Original Article

To Evaluate the Safety and Efficacy of Intravenous Iron Sucrose Complex Versus Oral Ferrous Sulphate in Treatment of Postpartum Iron Deficiency Anaemia

Asia Kanwal, Wajeha Shadab, Afshan Rehman

[1] Ex Postgraduate Trainee at Benazir Bhutto Hospital, Rawalpindi. Now Senior registrar, IIMC, Railway Hospital, Rawalpindi [2&3] Ex Postgraduate Trainee at Benazir Bhutto Hospital, Rawalpindi.
Correspondence: *Dr. Wajiha Shadab, Senior registrar Obs and Gynae deptt, IIMC, Railway Hospital Rawalpindi.*
EMAIL:drwajeha@hotmail.com

Abstract

Objective: **To evaluate the safety and efficacy of intravenous iron sucrose complex versus oral ferrous sulphate in treatment of postpartum iron deficiency anaemia**

Study Design: **Randomized controlled trial.**

Place and Duration of Study: **Department of Obstetrics and Gynaecology, Benazir Bhutto Hospital (BBH), Rawalpindi from September 2012 to February 2013.**

Methodology: **A total of 322 patients with confirmed diagnosis of postpartum iron deficiency anaemia (based on laboratory evaluation) were included in the study and divided equally into group A and B i.e. 116 patients in each group. The patients in both groups were counseled regarding treatment, dosage and side effects of intravenous iron and oral ferrous sulphate and follow up. Two groups were randomly constituted by probability systematic sampling technique. Treatment was started at 24-48 hours after delivery. Patients of Group "A" were given intravenous ferrous sucrose (Venofer) on day 2 and 4 following recruitment. The dose was calculated by using the formula: Total iron requirement=required Hb-actual Hbx250 . In Group-B women were advised to take 200 mg ferrous sulphate twice daily together with meals for six weeks from the day of recruitment. Laboratory procedures including Hb, Haematocrit, red cells indices, mean corpuscular volume, mean corpuscular Hb, and serum ferritin as an indicator of iron status on days 0, 5, 14 and 40.**

Results: **In Group-A Mean and standard deviation of age was 24.55±0.67 and it was 23.99±1.02 in Group-B. Parity 2-4 was common in both groups being, 101 (62.73%) in Group-A and 98 (60.87%)**

in Group-B. (Table II). Hb, MCV, Haematocrit and ferritin were significantly higher in Group-A on day 5, 14 and 0. (Table I and II). Regarding comparison of adverse effects of both drugs, 35 (21.74%) metallic taste, 2 (1.24%) nausea, 12(7.45%) infusion site burning and no complications in 112(69.57%) in Group-A while 10(6.21%) cases had metallic taste, 12(7.45%) nausea, 5(3.11%) constipation, 9(5.59%) colicky pain, 9(5.59%) diarrhoea and 98(60.87%) had no complications in Group-B. (Table III)

Conclusion: Iron sucrose compared to oral iron administration is more efficient in treating postpartum anaemia without any significant adverse effects.

Key Words: Post partum anaemia, management, intravenous iron sucrose complex, oral ferrous sulphate.

Introduction

Nutritional iron deficiency is the most common deficiency disorder in the world, affecting more than one billion people, with pregnant women at particular risk.[1,2] World Health Organization (WHO) data show that iron deficiency anaemia (IDA) in pregnancy is a significant problem throughout the world with a prevalence ranging from 15% of pregnant women in industrialized countries to an average of 56% (range 35–75%) in developing countries.[1,2] Postpartum haemoglobin (Hb) levels of <10 g/dl are observed in up to 30% of women, with more severe anaemia (Hb < 8 g/dl) seen in 10%.[3] Iron deficiency is the principal cause. This is partly attributable to an iron deficit during pregnancy caused by the increased iron demands of the foetoplacental unit and an increased maternal red cell mass.[4] Irrespective of mode of delivery, blood loss is a contributing factor, with 5% of deliveries involving loss of more than 1 litre.[5,6]

IDA is thought to contribute to a variety of morbidities such as lethargy, lactation failure and postpartum depression. The standard approach to treatment in the majority of UK institutions is oral iron supplementation, with blood transfusion reserved for more severe or symptomatic cases.[7] However, the transfusion trigger is clinician dependant and a number of studies and audits have shown that the transfusion level varies widely between medical teams and institutions, with a significant proportion of transfusions given inappropriately.[8] There are a number of hazards of allogenic blood transfusion including transfusion of the wrong blood, infection, anaphylaxis and lung injury, any of which would be devastating for a young mother. These hazards, together with the national shortage of blood products, mean that transfusion should be viewed as a last resort in otherwise young and healthy women.[7]

