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Original Research Article

Role of IV administered Iron sucrose with recombinant erythropoietin in the treatment of moderate and severe iron deficiency anemia in the third trimester of pregnancy

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ABSTRACT

Background: Iron deficiency Anemia in pregnancy is one of the most common and intractable nutritional problems in the world today. The objective of this study was to investigate the therapeutic efficacy and safety of rHuEPO combined with IV iron sucrose, in the treatment of pregnant women in third trimester with moderate and severe iron deficiency anemia and whether addition of erythropoietin will increase the rate of rise of Hb without compromising on the safety of the therapy.

Methods: 60 pregnant women in the third trimester, diagnosed as cases of moderate and severe iron deficiency anemia were enrolled in this study with 30 subjects in each of the 2 groups. Recombinant Erythropoietin 2000 IU s/c and Inj Iron sucrose 100 mg slow intravenously in 100 ml 0.9% NS over 1 hr on alternate days was administered to the case group and the control group was administered only iron sucrose slow IV in the same dose on alternate days till target Hb (11gm%) was reached. Efficacy measures were reticulocyte count, increase in Hb/week, time to target Hb level and need for continued therapy after 4 weeks.

Results: In the case group, the increases in Hb were greater after 1 week of treatment and this was found to be significant ($P < .01$), the median duration of therapy was shorter in the case group (22 versus 34 days), with more patients reaching the target hemoglobin level by 4 weeks as opposed to 7 weeks in the control group. Average rise in Hb/week was much more in the case group. The groups did not differ with respect to maternal and fetal safety parameters.

Conclusions: Iron sucrose plus rhEPO is an effective treatment for iron deficiency anemia in pregnancy probably because of a synergistic action, with rhEPO stimulating erythropoiesis and iron sucrose delivering iron for hemoglobin synthesis.

Keywords: Haemoglobin, Inj Iron sucrose, Iron deficiency anemia, Recombinant Erythropoietin, Reticulocyte count, Serum Ferritin, Third trimester pregnancy

INTRODUCTION

Iron deficiency Anemia in pregnancy is one of the most common and intractable nutritional problems in the world today. Oral supplementation due to its low cost and high

effectiveness has been the treatment of choice in Iron deficiency anemia (IDA).¹ However, alternate therapies become necessary due to the inability to tolerate side effects of oral iron, noncompliance, documented iron malabsorption and pregnancies near term.² Blood

transfusion, though has been widely used, comes with its own set of complications.^{3,4}

Parenteral administration of iron is the only effective therapy to supply enough iron for erythropoiesis. Singh et al reported a faster increase in hemoglobin, ferritin and iron stores by intravenous iron therapy.⁵ During the last decade, rHuEPO supplementation has also been used in the treatment of anemia in pregnancy and post partum.⁶

In cases of severe anemia of pregnancy, with the threat of mortality and morbidity looming large, safe and effective treatment is mandatory. This has been the motivation in genesis of this study, the objective of which is to investigate the therapeutic efficacy and safety of rHuEPO combined with IV iron sucrose, in the treatment of pregnant women in third trimester of pregnancy with moderate and severe iron deficiency anemia and whether addition of erythropoietin will increase the rate of rise of Hb without compromising on the safety of the therapy.

METHODS

A prospective case control study was conducted at a tertiary care centre over a period of 2 years i.e. from August 2009 to August 2011, after taking approval from the ethical committee of our hospital. A total of 60 pregnant women in the third trimester booked at our antenatal clinic, who were diagnosed as cases of moderate and severe iron deficiency anemia and who fulfilled our clinical criteria were enrolled in this study. There were 2 groups, case and control group with 30 subjects in each group. All patients had received oral iron supplements (80 mg iron sulfate daily) on a routine basis since the beginning of the second trimester, but developed anemia. Minimum duration of oral iron supplementation was 4 weeks, before intravenous therapy was commenced.

Inclusion criteria

- Age 18-45 years old
- Singleton pregnancy between 29 weeks to 36 weeks gestation
- Hb <8.1g/dL and >5.0 gm /dl
- MCV <80 fl
- MCH <27 pg
- MCHC <34 g/dl
- Normal Hb electrophoresis
- Peripheral blood smear suggestive of iron deficiency anemia
- With no co-morbidities, e.g. hypertension, gestational diabetes mellitus, heart disease, peptic ulcer etc.
- Giving consent and having signed the consent form for this study.

Exclusion criteria

- Hb >8 gm /dl and Hb <5 gm/dl

- C-reactive protein >3 mg/L
- Serum ferritin >15 mcg/L
- MCV >80 fl
- MCHC >34 gm/dl
- MCH >27 pg
- PBS: any other type of anemia other than microcytic hypochromic anemia
- History of allergy to iron containing medication
- History of any other allergic condition or asthma
- History of bleeding tendency
- History of blood transfusion within the last 120 days
- History of delivery before 36 weeks gestation in previous pregnancies.

The diagnosis of iron deficiency anemia was established by the measurement of the following hematological parameters: Hb, PCV, Serum ferritin, Total iron binding capacity (TIBC), Red blood cell indices (MCV, MCH, and MCHC), Peripheral blood smear (PBS), Hb electrophoresis and Reticulocyte count. Any other type of anemia other than iron deficiency was excluded. Blood samples were obtained at the initiation of the treatment and weekly thereafter. At the initiation of the treatment, Hb, PCV, MCV, MCH, MCHC, PBS for typing of anemia, reticulocyte count, serum ferritin, TIBC were sent. Creatinine and blood urea were measured before therapy and 4 to 6 weeks later to exclude nephropathy or possible renal impairment. Liver function tests were assessed. Serum ferritin and serum iron levels were determined at the beginning and after the completion of the therapeutic protocol.

