Intravenous Iron Sucrose *vs.* Blood Transfusion in the Management of Symptomatic Post Partum Iron Deficiency Anaemia

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ABSTRACT

Objective: To compare the efficacy and safety of intravenous iron with blood transfusion in post partum women with symptomatic iron deficiency anaemia.

Methods: Ninety women were included in the study. The inclusion criteria were: hemoglobin <9g/dl and/or haematocrit <28%, mean corpuscular volume <80fl, ferritin level <15ng/ml, and symptoms of anaemia within 48 hours of delivery. Women with postpartum haemorrhage and haemodynamic instability were excluded. Women were divided into two groups, group B received blood transfusion and group I received intravenous iron sucrose (400mg infusion in 250ml Normal Saline over half an hour) (Venofer, Vifor St Gallen's, Switzerland). The outcome measures were relief of symptoms of anaemia. Hemoglobin, haematocrit, mean corpuscular volume and ferritin levels were measured before and one week after the treatment.

Results: The two groups were comparable in terms of age, mode of delivery and symptoms. Group B had a mean age of 31.1 years (22-39) *vs.* 32.3 years (20-43). Twenty four women from group B had C/S *vs.* 23 women in group I. However, women in group B had a lower baseline mean hemoglobin (6.8 g/dl (4-8) *vs.* 7.7g/dl (6.1-9 g/dl) and lower haematocrit (23.2 %(18-26) *vs.* 25.3 %(18-28). At one week post treatment the mean rise in hemoglobin was 2.35 g/dl (34%) in group B *vs.* 2.15g/dl (27%) in group I. The mean rise in haematocrit was 7.0 % and 6.3% respectively. The mean rise in ferritin level was higher in group I (220%) *vs.* 150% in group B. Symptoms relief occurred in 29 cases in group B and in 28 cases in group I. No serious side effects occurred in either group.

Conclusion: Intravenous iron sucrose is an effective and safe treatment for postpartum iron deficiency anaemia. It is hoped that this treatment will reduce the need for blood transfusion.

Key words: Blood transfusion, Intravenous iron, Iron deficiency anaemia, Postpartum anaemia

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Introduction

Post partum anaemia complicates 10% of deliveries.[1] Milder forms of anaemia, defined as Haemoglobin (Hb) less than 10g/dl, still occurs in 30% of cases. Worldwide, iron deficiency is the most common cause of pathological anaemia in pregnancy.

The prevalence is 18% in the developed world, but reaches up to 56% in the developing world.[2] The negative iron balance in pregnancy is aggravated by blood loss around the time of delivery, especially after Caesarean section (C/S).[3]

Severe anaemia may cause cardiovascular strain

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and dyspnoea. More commonly it causes tiredness, headache and dizziness. This can be debilitating especially when caring for the newborn. Women may also have an increased risk of post partum depression.[4]

Blood transfusion in the postpartum period is not uncommon ranging from 2-10%.[5,6] It is more common after C/S than vaginal delivery.[7] The transfusion trigger is clinician dependant and varies between institutions. A significant proportion of transfusions are thought to be given inappropriately.[8] Blood transfusion may be necessary, but it is not without risk. Recipients may develop allogenic reactions, and more rarely, transfusion transmitted infections, as well as suffering immunological sequels such as red cell alloimmunisation. Additionally, there are the problems of incompatible transfusions, availability and rising costs. Unfortunately, information from randomised clinical trials to inform best practice is largely unavailable in the discipline of blood transfusion.[9] Therefore, blood transfusion should be given only when absolutely necessary.

Parenteral iron has been traditionally used in women intolerant to oral iron.[10] More recently, it has been shown to achieve a faster correction of haemoglobin levels and iron stores.[11,12] Previous preparations, namely iron dextran had a poor reputation of anaphylactoid reactions. However, iron sucrose has been safely administered in cases where previous intolerance to iron dextran has been encountered.[13] Iron sucrose has been used in a series of 500 patients with not a single reported anaphylactic reaction.[14]

In our study women with symptomatic post partum anaemia who would have had a blood transfusion, were given a trial of intravenous iron sucrose.