Oral iron supplementation is more commonly used than blood transfusion for postpartum IDA. However, it is unreliable in the treatment of severe anaemia due to its limited absorption and gastrointestinal adverse effects that affect compliance.[9,10] The introduction of second-generation i.v. iron formulations, including iron sucrose and ferric gluconate, was clearly an improvement over i.v. iron dextran. These formulations proved to be effective in the management of IDA and are not associated with the serious allergic reactions encountered with i.v. iron dextran. For these reasons, use of these

preparations became more widespread in the treatment of IDA across a wide range of clinical conditions. An important advantage of i.v. iron over oral iron is that it may by pass hepcidin actions by directly loading transferrin and making iron available to macrophages. In recent years, type II iron complexes have been developed which are better tolerated and can be used for a rapid reversal of iron deficiency anaemia.[11] There is increasing evidence that iron sucrose is effective for treating IDA and safe for the mother and the foetus when used during pregnancy, using the recommended dosages and treatment regimens. Parenteral iron administration with ferrous sucrose is now available and routinely used in a number of European countries. Unlike previous formulations, most notoriously ferrous dextran, which was associated with a significant risk of anaphylactoid reactions, ferrous sucrose has an excellent safety record.[12]

Primary measures were to assess the rise in haemoglobin and iron stores and secondary endpoints were designed to assess safety, tolerability and compliance for both treatment arms.

Methodology

This Randomized controlled trial was conducted at the Department of Obstetrics and Gynaecology, Benazir Bhutto Hospital, Rawalpindi from September 2012 t0 February 2013. After taking approval from hospital ethical committee, all patients with confirmed diagnosis of postpartum iron deficiency anaemia (based on laboratory evaluation) were included in the study and approval from ethical committee of hospital was taken. Choosing the formula $n=z^2 qp/e^2$, where p=prevalence, e=error at 5%, sample size (n) was 322, 161 patients in each group. Selected patients were evaluated and data was collected according to proforma designed. Two groups i.e. group A and group B were randomly constituted by probability systematic sampling technique. Inclusion criteria were age 18-44 years, HB <9gm/dl, Serum ferritin <15 µg/l and Hemodynamically stable patients. The patients with history of anaemia due to any other cause such as chronic blood loss, hemolytic anaemia, thalassemia and sickle cell anaemia, Previous parentral iron therapy during pregnancy, Peripartum blood transfusion, History of asthma, thromboembolism, seizure and alcohol or drug abuse, Women with signs of infection, Clinical or laboratory evidence of hepatic or renal, cardiovascular and hemolytic abnormalities, History of acid peptic disorder, esophagitis or hiatal hernia and malabsorption syndrome were excluded from the study. A detailed informed consent was taken. The patients in both groups were counseled regarding treatment, dosage and side effects of intravenous iron and oral ferrous sulphate and follow up. Treatment was started at 24-48 hours after delivery. Patients of Group “A” were given intravenous ferrous sucrose (Venofer) on days 2 and 4 following recruitment. After payment R&G Drug Company provided the iron sucrose (venofer) on demand for patient. The dose was calculated by using the formula: Total iron requirement=required Hb-actual Hbx250. Ferrous sucrose was administered as infusion in 250 ml of 0.9% sodium chloride for more than 30 minutes in hospital with monitoring of vitals signs during infusion. Patients were asked to note any symptoms or adverse effects of treatment e.g. metallic taste, flushing of face and burning at injection site. In Group-B women were advised to take 200 mg ferrous sulphate twice daily together

