CLINICAL EVALUATION OF INTRAVENOUS IRON SUCROSE IN PREGNANT ANEMIC FEMALES

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Abstract

The standard treatment in majority of the institutions is oral iron (OI), with blood transfusion reserved for severe or emergency cases. However, it is unreliable in the treatment of severe anemia. Blood transfusion has its own hazards, including transfusion of wrong blood and deadly infections like HIV, CMV, hepatitis and anaphylaxis. Thus, there is a need for a safe and effective alternative to OI or blood transfusion in the treatment of anemia. Iron dextran, the first parenteral iron used, lost its popularity due to anaphylaxis. Iron sucrose was then discovered as a parenteral iron that could be safe and effective. Hence based on above findings the present study was planned for Clinical Evaluation of Intravenous Iron Sucrose in Pregnant Anaemic Females.

The present study was planned in Department of Obstetrics and Gynaecology, Madhubani Medical College and Hospital, Madhubani, Bihar. In the present study 50 females presenting in antenatal clinic with haemoglobin between 5-9 g% were enrolled in the present study. Iron sucrose (Injection Orofer S, Emcure Pharmaceuticals Limited, India) was given in a dose of 200 mg intravenously twice weekly in 200 ml normal saline over a period of 15-20 min. First dose was given in the ward where equipment for cardiopulmonary resuscitation was available. The following doses were given on outpatient basis. Patients were observed for side effects or anaphylactic reactions. Any minor or major side effects were documented. All parameters were repeated at 2 wk interval till 8 wk.

The data generated from the present study concludes that intravenous iron sucrose therapy was effective to treat moderate anaemia in pregnant women. Intramuscular preparations are known to be associated with local side-effects. Iron sucrose complex iv therapy was with negligible side effects. It caused rapid rise in haemoglobin level and the replacement of stores was faster.

Keywords: Intravenous, Iron Sucrose, Pregnant, Anemic Females, etc.

Introduction

Anemia is a medical condition in which there is not enough healthy red blood cells to carry oxygen to the tissues in the body. When the tissues do not receive an adequate amount of oxygen, many organs and functions are affected. Anemia during pregnancy is especially a concern because it is associated with low birth weight, premature birth and maternal mortality.

During pregnancy, the body produces more blood to support the growth of your baby. If you're not getting enough iron or certain other nutrients, your body might not be able to produce the amount of red blood cells it needs to make this additional blood. It's normal to have mild anemia when you are pregnant. But you may develop

severe anemia from low iron or vitamin levels or from other reasons.

Anaemia during pregnancy is one of the important factors associated with a number of maternal and foetal complications. It decreases the woman's reserve to tolerate bleeding either during or after child birth and makes prone to infections. Anaemia during pregnancy also has been associated with increased risk of intra uterine growth restriction, premature delivery, low birth weight (LBW) and maternal and child mortality.

World Health Organization (WHO)/World Health Statistics data shows that 40.1% of pregnant women worldwide were anemic in 2016. The condition is prominent in Southeast Asian countries where about half of all global maternal deaths are due to anemia and India contributes to about 80% of the maternal death due to anaemia in

South Asia. There is marginally decrease in prevalence of anemia in pregnant women in India from 58% in NFHS-3 (National Family Health Survey-2005-06) to 50 % in NFHS-4 survey (2015-16).

Among the various causes of anaemia in women, iron deficiency is the most common cause, primarily due to their recurrent menstrual loss and secondary due to poor supply of iron in the diet. During pregnancy anemia is common due to increased demand of iron for the growing fetus and placenta; and increased red blood cell mass (with expanded maternal blood volume in the third trimester), which is further aggravated with other factors such as childbearing at an early age, repeated pregnancies, short intervals between pregnancies and poor access to antenatal care and supplementation. Indian Council of Medical Research considers haemoglobin (Hb) level below 10.9 g/dl as cutoff point for anemia during pregnancy.

The Ministry of Health and Family Welfare, Government of India has given emphasis to prevent anaemia under RMNCH+A services. National Health Policy 2017 also addressed malnutrition and micronutrient deficiencies interventions. “National Iron Plus Initiative” launched in 2013 is a comprehensive strategy to combat the public health challenge of iron deficiency anaemia (IDA) prevalent across the life cycle.