Methods

The study was a prospective controlled non-randomized study. Ninety women with symptomatic post partum anaemia were recruited from the postnatal ward within 48 hours of delivery. Patients were assigned to two groups. Group B received blood transfusion and group I received a total dose of 400mg of intravenous iron sucrose (Venofer Vifor St Gallen's, Switzerland). In our unit, Hb is checked at the time of presentation to labour ward. It is repeated 24 hours after C/S or if otherwise clinically indicated. Blood transfusion is rarely indicated in the stable patient when Hb is greater than 10g/dl and is almost always indicated when less than 6g/dl.[15] Therefore, our inclusion criteria were: Hb level between 6 and 9g/dl and or Haemotocrit (Hct) level between 20% and 28%, Mean corpuscular volume (MCV) < 80fl and ferritin level <15ug/l.

Symptoms and signs of anaemia included tiredness, dizziness and pallor. More severe symptoms, namely fainting and evidence of cardiovascular strain were excluded from the study as these patients should receive blood transfusion. However, all patients recruited into the study, would have received blood transfusion according to our local practice of managing post partum anaemia. Other exclusion criteria were haemodynamic instability, intolerance to iron therapy, asthma, hepatorenal disease, anaemia from causes other than iron deficiency and blood transfusion in the peripartum period.

The assigned treatment was started 24-48 hours after delivery on the post natal ward. Intravenous iron (Venofer) was given in two divided doses 200mg on day 1 and 200 mg on day 2 after delivery. Venofer was diluted in 250 ml of normal saline and given over half an hour. Pulse and Blood pressure were checked before, during and after each infusion. Facilities for cardiopulmonary resuscitation were available on the ward. In group B, blood transfusion was carried out on the post natal ward. Packed RBC's were used as women were haemodynamically stable. On average women received 2.3 units of blood (range 1-4). Each unit was given over two hours. Blood pressure, pulse and temperature were measured half hourly during the transfusion.

The primary outcome measures were: Hb level and relief of symptoms of anaemia one week after treatment. Secondary outcome measures included Haematocrit and ferritin levels one week after the treatment, and reported adverse events encountered during and after both treatments.

Complete blood counts were measured by Haematology analyzer (Sysmex K-1000, Japan). Ferritin level was measured by new fully Automated Assay (Immulite 2000, Siemens, Germany).

Statistical analysis was conducted using the two tail t-test for equality of variances. Statistical significance was confirmed when P was < 0.05.

Results

All women received the treatment they were assigned (n = 90). The two groups were similar in baseline clinical characteristics (Table I) and

Table I. Baseline clinical characteristics

Characteristics	Group B (n=45)	Group I (n=45)	P value
Age	31.2 (6.5)	30.72 (5.5)	0.624
Caesarean section	38(84%)	36(80%)	0.581
Hb (before treatment) (g/dl)	7.7 (0.85)	7.9 (0.76)	0.146
Haematocrit (%)	24.5 (1.85)	25.0 (1.77)	0.208
Ferritin (ng/ml)	7.1 (3.9)	7.4 (4.72)	0.673
MCV	71 (4.81)	69.3 (4.92)	0.233

Data are given as mean (SD)

Table II. Laboratory data 7 days after treatment

	Group B (n=45)	Group I (n=45)
Hb (g/dl)	10.05 (8.9-11.8)	10.1(8.8-11.5)
Haematocrit (%)	32.3(29-36)	31.8(29-35)
Ferritin (ng/ml)	17.6(2.4-28)	22.6(4.3-40)

Data are given as mean(range)

Table III. Laboratory parameters differences after treatment

	Group B	Group I	P value
Hb day7 - **Hb** baseline	2.35	2.15	<0.05
Hct day7-**Hct** baseline	7.0	6.3	< 0.05
Ferritin day7- **Ferritin** baseline	10.5	15.2	0.10

