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Oral versus Parenteral Iron Supplements: Which is better in Postpartum Iron Deficiency Anemia?

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Authors' contributions

This work was result of joint effort by all authors. Author AN did the study conception, data acquisition and analysis, and drafting of the manuscript. Author AA managed the data acquisition and interpretation, revision and final approval. Author QUA did the counseling of patients, got consent from participants, and data acquisition and analysis. All authors independently read and approved the final manuscript. All authors agreed to be accountable for all aspects of the work.

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ABSTRACT

Aims: To assess the safety and effectiveness of iron sucrose complex given intravenously versus ferrous sulphate taken orally in the treatment of iron deficiency anemia in the postpartum period.
Study Design: Randomized Clinical Trial.
Place and Duration of Study: Sahiwal Medical College, Sahiwal (Pakistan) from August to November, 2017.
Methodology: We included 386 patients with Iron Deficiency Anemia in postpartum period according to our criteria and distributed them among two groups. Group-A patients received intravenous Iron Sucrose complex while Group-B patients were treated with oral iron sulfate. Hemoglobin level, hematocrit, mean corpuscular volume and serum ferritin were used as indicators of anemia and results obtained for reversal of anemia and frequency of adverse effects were later analyzed.
Results: Varying degree of reversal of anemia was obtained in 386 patients included in the study.

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Patients treated with intravenous therapy had better reversal of anemia as compared to those who received oral iron sulfate with a P-Value of 0.03, 0.08, 0.049, and 0.01 for Hemoglobin, hematocrit, mean corpuscular volume, and serum ferritin, respectively with a margin of error of 5% and within the confidence interval of 95%. Comparison of adverse effects in both groups proved safer profile of intravenous therapy with a Pearson's Chi-square value at 0.046.

Conclusion: Intravenous iron sucrose complex has higher clinical efficacy as compared to oral iron sulfate tablets in the treatment of iron deficiency anemia in postpartum women. Furthermore, intravenous iron therapy has a good safety profile with infrequent tolerable adverse effects.

Keywords: Iron deficiency anemia; postpartum; iron sucrose; iron sulfate.

ABBREVIATIONS

Ferritin: *Serum ferritin level*
fL: *Femtoliter which is one millionth of a microliter*
g/dL: *Grams per deciliter*
g/L: *Grams per liter*
Hb: *Hemoglobin level*
Hct: *Hematocrit percentage*
IDA: *Iron deficiency anemia*
IV iron: *Intravenous iron (II) sucrose complex*
MCV: *Mean corpuscular volume in femtoliter*
mg: *Milligrams*
mL: *Milliliter*
Oral Iron: *Iron (II) sulfate tablets which are taken orally*
SD: *Standard deviation*
SPSS: *Statistical package for Social Sciences, a software commonly used for data collection and statistical analysis.*
WHO: *World Health Organization*

1. INTRODUCTION

Iron deficiency anemia (IDA) has the highest prevalence among all other nutritional deficiency disorders worldwide with figures standing at more than 1 billion of world's population, of which the proportion of pregnant ladies is peaking [1]. Statistics released by World Health Organization (WHO) put emphasize on the dilemma of IDA in pregnancy, with as high as 15% of pregnant women suffering from it, in developed or industrialized countries. While the numbers for under-developed or developing countries is even higher and range from 35-75%, with an average of 56% of pregnant women diagnosed with IDA [2]. Level of hemoglobin (Hb) during the first week of puerperium is below 10 g/dL (100 g/L) in almost one third of women who successfully completed a pregnancy, in turn, one third of these (about 10% overall) have relatively severe anemia with hemoglobin levels below 8 g/dl [3]. The pathophysiology can be traced back to nutritional iron deficiency followed by an iron deficit which appears in response to higher needs of developing embryo and growing fetus along with rising total red cell mass of maternal bloodstream [4]. In addition, blood loss during any mode of delivery worsens the scenario and postpartum hemoglobin is further decreased as around 5% of all deliveries result in loss of more than 2 pints of blood [5]. Postpartum complaints like lethargy and problems like lactation failure or depression have a higher risk in women with IDA.