National Nutrition Mission has been setup under the oversight of the Ministry of Women and Child Development with the aim to reduce anaemia among young children, adolescent girls and women of reproductive age (15–49 years) by one third of NFHS-4 levels by 2022. [1]

Iron deficiency anemia develops when body stores of iron drop too low to support normal red blood cell (RBC) production. Inadequate dietary iron, impaired iron absorption, bleeding, or loss of body iron in the urine may be the cause. Iron equilibrium in the body normally is regulated carefully to ensure that sufficient iron is absorbed in order to compensate for body losses of iron.

In the simplest of terms, anemia results from impaired production of red blood cells, increased destruction of red blood cells or blood loss. [2] Anemia can be congenital (ie, conditions such as sickle cell anemia and thalassemia) or acquired (ie, conditions such as iron deficiency anemia or anemia as a result of an infection).

The most frequent cause of anemia in pregnancy worldwide is iron deficiency anemia (IDA). Iron is needed for many physiological processes in the body, and observational studies indicate that iron deficiency during pregnancy may independently result in cognitive or behavioral abnormalities in the child.[6] Babies of women with IDA have an increased risk of being low birthweight,

being born prematurely, being more susceptible to infections, and suffering death in utero. [3]

Aside from iron deficiency, other causes of anemia in the peripartum woman include nutritional deficits such as folate and vitamin B12 deficiencies. Congenital causes of anemia that may worsen during pregnancy include: hemoglobinopathies, such as sickle cell anemia and thalassemia, as well as conditions of red cell structural and enzymatic abnormalities such as hereditary spherocytosis and elliptocytosis. Bacterial, viral, fungal, and protozoal infections (such as malaria and hookworm) may also result in anemia. Hemolytic anemia, aplastic anemia and anemia due to hematologic or non-hematologic (ie, colonic adenocarcinoma) malignancy may rarely occur during pregnancy as well. Peri and postpartum hemorrhage may induce or worsen pre-existing anemia in the postpartum woman.

Prevention and treatment, especially of iron deficiency anemia, is widely available, but not consistently performed. Severe anemia may require red blood cell transfusions especially if there is also significant blood loss at birth.

- Maternal deficiency of iron is by far the most common cause of obstetric anemia and is a treatable condition
- Maternal anemia is frequent despite guidelines and widely available treatment
- Maternal anemia is thought to be the most frequent cause of maternal death worldwide
- Anemia during pregnancy increases the risk of induction of labor and cesarean section
- Anemia during pregnancy increases the risk of postpartum anemia
- Iron deficiency during pregnancy is linked to a number of harmful effects on the fetus such as intrauterine growth restriction, death in utero, infection, preterm delivery and neurodevelopmental damage, which may be irreversible [4]
- Failure to treat maternal iron deficiency may carry over to a woman's next pregnancy

Iron deficiency is the most common cause of anemia in the pregnant woman. During pregnancy, the average total iron requirement is about 1200 mg per day for a 55 kg woman. This iron is used for the increase in red cell mass, placental needs and fetal growth. About 40% of women start their pregnancy with low to absent iron stores and up to 90% have iron stores insufficient to meet the increased iron requirements during pregnancy and the postpartum period.

Deficiencies of folate and vitamin B12 can lead to anemia in the pregnant patient. Parasitic infestations with hookworm or *Plasmodium* species may also result in anemia. Other infectious causes include: bacterial, fungal

and viral infections. Congenital anemias such as sickle cell anemia and thalassemia may worsen during pregnancy due to increased demands. Even less common causes include hemolytic anemia, aplastic anemia, and hematologic malignancies in the pregnant woman.

The majority of women presenting with postpartum anemia have pre-delivery iron deficiency anemia or iron deficiency anemia combined with acute blood loss during delivery. [5]

Postpartum hemorrhage is typically defined as blood loss in excess of 500 mL following vaginal delivery and in excess of 1000 mL following cesarean delivery. Primary PPH is that which occurs within 24 hours after delivery, while secondary PPH can occur up to 12 weeks following delivery. PPH is relatively common with an incidence of 5–15% of all births. However, life-threatening PPH, defined by the Royal College of Obstetricians and Gynaecologists (RCOG) as an estimated blood loss in excess of 2500 mL or receipt of > 5 units of blood products or treatment of coagulopathy, occurs in an estimated 3.7 per 1000 pregnancies. [6]

The most useful test with which to render a diagnosis of anemia is a low RBC count, however hemoglobin and hematocrit values are most commonly used in making the initial diagnosis of anemia. It is important to note that reference ranges for these values are often not the same for pregnant women. Additionally, laboratory values for pregnancy often change throughout the duration of a woman's gestation. [7]

Testing involved in diagnosing anemia in the pregnant woman must be tailored to each individual patient. Suggested tests include: hemoglobin and hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), erythrocyte count, red cell distribution width (RDW), reticulocyte count, and a peripheral smear to assess red blood cell morphology. If iron deficiency is suspected, additional tests such as: serum iron, total iron-binding capacity (TIBC), transferrin saturation, and plasma or serum ferritin may be warranted.