Hemoglobin(Hb) g/dl. Haematocrit (Hct) %. Ferritin ng/ml

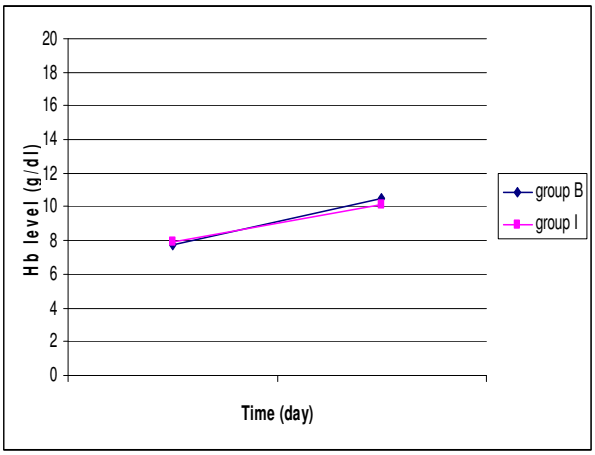

Fig. 1. Hb level before and one week after treatment

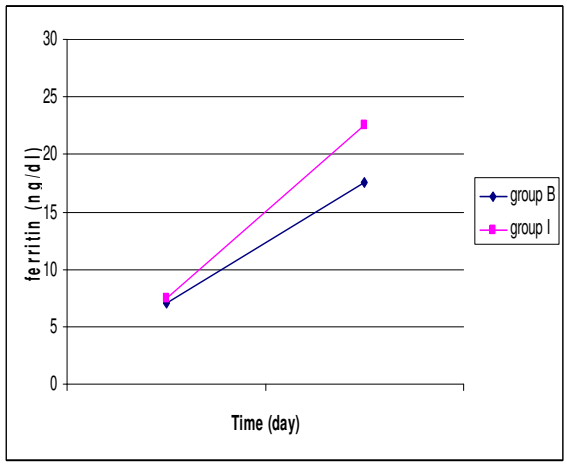

Fig. 2. Ferritin level before and one week after treatment

symptoms profile. Most cases (80%) of anaemia in both groups followed C/S. This is compatible with previous studies.[5,7]

Both treatments significantly increased Hb (2.35g/dl for group B *vs.* 2.15g/dl for group I) and Hct (7.0% *vs.* 6.3%) levels 7 days after treatment (see Table II and Fig. 1). This increase was higher in group B than group I. The difference was statistically significant regarding both parameters, (t=38.2 and 27.2 respectively, P < 0.05 for both). Patients in group I increased their ferritin level by 220% compared to 150% in group B (see Table III and Fig. 2). This difference was also statistically significant, but in favour of group I (t=18.6 (P < 0.05).

Symptoms relief occurred in 29 cases in group B and in 28 cases in group I. In those cases where symptoms persisted, a repeat course of treatment was performed.

No anaphylaxis or other serious side effects were encountered with Iron Sucrose. However, two patients reported facial flushing and three patients described a metallic taste. Neither of these necessitated stopping the infusion.

In the blood transfusion group, two cases developed pruritis, two cases developed pyrexia, one case of rash, and one case of jaundice secondary to haemolysis, that resolved after four days. Women, who developed mild symptoms, were treated and re-transfused. There were no severe side effects as to completely abandon the transfusion. One woman developed jaundice one day after completion of 4 units of blood transfusion. She was managed conservatively and jaundice gradually resolved.

Discussion

The study was performed to ascertain whether intravenous iron sucrose can be used in women with symptomatic iron deficiency anaemia, who otherwise would receive blood transfusion.

In an audit of three obstetric units (total of 13,000

deliveries per annum) prior to this study, we found the transfusion rate to be 15% following C/S and 4% following vaginal delivery. This mounts to 728 blood transfusions per year (6.2% of all deliveries).[6] Transfusion rate was estimated to be lower in other studies (0.3% to 1.7% for vaginal delivery and 0.7% to 6.8% for C/S).[16,7] The higher transfusion rate in our audit was due to the high incidence of pre-existing anaemia, but also possibly due to lower physician's threshold for initiating a transfusion**.** Anaemia in our population is more common due to grand multiparity, nutritional deficiency and poor compliance with antenatal oral iron supplementation. Indeed, a significant proportion (15%) of women, in our audit enter labour with Hb level<10g/dl and 5% of cases have Hb<8 g/dl.

