Original Article

Intravenous iron sucrose when administered to moderately anemic pregnant women raises the hemoglobin concentration and replenishes body iron at 6 months

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Abstract

Introduction: Intravenous iron sucrose (IVIS) is a rapidly acting, safe, and effective treatment for moderate anemia among pregnant women. The effectiveness of IVIS at 6 months post IVIS infusion was unknown. We, therefore, assessed the mean increase in hemoglobin concentration and body iron replenishment status at 6 months after the last dose of IVIS infusion. **Methods:** The study was conducted in 28 villages served by two primary health centers in district Faridabad, Haryana. The participants (n = 129), when originally recruited in 2020, were all moderately anemic (hemoglobin level 7.0 to 9.9 g/dL) pregnant women in either the second or third trimester of pregnancy. Their iron deficiency was calculated by Ganzoni's formula with additional allowance of 500 mg of depot iron. The calculated deficit was rounded off to the nearest 100 mg. The dose of IVIS was 300 mg of iron diluted in 300 ml of normal saline administered intravenously every third day till the full calculated dose was administered. In this study, we collected the follow-up blood specimen 6 months after the last dose of IVIS and measured the hemoglobin concentration, C-Reactive protein (CRP), and serum ferritin level. Hemoglobin concentration was measured using an automated hematology analyzer (Sysmex XS-1000i). Serum ferritin and CRP were measured by enhanced chemiluminescence immunoassay and the enzymatic heterogeneous, sandwich immunoassay method, respectively (VITROS ECiQ, Ortho Clinical Diagnostics, New Jersey, USA). **Results:** The mean [standard deviation (SD)] duration of time elapsed since the administration of the last dose of IVIS infusion was 6.4 (0.9) months. The mean (SD) hemoglobin level at the time of original recruitment (baseline) was 8.7 ± 0.8 g/dL. The mean (SD) increase in the hemoglobin concentration at 6 months follow-up was 3.2 [95% confidence interval (CI): 3.0–3.4)] g/dL. The median [interquartile range (IQR)] serum ferritin level (ng/mL) at follow-up was 28.1 (12.7, 61.5). A total of 10.2% of the participants had a raised (>10 mg/L) CRP level. Adjusting for CRP level and based on serum ferritin level, the proportion of participants who were iron-deficient was 35.3%. The proportion of participants who had any degree of anemia was 70.5%. **Conclusion:** Administration of IVIS infusion was effective in raising the mean hemoglobin concentration and in replenishing the body iron reserve at 6 months post infusion.

Keywords: Anemia, hemoglobin, intravenous iron sucrose, IVIS, iron deficiency, parenteral iron therapy, pregnancy

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Introduction

Anemia is a condition marked by low hemoglobin concentration, leading to poor health, economic loss, and social burden.[1] It is a major public health problem.[2] Globally, 38.2% pregnant women

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and 29.0% nonpregnant women were suffering from anemia.[3] As per 2019–2021 National Family Health Survey (NFHS-5), 57.2% of nonpregnant women (15–49 years) in India were anemic.[4] The prevalence of anemia in rural Haryana was 62.1%.[5] The most common cause of nutrient deficiency anemia is iron deficiency. Intravenous iron sucrose (IVIS) formulation is an accepted modality of treatment for moderate anemia during pregnancy.[2] The majority of the studies had measured the effectiveness of IVIS among women who had received IVIS during pregnancy for treatment of moderate anemia, 4 weeks post infusion. There was limited information on the effect of IVIS on hemoglobin (Hb) concentration and body iron reserve at 12 weeks or later.

Objective

To estimate the hemoglobin concentration and body iron reserve among women in a rural area of Haryana, who had received IVIS during pregnancy for treatment of moderate anemia, 6 months post IVIS infusion.