with meals for six weeks from the day of recruitment. Date was given when to stop oral supplementation. Groups were advised to note side effects like dyspepsia, nausea, constipation etc. Compliance was emphasized by telephonic contact. Laboratory procedures including Hb, Hematocrit, red cells indices, mean corpuscular volume, mean corpuscular Hb, and serum ferritin as an indicator of iron status on days 0, 5, 14 and 40. Research assistant who evaluated the outcome variables of study were blinded to the study group of patients to reduce any chance of bias. The data was analyzed using SPSS version 13.0 and descriptive statistics were calculated, mean and S.D. for age, parity, BMI, Hb, MCV, hematocrit and ferritin before delivery, at day 0,5,14 and 40. Frequency and percentages were presented for delivery methods and adverse events (metallic taste, nausea, dyspepsia, constipation, diarrhea, colicky pain, infusion site burning and haemodynamic disturbance). Independent sample test was used to analyze the effect of iron supplementation on Hb, MCV, Hematocrit and ferritin levels by both treatments at days 5, 14 and 40. Chi square test was used to compare the adverse events (metallic taste, nausea, dyspepsia, constipation, diarrhea, colicky pain, infusion site burning and hemodynamic disturbance) at days 5, 14 and 40. P value of <0.05 was considered statistically significant.

Results

In this study, a total of 322 patients were recruited after fulfilling the inclusion/exclusion criteria to evaluate the safety and efficacy of intravenous iron sucrose complex versus oral ferrous sulphate in treatment of postpartum iron deficiency anaemia. In this research, majority of the patients were found between 21-30 years of age in both A & B groups, in Group-A 105 (65.22%) and in Group-B 111(68.94%), the subjects with 18-20 years of age in Group-A were 23(14.2%) and in Group-B 19(11.80%) while 33(20.49%) of Group-A and 31(19.26%) in Group-B were found between 31-44 years of age. Mean and standard deviation was calculated it was found 24.55±0.67 in Group-A and 23.99±1.02 in Group-B.

Regarding parity, whereas in Group-A 34(21.12%) and in Group-B 39(24.22%) were found with primi parity, patients with 2-4 para were found 101(62.73%) in Group-A and 98(60.87%) in Group-B, while 26(16.15%) in Group-A and 24(14.91%) in Group-B were found with para >4.

The comparison of investigations in both groups (day 0) is computed in Table I, the values are recorded in mean.

Table I. Comparison of Investigations in Both Groups (at Day 0)

Investigations	Group-A	Group-B
	Values in mean	Values in mean
BMI	25	26
Hb	7.2±0.1	7.1±0.3
MCV	70	71
Haematocrit	26	27.5
Ferritin	11	12.5

The comparison of investigations in both groups at day 5 showed BMI 25, Hb 7.2, MCVf 80, Hematocrit 33 and ferritin 46 in Group-A while in Group-B BMI was found 26, Hb 7.9, MCVf 72, Hematocrit 29 and ferritin 12.

The investigations at day 14 shows 25 BMI, Hb 11, MCVf 84, Hematocrit 35 and ferritin 37 in Group-A

while in Group-B BMI was found 26, Hb 9, MCVf 80, Hematocrit 33 and ferritin 16.

Day 40 after treatment shows comparison of investigations in Table II.

Table No II. Comparison of Investigations in Both Groups (Day 40)

Investigations	Group-A (n=161)	Group-B (n=161)	P Value
	Values in mean	Values in mean	
BMI	25.05	26.	
Hb	11.49+0.08	11.17+0.04	0.02
MCV	86	85.5	0.07
Haematocrit	35	34.8	0.06
Ferritin	42.2	15	0.02

Regarding comparison of adverse effects of both drugs, Table III shows metallic taste in 35 (21.74%), nausea 2(1.24%), infusion site burning 12(7.45%) and no complications in 112 (69.57%), in Group-A, while 10(6.21%) cases had metallic taste, 12(7.45%) nausea, 5(3.11%) constipation, 9(5.59%) colicky pain, 9(5.59%) diarrhea and 98(60.87%) had no complications in Group-B.

Discussion

The study was performed to ascertain whether administering intravenous ferrous sucrose to women with postpartum anaemia results in higher Hb concentrations and improved iron stores than using standard treatment with oral iron.

