COMPARATIVE STUDY OF INTRAVENOUS IRON SUCRose VERSUS ORAL IRON THERAPY IN IRON DEFICIENCY ANEMIA DURING POSTPARTUM PERIOD

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Abstract

Background:- Nutritional anemia is one of major contributory factor in high maternal mortality and morbidity in third world countries. Iron deficiency is the principle cause for nutritional anemia. The aim of the study was to compare the efficacy of oral iron therapy with intravenous iron therapy in the treatment of iron deficiency anemia during postpartum period.

Material and Methods:- A clinical observational study was undertaken at tertiary care teaching hospital over a period of 15 months in one hundred recently delivered women. The baseline hemoglobin and serum ferritin levels were recorded prior to treatment. After completion of the treatment the women were followed up for changes in hemoglobin and serum ferritin levels on day 5, 14 and 40.

Results :- On day 5 of the intravenous iron group, there was statistically significant increase in serum ferritin level from 11.47 ±1.655 µg/l to 41.44 ±6.500 µg/l (p value <0.01), and the ferritin level remained elevated on day 14 and day 40. There was significant increase in mean Hb level from 7.76±0.7137 g/dl to 10.78±0.7679 g/dl on day 40 (p value < 0.01) in oral iron group. There was increase in mean Hb level from 7.47±0.7678 g/dl to 11.41±0.7908 g/dl on day 40 in injectable iron group, which was statistically significant. (p value < 0.01) Intravenous iron sucrose did not result in any serious adverse reactions.

Conclusion: - Intravenous iron sucrose administration increases the hemoglobin level and serum ferritin levels more rapidly, without any serious adverse effect in comparison with oral ferrous sulphate in women with iron deficiency anemia in the postnatal period.

Keywords: Iron deficiency anemia, Intravenous iron sucrose, serum ferritin, Maternal mortality

1. Introduction

Anemia is one of major contributing factor in maternal mortality and morbidity in third world countries and according to the WHO, contributes to 20% maternal deaths. Postpartum anemia is observed in up to 27% of women. Iron deficiency anemia is very much prevalent in the tropics particularly amongst women of child bearing age, especially in under privileged population. Nutrition of a woman in the family is always at bay because of various social and cultural practices and on top of it she always remains in the dark about her own health. High prevalence of iron deficiency is attributable to faulty dietetic habit, faulty absorption mechanism because of high prevalence of intestinal infestation and increased iron loss as consequence of repeated pregnancies at short intervals, excessive blood loss during menstruation, hookworm infestation and chronic malaria. Postpartum anemia is associated with longer hospital stays, depression, anxiety, and delayed infant development. At the present time, there is no consensus on the management of postpartum anemia, and clinical practice varies from one clinic to another. The standard approach to treatment in the majority of institutions is oral supplementation, with blood transfusion reserved for more severe or symptomatic cases. There are number of hazards of blood transfusion including transfusion of wrong blood, anaphylaxis and risk of transmission of infections, any of which would be devastating for the young mother. Oral iron is unreliable in treatment of severe anemia due to its limited absorption and gastrointestinal side
effects that affect compliance. Parenteral iron therapy by intramuscular injection of iron dextran is a painful alternative with a variable degree of efficacy. In practice the use of iron dextran is not generally recommended due to the unpredictable risk of life-threatening or serious acute reactions in 0.6 to 2.3% of patients and the availability of safer alternative drugs. Parenteral iron administration with ferrous sucrose is now available and can be used for treatment of iron deficiency anemia in postpartum period. Present study was a prospective randomized comparison between intravenous iron sucrose and oral iron in treatment of postpartum anemia. Specific objectives of the study were 1) To compare the efficacy of treatment with oral ferrous sulphate or intravenous ferrous sucrose on iron deficiency anemia during postpartum period. 2) To note the untoward reactions and complications of intravenous iron sucrose therapy.

2. Material and methods
The present study was a prospective randomized study conducted during February 2008 to April 2009.

2.1 Study design – Prospective randomized controlled trial, Concealed Randomized Allocation, Comparative, Single Center Study.

2.2 Study population:-
Postpartum women with iron deficiency anemia (IDA) consenting to participate in the study.

2.3 Study Setting:- Maternity ward of Pravara Rural Hospital, Loni, Maharashtra.

2.4 Study duration:- The study took place over a period of 15 months (1st February 2008 to 30th April 2009).

2.5 Inclusion criteria
a) Women aged 18 years or more with Hemoglobin of less than 10 g/dl but more than 6g/dl at 24 to 48 hours after delivery. b) Serum ferritin level less than 15µg/l.