Hemoglobin < 10 g/dL in the postpartum woman is classified as anemia.

Hormonal changes in the pregnant woman result in an increase in circulating blood volume to 100 mL/kg with a total blood volume of approximately 6000–7000 mL. While red cell mass increases by 15–20% during pregnancy, plasma volume increases by 40%. [8]

Hemoglobin levels less than 11 g/dL during the first trimester, less than 10.5 g/dL during the second and third trimesters and less than 10 mg/dL in the postpartum period are considered anemic. Iron deficiency anemia can be prevented by taking 15–60 mg of iron orally daily. [9]

Treating anemia during pregnancy and managing obstetric hemorrhage reduces the incidence of iron deficiency anemia.

For treatment of pregnant woman with iron deficiency anemia, doses of oral elemental iron between 65–200 mg per day are recommended. While oral iron is presently the gold standard for mild to moderate iron-deficiency anemia, treatment doses of elemental iron often result in significant gastrointestinal side effects, resulting in reduced compliance. If oral iron cannot be tolerated or is proven ineffective, intravenous iron can induce repletion of iron stores within 1–2 days and normalization of hemoglobin levels in 1–3 weeks.

The majority of obstetric anemia cases can be treated based on their etiology if diagnosed in time. Oral iron supplementation is the gold standard for the treatment of iron deficiency anemia and intravenous iron can be used when oral iron is not effective or tolerated from the second trimester of pregnancy onwards. [10]

Treatment of postpartum hemorrhage is multifactorial and includes medical management, surgical management along with blood product support. [6, 11]

Blood product transfusion carries a number of risks both infectious as well as non-infectious. Transfusion transmissible diseases include, but are not limited to the following: human immunodeficiency virus (HIV), hepatitis C virus, hepatitis B virus, West Nile virus, syphilis, Chagas disease, Zika virus, Dengue fever and Chikungunya virus. Non-infectious risks of blood product transfusion include, but are not limited to: hemolytic transfusion reactions, allergic and anaphylactic transfusion reactions, transfusion associated circulatory overload, transfusion related acute lung injury, transfusion associated graft versus host disease and febrile non-hemolytic transfusion reactions. Because of these risks, blood product transfusion should only be used in cases of acute bleeding, severe cases of refractory anemia and in conditions where maternal hemoglobin levels are so low, that there is thought to be imminent risk to mother or fetus.

In healthy women after normal delivery, the prevalence of anemia (defined as hemoglobin < 11 g/dL) 1 week postpartum is 14% in iron supplemented women and 24% in non-supplemented women. [6]

The standard treatment in majority of the institutions is oral iron (OI), with blood transfusion reserved for severe or emergency cases. However, it is unreliable in the treatment of severe anemia. Blood transfusion has its own hazards, including transfusion of wrong blood and deadly infections like HIV, CMV, hepatitis and anaphylaxis. Thus, there is a need for a safe and effective alternative to OI or blood transfusion in the treatment of anemia. Iron dextran, the first parenteral iron used, lost its popularity

due to anaphylaxis. Iron sucrose was then discovered as a parenteral iron that could be safe and effective. Hence based on above findings the present study was planned for Clinical Evaluation of Intravenous Iron Sucrose in Pregnant Anaemic Females.

Methodology:

The present study was planned in Department of Obstetrics and Gynaecology, Madhubani Medical College and Hospital, Madhubani, Bihar. In the present study 50 females presenting in antenatal clinic with haemoglobin between 5-9 g% were enrolled in the present study. Iron sucrose (Injection Orofer S, Emcure Pharmaceuticals Limited, India) was given in a dose of 200 mg intravenously twice weekly in 200 ml normal saline over a period of 15-20 min. First dose was given in the ward where equipment for cardiopulmonary resuscitation was available. The following doses were given on outpatient basis. Patients were observed for side effects or anaphylactic reactions. Any minor or major side effects were documented. All parameters were repeated at 2 wk interval till 8 wk.