In our study, ferritin and serum iron were used as indicators of iron storage. Although ferritin levels are low in pregnancy due to plasma dilution, ferritin remains a reliable indicator of iron deficiency, where a cutoff level of <15 microgram/l is used.[13] A spontaneous restoration of ferritin levels due to physiological changes and fluid shifts postpartum is known to occur, but it had little effect in this study as there was minimal change in the ferritin levels in those treated with oral iron. In group A ferritin and haematocrit level were significantly improved as compared with group B. Similar results had been reported by Breymann,[14] Shrivastava[15] and Bigger,[16] Rosario.[17] The results of the study reveal that intravenous therapy significantly increases Hb levels and rapidly replenish iron stores within shortest possible time i.e. 5 days. Though Hb levels were

Table no III. Comparison of side effects in both groups

Investigations	Group-A (n=161)		Group-B (n=161)		P Value
	No. of cases	Percentage	No. of cases	Percentage	
Metallic taste	35	21.74	10	6.21	0.00
Nausea	2	1.24	12	7.45	0.06
Dyspepsia	0	0	5	3.11	0.02
Constipation	0	0	18	11.18	0.00
Diarrhea	0	0	9	5.59	0.00
Colicky Pain	0	0	9	5.59	0.00
Infusion site burning	12	7.45	0	0	0.00
Haemodynamic disturbances	0	0	0	0	00
No complications	112	69.57	98	60.87	0.12
Total	**161**	**100**	**161**	**100**	

similar in both groups by day 40, but intravenous ferrous sucrose has restored the iron reserves and its statistical difference was higher throughout the treatment period. The study conducted by Bhandal [7] showed that the rapid and profound response can be directly attributed to the high amount of iron that could be delivered directly to the haemopoietic tissues which in turn restores iron reserves.

Postpartum Hb levels of <10 g/dl are observed in up to 30% of women, with more severe anaemia (Hb < 8 g/dl) seen in 10%.[3] The treatment of postpartum anaemia depends on the severity of the anaemia and/or additional maternal risk factors or co-morbidities. Administration of oral iron supplementations is not sufficiently enough in order to reverse anaemia promptly, due to the limited absorption, the gastrointestinal symptoms and the poor compliance for long treatment of the patients as evident from the result of our study in which Hb level in the patients under Group-B (treated with oral ferrous sulphate) were significantly lower than Group-A (treated with intravenous iron sucrose complex).

Historically, other intravenous iron preparations have been used e.g. ferrous dextran, but now their use is very limited due to their high anaphylactoid risk. In our study, intravenous ferrous sucrose was well tolerated and did not show any serious adverse effects. The results of our study are in agreement with the larger studies that have investigated the safety profile of intravenous ferrous sucrose both during pregnancy and in the postpartum period.[14] Perewunsnyk et al [12] studied 400 women and found minor general adverse effects including a metallic taste, and burning at the injection site occurred in 0.5%, with doses up to 200 mg. The high tolerance of the drug has been partly attributed to slow release of iron from the complex and also due to the low allergenicity of sucrose. Higher doses are reported with adverse effects but without a significant effect on haematological parameters.[18]

The results of the current study regarding side effects of the drugs show significant increased incidence in Group-B. In our study, intravenous ferrous sucrose appeared to provide a rapid resolution of both iron stores and Hb for women with postpartum IDA. . Higher doses appear to increase reported adverse effects without a significant effect on haematological parameters.[18] Gastrointestinal adverse effects are thought to be dose related and occur more frequently at higher doses.[18] Al-Momen[19] described gastrointestinal adverse effects with a frequency of up to 30% in women treated with oral iron.

The general health effects of iron deficiency in the obstetric population have been identified as an area of research priority.[20] It is well known that women with anaemia suffer from increased cardiovascular strain, reduced exercise performance and various symptoms including a feeling of reduced wellbeing, headaches, tiredness and dizziness. All these symptoms can be debilitating, especially when caring for a newborn. Women suffering from early postpartum anaemia may also have an increased risk of developing postpartum depression.[21]

Conclusion

Intravenous iron sucrose increases the Hb level more rapidly than oral ferrous sulphate in women with postpartum IDA. It also appears to replenish iron stores more rapidly without any significant adverse effects. Our results suggest that IV iron

sucrose is an effective drug for treating puerperal anaemia, leading to a rapid recovery of Hb levels. The current availability of generic iron sucrose preparations, with considerably lower acquisition costs, may facilitate in-hospital access to this treatment option in low-resource countries