2.6 Exclusion criteria:
a) Anemia not linked to iron deficiency b) Intolerance to iron derivatives, c) History of asthma, thromboembolism, seizures or drug abuse. d) Women with signs of infection or evidence of renal or hepatic dysfunction.

2.7 Methodology:
This was a hospital based, randomized, comparative, prospective, clinical study. The sample size of 100 subjects was selected from the postpartum women admitted in maternity ward after fulfilling the selection criteria. After careful history taking, clinical examination and minimal investigations other causes of anemia were ruled out. The initial iron status of the woman was assessed by the clinical and laboratory examinations (complete blood picture and serum ferritin levels). Women having Hb levels less than 10 gm/dl and serum ferritin level less than 15 ng/ml at 24-48 hours post delivery were included in the study. They were randomly divided into two groups. One study group [Group A] received two doses intravenous iron sucrose 200 mg on day 2 and day 4 following recruitment in study and the other group [Group B] received oral ferrous sulphate 200 mg twice daily for 6 weeks. Iron sucrose was administered as an infusion in 250ml of 0.9% sodium chloride over a period of more than 30 minutes. Patients were monitored for 30 minutes for signs of intolerance such as anaphylactic reactions, skin rash, dyspnoea, facial flushing, metallic taste, urticaria, hypotension, headache, chest pain, tachycardia, breathlessness etc. The treatment was stopped after the administration of total dose of 400 mg and received no further iron supplementation. The other group receiving oral treatment received two tablets of Ferrous sulphate 200 mg twice daily for 6 weeks. Adverse effects of oral treatment, if any were noted. The post therapy evaluation was done with the estimation of Haemoglobin and serum ferritin levels for both the treatment groups on day 5, day 14, and day 40.

2.8 Medications:-
1. Oral Ferrous sulphate 200 mg (60 mg elemental iron) was given twice daily.
2. Intravenous Iron Sucrose corresponding to 200 mg of Fe³⁺ diluted in 250 ml of 0.9% sodium chloride solution was given intravenously slowly over 30 minutes on day 2 and day 4 after recruitment in study.

2.9 Statistical analysis:- The statistical analysis was performed using Z test. Variations of P<0.05 were considered to be statistically significant.
3. Results

Table 1. Comparison between the two modalities of iron therapy in relation to improvement in Hb levels.

| days | Oral Iron | Injectable Iron |
|------|-----------|-----------------|
| Hb gm% | Day 0 | Day 5 | Day 14 | Day 40 | Day 0 | Day 5 | Day 14 | Day 40 |
| <7 | 02 | 01 | 00 | 00 | 12 | 00 | 00 | 00 |
| 7 – 8 | 36 | 30 | 02 | 00 | 30 | 00 | 00 | 00 |
| 8 – 9 | 07 | 11 | 30 | 00 | 06 | 06 | 00 | 00 |
| 9 – 10 | 05 | 08 | 10 | 00 | 02 | 20 | 05 | 00 |
| 10 – 11 | 00 | 00 | 08 | 28 | 00 | 16 | 16 | 10 |
| 11 – 12 | 00 | 00 | 00 | 14 | 00 | 08 | 20 | 25 |
| >= 12 | 00 | 00 | 00 | 08 | 00 | 00 | 09 | 15 |
| Total | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 |

Table 2. Comparison between two modalities of iron therapy in relation to improvement in serum ferritin level.

| Serum Ferritin (µg/l) | Oral Iron | Injectable Iron |
|-----------------------|-----------|-----------------|
|                      | Day 00 | Day 05 | Day 14 | Day 40 | Day 00 | Day 05 | Day 14 | Day 40 |
| <15| 50 | 50 | 43 | 17 | 50 | 00 | 00 | 00 |
| 15-50| 00 | 00 | 07 | 33 | 00 | 44 | 34 | 17 |
| >=50| 00 | 00 | 00 | 00 | 00 | 06 | 16 | 33 |
| Total | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 |

Table 3. Comparison of mean and standard deviation in hemoglobin level in both treatment modalities.

| Day of Hemoglobin estimation | Mean Hb in the oral iron group (g/L) | Standard Deviation | Mean Hb in the injectable iron group (g/L) | Standard Deviation |
|-------------------------------|--------------------------------------|--------------------|-------------------------------------------|--------------------|
| Hb on day 0                   | 7.76                                 | 0.7137             | 7.47                                      | 0.7678             |
| Hb on day 5                   | 7.84                                 | 0.6917             | 9.84                                      | 0.7603             |
| Hb on day 14                  | 8.69                                 | 0.7525             | 10.87                                     | 0.8221             |
| Hb on day 40                  | 10.78                                | 0.7679             | 11.41                                     | 0.7908             |