Moving on to therapeutic option, oral iron supplementation in the form of iron sulfate tablets is the first line treatment in most of the countries who follow guidelines from Royal College of Obstetrics and Gynecology (RCOG), UK [6]. Blood transfusion, on the other hand, is an option when anemia is severe, symptoms are troublesome or the levels of hemoglobin are refractory to the oral therapy but blood transfusions are blamed for myriads of adverse effects and hazards involved, discussion of which is not the scope of this study [6]. Although the blood transfusion can be the savior in a handful of incidences of IDA in pregnancy and puerperium, intravenous iron preparations offer a middle ground with much fewer hazards as compared to those of allogenic blood transfusion, at the same time providing reversal of IDA. First generation preparation for intravenous iron supplementation known as iron dextran was associated with hypersensitivity reactions and was subjected to the action of hepcidin, while development of second-generation formulations is an improvement [7]. Iron (II) sucrose and Ferrous (II) gluconate do not have these downfalls and offer a therapy which is comparable to oral iron tablets in efficacy as well as safety.

The primary objective of this study was to compare the improvement in levels of hemoglobin along with iron stores while next in the list is to compare the rate of undesirable effects and adverse drug events.

2. METHODOLOGY

A randomized controlled trial was carried out, during August 2017 to November 2017, in the Department of Obstetrics and Gynecology at DHQ Teaching Hospital, Sahiwal which is a district level tertiary care healthcare facility in Pakistan. Approval from the ethical committee of the hospital was followed by inclusion of patients who presented during August and September 2017 based on following criteria:

2.1 Inclusion Criterion

- Patients with age 18-44 years, hemoglobin level below 9 g/dL and serum ferritin below 15 mcg/L during the first week of puerperium.
- Patients who gave birth between 37th-41st weeks of gestation.

2.2 Exclusion Criteria

- Patients who needed blood transfusion for any reason in the perinatal period.
- Patients with anemia with any other etiology besides iron deficiency.
- Patients with any known hematological pathology besides the one under discussion.
- Patients who received any iron supplementation during antenatal period.
- Patient with past medical history of thromboembolism, alcohol or drug abuse, hepatic, renal or cardiac impairment, acid peptic disease or malabsorption syndrome.
- Patients who didn't consent to inclusion in the study.

A total of 386 patients were chosen, from a population size of 2,517,560, which is approximate population of Sahiwal district. After calculation of sample size using WHO sample size calculator for medical research studies by taking level of confidence of 95% and tolerated margin of error within 5%. These patients were divided into Group A and Group B with 193 patients in each group, using probability systematic sampling technique, applied on the list formulated in the sequence patients were admitted to maternity ward. Preceding the signing of detailed informed consent, patients were made aware of treatment options, dosage schedule and possible complications of intravenous iron (II) sucrose complex and oral ferrous sulfate tablets. Treatment was initiated during first or second postpartum day.

Patients included in Group A were administered intravenous iron (II) sucrose complex (hereinafter referred to as IV iron) on 3rd and 5th day of inclusion in the study. Average cost of this treatment course is 600pkr in Pakistan (~$6), although it ranged from 400pkr to 800pkr depending upon calculated dose. Dose for IV iron was calculated by the formula, iron requirement (mg) = [(Target Hb – Actual Hb)x250]+1000 mg. IV iron was dispensed in the form of slow infusion given over more than 30 minutes in 100 mL of 0.9% sodium chloride solution in the indoor setting of the hospital along with measurement of vital signs of patients before, during and after infusion. Patients were counseled regarding reporting any symptoms or undesirable effects including metallic taste, itching, facial flushing or burning at the site of injection.