References

1. World Health Organization [WHO], Division of Family Health, Maternal Health and Safe Motherhood Programme, Division of Health Protection and Promotion, Nutrition Programme; WHO. The Prevalence of Anaemia in Women: A Tabulation of Available Information, 2nd ed. Geneva, Switzerland: World Health Organization, 1992.
2. ACC/SCN (United Nations Administrative Committee on Coordination/Standing Committee on Nutrition). 2004. Fifth report on the world nutrition situation: Nutrition for improved development outcomes. Geneva, 2004, Available at http://www.unscn.org/en/publications/rwns.
3. Aggett P. Iron and women in the reproductive years. In: The British Nutrition Foundation's Task Force, editors. Iron: Nutritional and Physiological Significance, 1st edn. London: Chapman and Hall; 1995. p. 110–118.
4. Baker W. Iron deficiency in pregnancy, obstetrics and gynecology. Hematol Oncol Clin North Am 2000;14:1061–1077.
5. Gulmezoglu AM, Villar J, Ngoc NT, Piaggio G, Carroli G, Adetoro L, et al. WHO multicentre randomised trial of misoprostol in the management of the third stage of labour. Lancet 2001;358: 689–695.
6. Kotto-Kome AC, Calhoun DA, Montenegro R, Sosa R, Maldonado L, Christensen MD. Effect of administering recombinant erythropoietin to women with postpartum anaemia: a meta-analysis. J Perinatol 2004;24:11–15.
7. Bhandal N, Russell R. Intravenous versus oral iron therapy for postpartum anaemia. BJ Obstet Gynecol 2006;113:1248-1252.
8. Silverman JA, Barrett J, Callum JL. The appropriateness of red blood cell transfusions in the peripartum patient. Obstet Gynecol 2004;104:1000–1004.
9. Breymann C, Krafft A. Treatment of iron deficiency anaemia in pregnancy and postpartum. Transfusion Alternatives in Transfusion Medicine 2012;12:135-142.
10. Khalafallah A, Dennis A, Bates J, Bates G. A prospective randomized controlled trial of intravenous versus oral iron for moderate iron deficiency anaemia of pregnancy. J of Internal Medicine 2010;268:286-295.
11. Auerbach M, Ballard H, Glaspy J. Clinical update: intravenous iron for anaemia. Lancet 2007; 369: 1502–1504.
12. Perewunsnyk G, Huch R, Huch A, Breymann C. Parenteral iron therapy in obstetrics: 8 years experience with iron-sucrose complex. Br J Nutr 2002;88:3–10.
13. Mei Z, Cogswell ME, Parvanta I, Lynch S, Beard JL, Stoltzfus RJ, et al. Haemoglobin and ferritin are currently the most efficient indicators of population response to iron interventions: an analysis of nine randomised controlled trials. J Nutr 2005;135:1974–1980.
14. Breymann C. Modern therapy concepts for severe anaemia in pregnancy and postpartum. In: Huch A, Huch R, Breymann C, editors. Prevention and Management of Anaemia in Pregnancy and Postpartum Haemorrhage. Zurich, Switzerland: Schellenberg Druck AG, 1998. p. 107–122.

15. Armand-Ugón A, Cheong T, Matapandewu G, Rojo-Sanchís A. Efficacy of Intravenous Iron for Treating Postpartum Anaemia in Low-Resource African Countries: A Pilot Study in Malawi . Journal of Women's Health 2011; 20: 123-127.
16. Biggar P, Hahn KM. Importance of the different i.v. iron generations for everyday medical practice. MMW Fortschr Med 2013;155:18-24.
17. Dewan B, Philipose N, Balasubramanian A. Assessment of Intravenous Iron Sucrose in the Management of Anaemia in Gynecological and Obstetrical Practice. J Obstet Gynaecol India 2012; 62: 281–285.
18. Hallberg L, Ryttinger L, Solvell L. Side effects of oral iron therapy. A double-blind study of different iron compounds in tablet form. Acta Med Scand Suppl 1966;459:3–10.
19. Al-Momen AK, Al-Meshari A, Al-Nuaim L, Saddique A, Abotalib Z, Khashogji T, et al. Intravenous iron sucrose complex in the treatment of iron deficiency anaemia during pregnancy. Eur J Obstet Gynecol Reprod Biol 1996;69:121–124.
20. Stoltzfus RJ. Iron-deficiency anaemia: re-examining the nature and magnitude of the public health problem. Summary: implication for research and programs. J Nutr 2001;131:697S–700S.
21. Corwin EJ, Murray-Kolb LE, Beard JL. Low haemoglobin is a risk factor for postpartum depression. J Nutr 2003;133:4139–4142.

" So the stout foetus kicking and alive leaps from the fundus for its final dive.
Tired of the prison where its legs were curled it pants for a wider world"

Oliver Wendell Holmes
A physician and a Poet