Table 4. Mean and standard deviation of serum ferritin in both treatment modalities.

| Day of Serum Ferritin estimation | Mean level in the oral iron group (µg/l) | Standard Deviation | Mean level in the injectable iron group (µg/l) | Standard Deviation |
|----------------------------------|------------------------------------------|--------------------|-----------------------------------------------|--------------------|
| Serum ferritin on day 0          | 11.35                                   | 1.559              | 11.47                                         | 1.655              |
| Serum ferritin on day 5          | 12.82                                   | 1.056              | 41.44                                         | 6.500              |
| Serum ferritin on day 14         | 14.31                                   | 1.564              | 47.69                                         | 6.990              |
| Serum ferritin on day 40         | 15.40                                   | 1.049              | 53.47                                         | 5.011              |

Table 5. Adverse reactions to intravenous iron sucrose and oral iron therapy.

| Adverse effects of oral iron | No. of women | Adverse effects of intravenous iron | No. of women |
|------------------------------|--------------|------------------------------------|--------------|
| Heart burn                   | 02           | Anaphylaxis                        | 00           |
| Constipation                 | 04           | Hypotension                        | 00           |
| Vomiting                     | 00           | Headache                           | 00           |
| Nausea                       | 03           | Urticaria                          | 00           |
| Diarrhoea                    | 01           | Nausea                             | 00           |
| Metallic taste               | 03           | Flushing                           | 03           |
| Epigastric pain              | 00           | Metallic taste                     | 05           |
| Total                        | 13           | Total                              | 08           |
4. Discussion:-
In the present study, the baseline mean Hb level in the oral iron therapy group was 7.76±0.7137 g/dl and in the injectable iron therapy group it was 7.47±0.7678 g/dl. Five days after starting the therapy, there was no significant change in the Hb level in oral iron group but there was significant rise in the mean Hb level in the injectable iron group. The mean Hb rise in the injectable iron group was from 7.47±0.7678 g/dl to 9.84±0.7603 g/dl (p value <0.01). After completion of iron therapy on day 40, it was observed that the rise in Hb levels in oral group was significant.( increase of Hb from 7.76±0.7137 g/dl to 10.78±0.7679 g/dl ,p value < 0.01) . In injectable iron therapy group, the mean rise of Hb was noted from 7.47±0.7678 g/dl on day 0 to 11.41±0.7908 g/dl on day 40, which was statistically significant. (p value < 0.01) (Table.1,2.) If we compare day 1 and day 40 in both the group, there was no significant difference between the treatment groups. While comparing the body iron stores replenishment with the iron treatment in both the groups, it was found that on day 40 the mean serum ferritin was increased in the oral group from 11.35 ±1.559 µg/l to 15.40 ±1.049 µg/l (p value <0.01) which was statistically significant. However the body iron stores did not reach to the necessary levels i.e. >50µg/l in any of the individual after 40 days of completion of oral iron therapy whereas in the injectable group, the serum ferritin level improved from 11.47±1.655 µg/l to 53.47±5.011 µg/l (p value <0.01). The mean level of serum ferritin level was more than 50 µg/l in intravenous group. (Table.3, 4)

Bhandal N and Russell R et al (2006) 5 had done a study to compare the effect of treatment with either oral ferrous sulphate or intravenous ferrous sucrone on postpartum iron deficiency anemia. The study was prospective randomized controlled trial. Forty four women with Hb of <9g/dl and ferritin of <15 microgram/l at 24-48 hours post delivery were included in the study. Women were randomized to receive either oral ferrous sulphate 200 mg twice daily for 6 weeks or intravenous ferrous sucrone 200 mg, two doses given on day 2 and day 4 following recruitment. By day 5, the Hb level in women treated with intravenous iron had risen from 7.3 ±0.9 g/dl to 9.9±0.7 g/dl, while there was no change in those treated with oral iron. Women treated with intravenous iron had significantly higher Hb levels on days 5 and 14 (p<0.01) than those treated with oral iron; although by day 40, there was no significant difference between the two groups. Throughout the study, ferritin levels rose rapidly in those treated with intravenous iron than in those treated with oral iron (p<0.01).