Material and Methods

Study design and settings

This cross-sectional study was carried out among nonpregnant women aged 15–49 years who had received IVIS 6 (±1) months back during their pregnancy for the treatment of moderate anemia. The list of potential participants was prepared from the data contained in the IVIS register maintained at the primary health center (PHC) Dayalpur and PHC Chhainsa. These PHCs served 17 and 11 villages, respectively, in district Faridabad, Haryana.

The iron deficiency was calculated by Ganzoni's formula, which is as follows:

Total iron deficit (in mg) = Body weight (in kg) × (target Hb level in g/dL – actual Hb level in g/dL) × 2.4 + 500

Body weight refers to prepregnancy weight. If the prepregnancy weight was not available, the weight recorded during the first visit of the first trimester was used. The target Hb for pregnant women was set at 11.0 g/dL. Additional 500 mg of depot iron was prescribed for women weighing >35 kg. Depot iron was calculated as 15 mg/kg body weight for women weighing 35 kg or less.

The total calculated iron deficit was rounded off to the nearest 100 mg. Each dose of IVIS was 300 mg of iron, diluted in 300 ml of normal saline, administered intravenously over 30 minutes, every third day till the full calculated dose was administered.

A self-developed semistructured interview schedule was administered to the participants. Through this tool, we collected data on sociodemographic factors and antenatal, natal, and postpartum history. Dietary diversity was calculated by the MDDW (Minimum Dietary Diversity for Women) scale.[6] Under aseptic precautions, 5 mL of blood specimen was collected for measuring hemoglobin concentration, serum ferritin, and C-reactive protein (CRP) levels. Hemoglobin concentration was measured using an automated hematology analyzer (Sysmex XS-1000i). Serum ferritin and CRP were estimated by chemiluminescence immunoassay and enzymatic heterogenous sandwich immunoassay, respectively. Iron deficiency was defined as serum ferritin level <15.0 ng/dL in the absence of inflammation, that is, CRP ≤10.0 mg/dL, and <30.0 ng/dL in the presence of inflammation, that is, CRP > 10.0 mg/dL.[7-9]

Study period

This study was conducted from March 1 to April 15, 2021. The desired interval since the last dose of IVIS was 6 ± 1 months. Therefore, participants who had received IVIS from August 1 to November 15, 2020 were eligible for enrolment in this study.

Inclusion criteria

Women who had received IVIS between August 1 and September 15, 2020 for the treatment of moderate anemia (7.0–9.9 g/dL) during their pregnancy.

Exclusion criteria

Women who were currently pregnant; had history of major surgery requiring general anesthesia or blood transfusion during the period following IVIS therapy; or had history of hematemesis, melena, bleeding per rectum, or observable blood loss from any other site during the period following IVIS therapy were excluded from the study.

Sample size

There were a total of 129 eligible participants, and all of them consented to be part of the study. All consenting participants were recruited in the study.

Statistical analysis

Data were collected in Epicollect via ipad. Laboratory reports were entered in MS Excel. Data were analyzed using STATA v15 (StataCorp LLC, College Station, TX). Characteristics of participants were described as mean [standard deviation (SD)] or median [interquartile range (IQR)] for continuous variables (hemoglobin, ferritin, CRP levels). Frequencies and percentages were described for categorical variables (age-group, occupation, education). Prevalence and 95% confidence intervals (CIs) were calculated. *P* value < 0.05 was considered statistically significant.

Ethics

Ethical clearance was obtained from the AIIMS Ethics committee (Reference No. IECPG-415/26.08.2020 dated on 27.08.2020). Any participant found to be anemic was referred to the Senior Resident, Medicine in the OPD of CRHSP, Ballabgarh, for treatment of anemia.

Results

A total of 156 participants were listed in the IVIS registers. After removing the noncontactable participants, 138 participants remained in the list. We applied the exclusion criteria and found that 129 participants were eligible. All the eligible participants consented to be study subject and were therefore recruited in the study. The mean (SD) duration of time elapsed since the administration of the last dose of IVIS infusion was 6.4 (0.9) months. The mean (SD) age of the participants was 23.8 (3.6) years. Almost 14% of them were illiterate. Most (95.3%) of the participants were homemakers [Table 1].

