) would have been in second or third trimester (enrollment criteria). If one were to apply the Haryana state anemia prevalence rates to the eligible pregnant women, a total of 1,002 pregnant women (43% of 2,330) could be expected to be either moderately or severely anemic. A total of 990 pregnant women out of the expected 1,002 anemic pregnant women (98.8%) actually received IVIS infusion. Thus, the participation rate in the study was near universal. Anecdotal information while conversing with health workers in the field also confirmed this impression. Complete data were available for analysis for more than three-quarters of those who had received IVIS. We could not identify any reason(s) that could have led to those pregnant women where endline Hb level was not recorded to be systematically different from those where such information was available. Therefore, the findings appear to be generalizable.

Limitations

Ours being a retrospective analysis of routine service data, did not have a comparator arm. We had not measured serum ferritin level and therefore are unable to comment on the effect of IVIS on body iron reserve. We did not have data on nutritional status of pregnant women that could have acted as cofactor for the change in Hb level. Ours is probably the first study that evaluated the effectiveness of IVIS for the treatment of anemic pregnant women in a primary care setting. We had used a valid tool for measuring Hb level. The study had enrolled the largest number of pregnant women (763), the previous best being 256.[17] Therefore, the estimate for increase in Hb level is more precise. As explained earlier, we feel that the findings are likely to be valid and generalizable.

Conclusion

The mean increase in Hb level was 1.76 g/dL when 400 mg of IVIS was given to pregnant women with moderate and severe anemia in a rural primary care setting. Pregnant women with severe anemia had larger increase in Hb level when compared with pregnant women with moderate anemia. We recommend that the instead of a uniform dose of 400 mg of IVIS, Ganzoni`s formula should be used for calculating dose customized for individual pregnant woman. In addition, IVIS should be included as second choice for severely anemic pregnant women who are unable/unwilling to undergo blood transfusion.

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Conflicts of interest

There are no conflicts of interest.

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