Patients included in Group B were asked to take 200 mg ferrous sulfate (hereinafter referred to as oral iron) with meals two times a day 10-14 hours apart for six complete weeks. This treatment costs approximately 300pkr in Pakistan (~$3) for full course. A particular date was conveyed to patients to stop taking the tablets. Patients were instructed to record any symptoms or adverse effects like gastrointestinal complaints, metallic taste et cetera and adherence to therapy was ensured by telephonic contact between follow-up visits. Blood samples were taken on days 0, 6, 14 and 45 for laboratory investigation of Hb, hematocrit (Hct), mean corpuscular volume (MCV), and serum ferritin (hereinafter referred to as ferritin). All the medicines given to patients along with required materials like infusion sets are being provided in all Pakistani secondary care and teaching hospitals free of cost to all patients.

Version 20 of the software Statistical Package for Social Sciences (SPSS) was used to calculate mean and standard deviation (SD) of Age, Hb, MCV, Hct, and ferritin while percentages along with frequency were used to analyze adverse events. Effects of supplemental iron therapy were analyzed by independent sample t-test on days 6, 14 and 45 for Hb, MCV, Hct, and ferritin. Comparison of adverse effects (metallic taste, disturbance in hemodynamics, burning at infusion site, nausea, constipation, diarrhea, and dyspepsia) was made using Chi-square test on

days 6, 14 and 45. P value below 0.05 was considered significant statistically.

3. RESULTS

Of 386 subjects included in this study, the majority was between 21 and 30 years of age, with Group-A having 128 (66.3%) and Group-B having 122 (63.2%) patients. Group of patients with age between 18 and 20 years was smallest with 25 (13%) patients in Group-A and 24 (12.4%) patients in Group-B while 31-44 year age group had 40 (20.7%) and 47 (24.3%) patients in Group-A and Group-B respectively. Calculation of arithmetic mean and SD for the age of patients yielded 23.67±0.99 for Group-A and 24.02±1.02 for Group-B.

Table 1 compares the values recorded in mean for investigations on Day 0 in both groups A and B.

Above parameters were then compared on Day 6 for both groups and figures stood at Hb 7.9 g/dL, MCV 78fL, Hct 34% and ferritin 36.5 ng/ml for Group-A while in Group-B mean values showed Hb 7.2 g/dL, MCV 68fL, Hct 28% and ferritin 12 ng/ml. Similarly, results of laboratory testing done on Day 14 revealed that patients in Group-A had mean values of Hb 11.2 g/dL, MCV 85fL, Hct 36% and ferritin 38 ng/ml while patients of Group-B showed Hb 8 g/dL, MCV 75fL, Hct 32% and ferritin 15 ng/ml. Comparison of iron studies after treatment on Day 45 is assembled in Table 2.

On the flip side of the coin, talking about adverse or undesirable effects of these drugs (Table 3), in Group-A the highest incidence was reported for burning at the site of intravenous infusion with 36 patients (18.65%) suffering from this followed by 14 patients (7.25%) who felt metallic taste and 7 patients (3.62%) who complained of nausea. On the contrary in Group-B, metallic taste was most commonly received complaint with 25 patients making up 12.95% of Group B. Less common complaints have been logged in Table 3 which shows that 136 patients (70.5%) in Group A and 120 patients (62.17%) in Group B did not have any of those complaints.

Table 1. Comparison of parameters in Groups A and B on Day 0

Investigations	Group A	Group B	P value
	Arithmetic mean	Arithmetic mean	
Hb	7.0±0.2	6.9±0.4	0.85
MCV	68	67	0.99
Hct	27	26.5	0.99
Ferritin	11.5	12	0.99

Table 2. Comparison of parameters in Groups A and B on Day 45

Investigations	Group A	Group B	P value
	Arithmetic mean	Arithmetic mean	
Hb	13.65±0.04	11.88±0.09	0.94
MCV	87	86	0.55
Hct	36.5	35.2	0.78
Ferritin	43.1	18	0.01

Table 3. Frequency and percentage of adverse effects in both groups

Adverse effects	Group A		Group B	
	No of Patients	Percentage	No of Patients	Percentage
Metallic Taste	14	7.25	25	12.95
Burning at Infusion site	36	18.65	0	0
Anaphylaxis	7	3.62	0	0
Diarrhea	0	0	8	4.14
Colicky Pain	0	0	9	4.66
Nausea	0	0	12	6.21
Dyspepsia	0	0	4	2.07
Constipation	0	0	15	7.7
No Complication	136	70.5	120	62.17
Total	193	100	193	100