The primary outcome measures were haemoglobin and serum ferritin levels after 4 and 8 wk. Secondary outcome measures were improvement in serum iron levels, reticulocyte count, any adverse effects and perinatal outcome [period of gestation (POG) at the time of delivery, type of birth, postpartum haemorrhage, need of blood transfusion and foetal birth weight].

All the patients were informed consents. The aim and the objective of the present study were conveyed to them. Approval of the institutional ethical committee was taken prior to conduct of this study.

Following was the inclusion and exclusion criteria for the present study.

Inclusion criteria: Females presenting in antenatal clinic with haemoglobin between 5-9 g%

Exclusion criteria: causes other than iron deficiency anaemia, multiple pregnancy, high risk for preterm labour and recent blood transfusions, thalassaemia and other medical disorders.

Results & Discussion:

As one of the important factors influencing maternal morbidity and mortality and also the health of the newborn, Anemia has defied over 3 decades of public health intervention and continues to affect a majority of pregnant women in the state. Anemia in pregnancy is associated with high maternal morbidity and mortality.

Intravenous iron sucrose has a very high potential for reducing the burden of iron deficiency anemia because it overcomes the problems of compliance and absorption, compared to oral iron supplementation and has an

excellent safety record. Through a single total dose infusion of iron sucrose it is possible to handle the commonest medical disorder of pregnancy there by dramatically reducing maternal morbidity and mortality, while improving the quality of life of women in the developing world.

Anemia in pregnancy is associated with poor maternal and fetal outcomes. Almost one-fifth of the maternal deaths worldwide can be attributed to anemia directly, whereas another 50% of the deaths are associated with anemia. [12-13] Almost half of the pregnant women in India are anemic. [14] This situation persists despite the existence of a national anemia control program for the past many decades. [15] Since almost half of the anemic pregnant women in India have moderate anemia, [16] they deserve priority attention.

Oral iron, the standard drug for the treatment of iron-deficiency anemia, is poorly tolerated during pregnancy due to its side effects. [14] It takes 6-8 weeks to normalize hemoglobin (Hb) level. However, quick restoration of Hb level is possible by parenteral administration of iron. Studies report that intravenous iron sucrose (IVIS) is safe and an effective alternative for the treatment of anemia among pregnant women who did not tolerate oral iron. [17]

The main aim of parenteral iron administration ought to be replenishment of iron stores in the iron-deficient moderately anemic pregnant women. Studies have reported that optimum iron repletion often results in the patient not having to return for more iron for 9 months or longer. [18] Serum ferritin level is a good marker of body iron store.

The initial results with iv iron therapy were excellent; women had to be admitted only for two days for iv iron therapy; reaction to iv iron (for both preparations) were manageable; and the rise in Hb was satisfactory. [19] Those who were given im iron dextran therapy had to come daily for 10-15 days to the OPD for injections; many women found this difficult. By about a week after starting the iron dextran injections about 20 per cent developed joint pains; swelling in the joints and fever was seen in about 5 per cent. The women with these symptoms responded to paracetamol but many women discontinued the injection. Intramuscular injection of iron sorbitol citric acid complex was relatively free of side effects but it was costly as about a third of the drug got excreted in urine most women required 15-20 injections; many found it difficult to come to the OPD for 20 days for injection. [19]

In the last decade, iron sucrose had been widely used in treatment of anaemia associated with chronic renal failure in patients undergoing dialysis where it is convenient to give iv iron at weekly intervals along with erythropoietin.

[20] The side effects were mild and very few major complications were reported. Encouraged by these reports, some obstetricians in middle eastern countries started using iv iron sucrose for treatment of anaemic pregnant women. [21] Most of these studies were based on small number of cases and indications varied from poor compliance with iron folate therapy in women with mild anaemia to moderate anaemia management. [22]

Table 1: Basic Detail

Parameters	No. of Cases
Age:	
18 – 25 years	4
26 – 30 years	36
31 – 35 years	8
36 – 40 years	2
BMI (kg/cm2)	15.1 – 28.6
Diet:	
Veg	32
Non Veg	18
Type of Pregnancy:	
Primigravida	36
Multigravida	14
Gestation Age (weeks)	15 – 36