The present study had similar findings comparable to the above study. Giannoulis et al (2009) 11 compared the efficacy of oral and intravenous administration of iron supplements for treating postpartum anemia. One hundred and four anemic postpartum women were studied prospectively. The criteria for the diagnosis of anemia were Hb less than <8 g/dl and S.ferritin < 10µg/l. They were randomised into two groups. Group A consisted of 78 women who received i.v. a total amount of 300 mg iron sucrose in three days. Group B consisted of 26 women, who received orally 800 mg iron protein succinylate daily for four weeks. At the end of the study, in group A the increase of mean Hb level was 4.6 g/dl and of mean S.ferritin level was 105µg/l. In group B the increase in mean hemoglobin level was 2.3 g/dl and mean S.ferritin level was 68µg/l. There was significant difference in the increase of hemoglobin level (p= 0.0001) and also in the increase in S.ferritin level (p=0.0004) between the two groups. In present study rise in haemoglobin at the end of treatment i.e 4 weeks was comparable to this study. Rise in S.ferritin at the end of treatment was higher than present study. But the rise in Hb in oral group in above was less as compared to present study. In a 12-week randomised study comparing intravenous iron sucrose versus oral ferrous sulphate for treatment of postpartum anemia by Westad et al 12, after 4 weeks the mean hemoglobin values in both groups were similar (11.9 g/100ml vs. 12.3g/100ml, p=0.89). The mean serum ferritin value after 4 weeks was significantly higher in the intervention group with 13.7 micrograms/L vs. 4.2 micrograms/L in the control group (p<0.001). At 8 and 12 weeks the hematological parameters were similar. It was concluded that, women who received 600 mg intravenous iron sucrose followed by standard oral iron after four weeks, replenished their iron stores more rapidly. al-Momen et al (1996) 13 had done a study to evaluate the safety and efficacy of intravenous iron sucrose as compared with oral ferrous sulfate in the treatment of IDA during
pregnancy. They concluded that iron sucrose is safe and effective in the treatment of iron deficiency anemia during pregnancy. When the oral iron therapy becomes inadequate because of poor compliance, IV iron preparations are a therapeutic mainstay for severely iron-deficient individuals. (Hallak et al 1997) In practice, physician often face the problem of poor compliance, justified by digestive side effects leading to worsening of anemia. In these cases parenteral forms of iron administration are indicated. Bayoumeu et al (2002) in his study also suggested that the IV iron sucrose tolerance seemed to be excellent without adverse side effects and was in accordance with the literature. In 2005, the FDA approved iron sucrose for the treatment of iron deficiency anemia in predialysis in chronic kidney disease (CKD) patients with or without an erythropoietin. Data from one study found IV iron sucrose to be superior to oral iron therapy in the treatment of anemia of CKD (Charytan et al 2005). In the first trial, 96 adults in CKD patients with anemia (Hb < 10.5 g/dl, TSAT < 25%, and ferritin < 300 ng/ml) were randomized to ferrous sulfate 325 mg three times daily or iron sucrose 200 mg by IV injection once weekly for five weeks. Recombinant human erythropoietin (rHuEPO) was held constant in both groups. Significant mean increases in Hb values were noted in both treatments groups from baseline to day 43 (1.0 g/dl for IV iron and 0.7 g/dl for oral iron, p <.0001 for both groups). Significant increases in mean values of S.ferritin occurred in the IV iron group (288 ng/ml and 4.5%, respectively, p <.0001 for both values), but not in the oral iron group (5.1 ng/ml and 0.5%, respectively). Adverse events were similar between the two groups, although GI side effects were more common in the oral iron group. No serious adverse events or deaths were noted. (Table.5)Most recent clinical trial by Seid et al (2008) also found encouraging results with the use of IV iron therapy as compared to oral ferrous sulphate in anemic patients during postpartum period. Observers found that injectable iron treated subjects were significantly more likely to (1) achieve a Hb greater than 12 g/dl in a shorter time period with a sustained Hb greater than 12 g/dl at day 42, (2) achieve Hb rise 3 g/dl or greater more quickly and (3) attain higher serum transferrin saturation and S.ferritin levels. Drug-related adverse events occurred less frequently with injectable iron. It was concluded that IV iron therapy was safe and well tolerated with an efficacy superior to oral iron therapy in the treatment of iron deficiency anemia in postpartum period. Considering the risks of transmision of HIV and Hepatitis, one of the main strategies must be to use alternative method and therefore avoid the need for transfusion. If used appropriately, intravenous ferrous sucrose may help reduce the incidence of blood transfusion during the post natal period, with transfusion being reserved for women with hemodynamic instability.

Conclusion
Intravenous iron sucrose administration increases the hemoglobin level more rapidly than oral intake of ferrous sulphate in women with iron deficiency anemia in the postnatal period. Intravenous iron sucrose also replenishes iron stores more rapidly than oral iron. Intravenous iron sucrose can be used as safe and effective alternative to blood transfusion and oral iron therapy in the treatment of iron deficiency anemia in the postpartum period.

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