Degree of Freedom = 8, Pearson's Chi-square value = 0.046

4. DISCUSSION

The primary objective of this study was to confirm if there is a significant difference in the hemoglobin concentration achieved as a result of two different therapeutic approaches towards the treatment of postpartum anemia where etiology is specifically iron deficiency. In this study, besides hemoglobin concentration, some other indicators were measured including MCV and Hct as indicators of reversal of IDA and serum ferritin as an indicator of iron reserves. Serum ferritin is observably decreased during pregnancy as a result of physiological changes including hemodilution but still, levels below 15ng/ml are indicative of iron deficiency anemia (IDA). (3) It is said that physiological changes that occur during postpartum lead to rising ferritin levels but that had little effect on the measurement during this study as ferritin levels increased only negligibly in Group-B as compared to Group-A.

Results of this study showed that intravenous iron sucrose complex was able to build hemoglobin levels successfully along with an increase in MCV as well as hematocrit. Furthermore, IV iron replenished body iron stores as well, which was exhibited by improved serum ferritin levels. Studies by Breymann [8], Armond-Ugon [9], Biggar [10], and Dewan [11] also reached similar conclusions in previous studies. Group-B patients were also able to reverse IDA during 6-weeks of therapy but iron stores did not see that much improvement which is evident from Ferritin levels. This difference can be attributed to variable absorption during oral therapy and direct delivery of iron to hematopoietic tissues as a result of intravenous therapy as revealed by a previous study done by Bhandal and Russel [12]. At day 6, 14 and 45 although statistical significance is seen between group A and B when comparing all the parameters, no such significance is seen in all the time frames when ferritin is excluded from the comparison. So for clinical purposes, the difference between the outcomes of two groups is not significant at day 6, 14 and 45. Grzywacz has described in a recent study that the decision of choosing between oral iron or IV iron should be made on patient to patient basis considering multiple factors [13].

The secondary objective of this study was to assess the safety profile of therapeutic options for the treatment of IDA in the postpartum woman. More than two-thirds of patients recruited in this study didn't complain of any adverse events. These results are in congruence with outcomes from larger studies which assesses the safety profile of intravenous iron sucrose complex both in pregnancy and during the postpartum period like the study done by Breymann and Krafft [14]. The safety profile of intravenous therapy can be explained on the basis of controlled release of elemental iron from iron (II) sucrose complex. Perewunsnyk et al. discovered in a study of 400 women that metallic taste and itch at the site of infusion are the only observable adverse effects and that too very rarely at low doses of iron [15]. Doses higher than optimal have an insignificant effect on indicators of iron and blood indices but more frequent side effects are reported in an attempt]t to achieve similar levels of hemoglobin. Same is the case of gastrointestinal side effects that are much more frequent at doses higher than optimal without much improvement in absorption as described in a study by Al-Momen [16].

5. CONCLUSION

IV iron is able to build up iron stores successfully and as compared to oral iron therapy there is markedly rapid (within the first week) reversal of anemia in women with postpartum IDA. IV iron though successfully replenishes iron stores and is a helpful measure in individuals who are not compliant with oral irons, for most clinical purposes oral iron and IV iron therapeutic options do not differ statistically, and the best decision needs to be made on a case to case basis using clinical judgment and prudence. Our study concluded that use of iron sucrose complex intravenously is associated with minimal adverse effects which are easily tolerable and therapy begets a good compliance. Then, iron sucrose is reachable at a small cost in developing countries and can be an answer to the dilemma of puerperal anemia with easy indoor management option.

CONSENT

All authors declare that written informed consent was obtained from the participants for publication of this study and its analyzed results along with drawn conclusions.

ETHICAL APPROVAL

Ethical approval was granted by Ethical Board of Research Committee, SMC, Sahiwal vide ethical clearance no. SMC/1079/2017 on August 07, 2017.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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