Among participants who were prescribed 3 and 4 doses of IVIS, 12.4% and 5.3% had not received all the prescribed doses, respectively. Overall, 10.9% participants had not received the prescribed doses of IVIS [Table 2]. The major cause [8 of 14, i.e., (57%)] for not receiving the full prescribed dose was the adverse side effect. The common adverse side effects were fever (1.6%), headache (1.6%), and burning at the injection site (1.6%), followed by generalized itching (0.8%).

The prevalence of mild and moderate anemia 6 months after the last dose of IVIS was 36.4% and 34.1%, respectively. No participant had severe anemia [Table 3].

Fifty-two (41.3%) participants had not consumed any iron folic acid (IFA) tablet in the postpartum period. Among those who did consume IFA tablets, the total number of IFA tablets consumed ranged from 1 to 29 tablets. The majority (64.3%) of the participants had adequate dietary diversity as per the MDDW score. A total of 34.9% of the participants had not started their menstruation. The mean (SD) duration (in months) to return to menstruation was 2.2 (0.8) months. The majority of the participants had normal blood loss during each menstrual cycle. Thirty-four (26.4%) participants had delivered by cesarean section. The majority (79.4%) of the cesarean sections were conducted at private hospitals. The mean (SD) duration (in months) of breast feeding was 3.7 (1.6).

The mean (SD) hemoglobin concentration at the time of starting the IVIS infusion was 8.7 ± 0.8 g/dL. The mean (SD) hemoglobin concentration after 6 months of IVIS infusion was 11.5 (0.84) g/dL. The mean (SD) increase in the hemoglobin concentration was 3.2 (1.0) g/dL (95% CI 3.0–3.4). This difference was statistically significant (*P* value <0.001).

The median (IQR) serum ferritin level (ng/mL) at 6 months post IVIS infusion was 28.1 (12.7, 61.5). A total of 10.2% of the participants had a raised (>10 mg/L) CRP level. Adjusting for CRP level and based on serum ferritin level, the proportion of participants who were iron-deficient was 35.3%.

Table 1: Distribution of participants by selected sociodemographic characteristics

Characteristics (*n*=129)	*n* (%)
Mean age (SD) in years	23.8 (3.6)
Age group (in completed years)	
• 18-25	104 (80.6)
• 26-30	18 (14.0)
• >30	7 (5.4)
Occupation	
• Homemaker	123 (95.3)
• Others (teacher, factory worker, sanitation worker, construction worker, shopkeeper)	6 (4.7)
Education	
• Illiterate	18 (13.9)
• Primary	67 (51.9)
• Up to high school	26 (20.2)
• Beyond high school	18 (14.0)

Discussion

We report, for the first time, the effect of IVIS on hemoglobin concentration and the body iron reserve at 6 months post infusion to moderately anemic pregnant women. We found that the mean (SD) increase in the hemoglobin concentration was 3.2 (1.0) g/dL. The proportion of participants who had any degree of anemia was 70.5%.

We had excluded participants who reported unusual blood loss due to any reasons during the postpartum period. Participants (n = 34, 26.4%) who underwent cesarean section delivery but had not received any blood transfusion were however not excluded. Unusual blood loss and blood transfusion could artificially affect the hemoglobin concentration. Exclusion of such participants helped us in reducing the confounding factors. Return to menstruation, blood loss during the menstrual period, and duration of breast feeding were all within the normal range. Consumption of IFA tablets during the postpartum period was negligible. We had not provided any specific dietary advice during the postpartum period. Therefore, the mean increase in the hemoglobin concentration may be attributable to the administration of IVIS.