Table 2: Initial Haematological Parameters & after Iron sucrose in treatment

Parameters	Initial	After 2 weeks	After 4 weeks	After 8 weeks
Mean Hb (g%)	7.5 ± 0.71	7.92 ± 0.65	9.5 ± 0.86	11.6 ± 0.92
Serum iron (µg/dl)	33.4 ± 4.6	43.5 ± 8.3	58.3 ± 11.7	86.3 ± 12.3
TIBC (µg/dl)	364.5 ± 41.3	333.7 ± 13.8	323.3 ± 9.8	311.4 ± 12.3
Serum ferritin (µg/l)	10.8 ± 5.2	18.3 ± 8.5	26.8 ± 9.1	71.3 ± 11.3
Reticulocyte count (%)	1.68 ± 0.72	4.57 ± 0.73	4.86 ± 1.3	5.7 ± 1.9
Mean corpuscular vol. (fl)	63.5 ± 4.3	74.6 ± 3.9	81.6 ± 4.3	87.6 ± 2.8
Mean corpuscular haemoglobin (MCH) (pg)	21.7 ± 3.2	26.5 ± 3.6	32.8 ± 2.6	46.5 ± 3.6
Mean corpuscular haemoglobin concentration (MCHC) (g/dl)	24.5 ± 2.2	32.5 ± 2.5	42.6 ± 3.9	58.4 ± 2.9

Table 3: Obstetrical complications

Obstetrical complications	Occurrence in No. of Cases
Pre-eclampsia	5
Intrauterine growth restriction	6
Preterm labour	4
Preterm premature rupture of membranes	2
Gestational diabetes mellitus	2
Intrahepatic cholestasis of pregnancy	2
Abruption	1

Studies have shown that moderate to severe anemia in pregnancy are associated with higher maternal and fetal morbidity, severe anemia is associated with cardiac decompensation and pulmonary edema. Blood loss even 200 ml in third stage of labour can cause shock and death in severe anemia. [23] The stores in Indian women are deficient and they require 100 mg elemental iron per day for prophylaxis. For the treatment of anemia the recommended dose is 200 mg elemental iron per day. [24]

Breyman [27] treated more than 500 antenatal women diagnosed with iron deficiency anaemia. Intravenous iron

sucrose was given according to the calculated dose as either iv push over 5-10 min or iv infusion over 20- 30 min. All injections were given on outpatient basis without any test dose. This study also emphasizes on the safety of iron sucrose injection. In the present study, the first dose was given in ward where facilities for emergency care were available. All subsequent doses were given on OPD basis. None of the patients required any emergency care. In other studies [25-26] target Hb for calculation of required dose has been taken 11 g/dl and for replenishment of stores 500 mg has been added. Keeping in mind very low iron stores in Indian women, we took 14 as index Hb and added 1000 mg for replenishment of stores. Even with this, maximum mean serum ferritin after 8 wk of starting therapy was 69 µg/l which is well within normal range. As compared to previous studies [25], ferritin levels in our study women showed a lesser increase. The reason can be due to severely depleted iron stores in Indian women. [27]

Carretti et al., observed that rise in hemoglobin was inversely correlated with initial hemoglobin value, and significantly larger proportions of high hemoglobin responses were observed after the 28th week of gestation as compared with the second trimester. This may be due to physiological hemodilution and blunted erythropoietin response of second trimester. There was no direct correlation of increase in hemoglobin with period of gestation in each individual group. [28]

Kumar et al. in a review concluded that oxidative stress worsens with anemia in most of the animal and human studies. Furthermore, in majority of the animal studies and studies in pregnant women, the oxidative stress increased when iron was supplemented. [29]

Cristop p et al [30], conducted a retrospective analysis of 206 pregnant women who were treated with ferric carboxy maltose or iron sucrose for IDA. They found that ferric carboxy maltose administration in pregnant women was well tolerated and was not associated with relevant clinical safety concern. It has complete safety profile to iron sucrose but offers the advantage of much higher iron dosage at the time reducing the need for repeated transfusion and increasing patients comfort.

Iron sucrose can be given without test dose and it has a favorable safety profile and it is an alternative to other forms of parenteral iron therapy in correction of iron store depletion and correction of anemia during pregnancy. [31] Hence intravenous iron sucrose is widely used for the treatment of IDA, when oral iron is inappropriate or ineffective or poorly tolerated and blood transfusion is inappropriate.

Conclusion:

The data generated from the present study concludes that intravenous iron sucrose therapy was effective to treat

moderate anaemia in pregnant women. Intramuscular preparations are known to be associated with local side-effects. Iron sucrose complex iv therapy was with negligible side effects. It caused rapid rise in haemoglobin level and the replacement of stores was faster.

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