1 ***Original Research Article***

2 Oral versus Parenteral Iron Supplements:

3 Which is better?

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6 **ABSTRACT**

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Aims: To assess the safety and effectiveness of iron sucrose complex given intravenously versus ferrous sulphate taken orally in treatment of iron deficiency anemia in postpartum period.

Study design: Randomized Clinical Trial.

Place and Duration of Study: Sahiwal Medical College, Sahiwal (Pakistan) during 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. 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 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.

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 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 10g/dL (100g/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 8g/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 clearly 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 months of August and September 2017 based on following criteria:

2.1. Inclusion Criterion

- Patients with age 18-44 years, hemoglobin level below 9g/dL and serum ferritin below 15mcg/L during 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 for the purpose of this study 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 95%. 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. Dose for IV iron was calculated by the formula, iron requirement (mg) = [(Target Hb – Actual Hb)x250]+1000mg. IV iron was dispensed in the form of slow infusion given over more than 30 minutes in 100mL 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 200mg ferrous sulfate (hereinafter referred to as oral iron) with meals two times a day 10-14 hours apart for six complete weeks. 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).

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

TABLE I: 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

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

TABLE II: 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	0.03
MCV	87	86	0.08
Hct	36.5	35.2	0.049
Ferritin	43.1	18	0.01

On the flip side of the coin, talking about adverse or undesirable effects of these drugs (Table-III), 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-III below 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 III: 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. 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].

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 postpartum period like the study done by Breymann and Krafft [13]. 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. (14) 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 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 [15].

4. 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. 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.

COMPETING INTERESTS

This is collectively declared by all authors that no conflict of interest was involved in this research. And publisher has the right to assume and write this sentence: “Authors have declared that no competing interests exist.”

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. A copy of the written consent is available for review by the Editorial office/Chief Editor/Editorial Board members of this journal.

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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DEFINITIONS, ACRONYMS, 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