Table 2: Distribution of participants by their IVIS receipt status

No. of IVIS doses prescribed	Number (%) of participants who received all the prescribed doses	Number (%) of participants who missed some of the prescribed doses	Total (%)
2	4 (100)	NIL	4 (100)
3	92 (87.6)	13 (12.4)	105 (100)
4	18 (94.7)	1 (5.3)	19 (100)
5	1 (100)	NIL	1 (100)
Overall	115 (89.1)	14 (10.9)	129 (100)

Table 3: Prevalence of anemia among participants at 6 months post IVIS infusion

Anemia status	6 months post IVIS
n (%)	129 (100.0)
Nonanemic	38 (29.5)
Anemic	91 (70.5)
• Mild	47 (36.4)
• Moderate	44 (34.1)
• Severe	NIL

The reported mean increase in the hemoglobin concentration at 12 weeks post infusion was 2.21 g/dL.[10] The mean increase in the hemoglobin concentration at 8 weeks post infusion has been variously reported as 2.46 g/dL, 4.03 g/dL, and 3.57 g/dL.[11-13] Most other Indian studies have reported a mean increase of hemoglobin level 4 weeks following IVIS administration ranging between 2.0 and 3.0 g/dL.[14-17] The mean (SD) increase in hemoglobin level in our study was within the range reported by other studies. We had measured the hemoglobin concentration 6 months after the IVIS infusion. However, the longest interval between IVIS infusion and hemoglobin measurement reported in the literature was 12 weeks, that is, half the follow-up period of our study.

The mean increase in hemoglobin concentration 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 the measurement of hemoglobin concentration.[18] We had calculated the iron deficiency based on widely accepted Ganzoni's formula. The proportion of participants who missed at least some of the prescribed IVIS dose was small (10.9%). Therefore, the participants had received an adequate amount of iron supplementation to treat their iron deficiency. The resultant increase in mean hemoglobin concentration at 6 months post IVIS infusion was 3.2 g/dL. This increase was clinically and statistically significant. We had made no extra effort or intervention, except for the availability of the routine health care service. Hence, the findings of this study likely reflect the effect of IVIS on hemoglobin concentration in real life/community settings.

At baseline, 85.0% of the participants were iron-deficient.[14] Six months after the IVIS infusion, we found that after adjusting for CRP level, the proportion of participants who were iron-deficient was 35.3%. Thus, the body iron reserve had remained replenished for 65% of the participants after 6 months after the IVIS infusion.

A complete list of all potential participants was available in the register kept at the PHC. Hence, the sampling frame was complete. We had abstracted the baseline information from the written records. Hence, the chance of recall bias was minimal. All eligible participants agreed to participate in the study. Therefore, the findings of the study are internally valid. The biochemical assays were done by experienced personnel in a laboratory who had an internal quality control mechanism. CRP levels were estimated to account for the presence of inflammation while interpreting the serum ferritin level. We, therefore, believe that findings of our study are valid and reliable.

We did not have a comparator arm which limits our ability to establish a causal relationship. However, to deny any treatment to the moderately anemic pregnant women merely for the sake of establishing a comparator arm would have been unethical. Due to the inadequate quantity of the available sera, serum ferritin and CRP estimation could not be performed for 16 and 2 participants, respectively. This loss of information on serum ferritin level could have resulted in loss of power of the study and hence adversely affected the validity of our findings. We used the MDDW scale to assess dietary diversity status. In general, such scales are often prone to recall bias and social desirability bias. It was not possible to either quantify or speculate the direction of these biases.

Conclusion

The mean (SD) increase in hemoglobin level at 6 months post IVIS infusion was 3.2 (1.0) g/dL. The body iron reserve had remained replenished for 65% of the participants after 6 months of IVIS infusion. Therefore, we conclude that IVIS infusion was effective in raising the mean hemoglobin concentration and in replenishing the body iron reserve at 6 months post infusion.

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Conflicts of interest

There are no conflicts of interest.

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