Oral iron, parenteral iron and erythropoietin are all treatments that have been used in postpartum iron deficiency anaemia. The use of oral iron is limited by its side effects, poor compliance and the fact that it takes a long time to correct low Hb and iron stores, taking 40 days in one study, before a satisfactory maximum effect was reached.[11]

It is generally accepted that intravenous iron induces a similar or slightly more rapid erythropoietic response than oral iron. However, this statement applies to iron dextran, sorbitol and gluconate treatment but may not be generalized to iron sucrose.[17] The latter seems to be effective within few days of administration. This is due to its rapid removal from plasma and incorporation into the bone marrow for eryhtropoiesis. Therefore, when a rapid effect is required parenteral iron is indicated, and iron sucrose seems to be the most appropriate. Both iron dextran and iron gluconate cause unpredictable anaphylactic reactions and require test dose before administration. However, iron sucrose is reported to be safe and effective and can be administered without a test dose.[18,14]

Intravenous iron sucrose has also been compared to intramuscular iron sorbitol. Not only was it more effective, but also 20% of patients in the Sorbitol group dropped out of the study due to intolerance.[19]

Despite widespread use of iron sucrose in dialysis patients, its use is not common in obstetrics, as many physicians are not familiar or comfortable with the use of this medication.[18] However, the safety of iron sucrose, demonstrated in previous studies,[18,13] somewhat reduced the anxiety associated with other parenteral iron preparations, namely iron dextran and gluconate.

Intravenous iron has also been shown not to interfere with lactation, emphasizing previous reports of active biological mammary gland regulation of milk iron concentration.[20] Intravenous iron sucrose avoids the risks associated with blood transfusion and is more cost effective.[21] In our study, we have shown that intravenous iron sucrose can be used safely and effectively in acute postpartum anaemia.

Recombinant Human Erythropoietin (rhEPO) is mostly used in the treatment of anaemia of end stage renal disease. However, it has also been used both antenatally and postpartum in women.[22] In one study, it has been shown to safely enhance the efficacy of intravenous iron sucrose in gestational iron-deficiency anaemia.[23] However, in a randomized controlled trial of 60 patients, the addition of rhEPO to iron sucrose did not further increase Hb levels one and two weeks after treatment of postpartum iron deficiency anaemia. Additionally, rhEPO is much more expensive.[24]

We performed a Medline search on anaemia and pregnancy. Although intravenous iron was compared to oral iron in the management of antenatal[25,12] and postpartum[11] anaemia, no studies where cited comparing blood transfusion to intravenous iron in symptomatic iron deficiency anaemia. However, a retrospective study observed the influence of the availability of intravenous iron for post partum anaemia. It demonstrated a reduction in blood transfusion (15 *vs*. 5) after the introduction of Venofer. The inclusion criteria did not refer to symptoms of anaemia.[21] In another retrospective study, it was shown that blood transfusion would be avoided by the use of IV iron in women with Hb<8g/dl. The study was not controlled, and intravenous iron was reserved for asymptomatic patients.[26]

Since the introduction of intravenous iron in our units the number of blood transfusions has been reduced by half without many negative effects on maternal well being.

In general, once haemostasis and haemodynamic stability around delivery has been achieved, the residual anaemia may be treated by intravenous iron. Iron sucrose seems to be the preferred choice.

The significant rise in Hb level (around 2g) in one week after IV iron is more than expected for non pregnant patients. This could be explained by the fact that haemodilution, a particular feature of pregnancy resolves after delivery and causes a higher than expected Hb level.

With the limited number of patients and power of the study, the study demonstrated that intravenous iron is almost as effective as blood transfusion in our cohort of patients. The statistically significant finfings demonstrating a better rise in Hb at 7 days, may not be clinically significant considering the minimal difference between the two Hb values achieved (2.35 vs. 2.15) and the overlapping confidence intervals of Hb post delivery(Group B Hb 10.05 (8.9-11.8) g/dl and group I Hb 10.1 (8.8-11.5) g/dl).

Limitation of the Study

Our study extended to one week after the treatment. However, further studies should be performed to assess the influence of both blood transfusion and intravenous iron over a longer period of time.

Conclusion

Intravenous iron sucrose is an effective and safe treatment for postpartum iron deficiency anaemia. It is hoped that this treatment will reduce the need for blood transfusion.

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