Our therapeutic protocol included administration of Recombinant Erythropoietin 2000 IU s/c and Inj iron sucrose 100 mg slow intravenously in 100 ml 0.9 % NS over 1 hr on alternate days to the case group till the target Hb (11gm%) was reached. The control group was administered only iron sucrose slow IV in the same dose on alternate days till target Hb (11gm%) was reached.

Formulae used to calculate the iron requirement of the patient to fulfil the deficit as well as to replenish the iron stores was as follows⁷

Amount of iron deficit (mg)= [Body wt. (Kg)×Hb deficit×2.4]+1000

[Hb deficit = target Hb-initial Hb]

Drug administration

An 18 gauge cannula was inserted into a forearm vein, and its position was confirmed by flushing with 5 mL saline solution and aspirating blood. We used Inj iron sucrose (Feronia), 1 ampoule = 5 ml = 100 mg. 100 mg of iron sucrose was added in 100 ml of 0.9% NS and administered slowly over a period of 1 hr and the cannula was flushed again with 5 mL saline solution. Studies have shown that no test dose is required with iron sucrose.⁸

Therefore, no test dose was administered. However, patients were observed for 24 hours for the development of any reaction or drug allergy.

In the case group, Inj rhEPO 2000 IU was administered s/c in the upper arm on alternate days. Pulse rate and blood pressure were monitored 10 min before and after administration of injection. In the weekly follow up, Hb (weekly till target Hb was met) and reticulocyte count (only for first week) were sent. Hematological parameters were measured using hematology auto analyser, except the reticulocyte count which was performed by manual method with the help of supravital staining. Patients were hospitalized and treated until Hb concentration either exceeded 9 g/dl or reached at least 8 g/dl with obvious clinical improvement. Patients with Hb levels constantly <8 g/dl and patients with anemia related symptoms were given in patient care, whereas patients with Hb >8gm were treated on outpatient basis.

Efficacy measures were reticulocyte count, increase in Hb/wk, time to target Hb level (duration of therapy in days/weeks) and need for continued therapy after 4 weeks.

Statistical analysis

The data was summarized as frequencies or percentages for categorical variables and as means and standard deviations or medians for continuous variables,

depending on the distribution. The data was analyzed with the help of SPSS software, version 8.

RESULTS

The demographic variables (mean age and weight) in both the groups were well matched. The mean Hb, reticulocyte count and the mean ferritin level were comparable in both the groups (Table 1).

Table 1: Demographic characteristic of study population.

Demographic variables	Case group (30)	Control group (30)	Significant (P value)
Mean age (years)	27.16	27.36	0.821 (ns)
Mean Ht (metres)	1.61	1.62	0.569 (ns)
Mean Wt (kilograms)	65.03	66.2	0.475 (ns)
Mean Hb (gm%)	6.69	6.72	0.897 (ns)
Mean retic count (%)	1.22	1.39	0.284 (ns)
Mean MCV (Fl)	65.51	67.06	0.267 (ns)
Mean MCH (picogram)	19.05	20.42	0.095 (ns)
Mean MCHC (g/dl)	25.96	26.8	0.174 (ns)
Mean ferritin (ng/ml)	7.01	7.15	0.785 (ns)

Table 2: Mean and standard deviation of weekly rise in Hb.

Group Statistics						
Hb% at	Group	N	Mean	Std. deviation	t value	
Start	Case group	30	6.6967	0.6360	0.131	
	Control group	30	6.7200	0.7434		
1 Week	Case group	29	8.0621	0.8011	6.66*	
	Control group	30	6.7200	0.7434		
2 Weeks	Case group	29	9.3862	0.9368	8.388*	
	Control group	29	7.4724	0.7950		
3 Weeks	Case group	27	10.6815	0.6599	11.71*	
	Control group	29	8.3414	0.8300		
4 Weeks	Case group	16	11.5625	0.3879	13.42*	
	Control group	29	9.1690	0.8058		
5 Weeks	Case group	0 (a)				
	Control group	28	9.9750	0.7281		
6 Weeks	Case group	0 (a)				
	Control group	23	10.7696	0.7320		
7 Weeks	Case group	0 (a)				
	Control group	3	11.6667	0.4163		

t value could not be computed after 4 weeks because there is no comparison group left as all patients in the case group met their target Hb. *significant at 0.01.

The mean Hb at the start of the therapy in the case group was 6.69±0.63 and in the control group was 6.72±0.74.

After one week of therapy, the Hb in the case group rose to 8.06 (The rise was significant at 0.01) where as in the

control group no significant rise was seen in the first week. A consistent rise in Hb was noted in the case group in the weekly follow up and all 29 responders, (barring one subject who had a reaction) had correction of their anemia within the first 4 weeks of treatment (Table 2).

Table 3: Mean rise of Hb/week.

Group	N	Mean rise of Hb/week	Std. deviation	t-value
Case group	29	1.3931	0.3139	8.10*
Control group	29	0.8572	0.1682	

*significant at 0.01.

Table 4: Represents time to attain target Hb in both groups.

Group	N	Time to attain target Hb	Std deviation	t-value
Case group	29	21.7586	4.5250	9.25*
Control group	29	34.4138	5.8096	

*significant at 0.01.

However in the control group the initial rise in Hb was noticed only from the second week, after which the rise

was consistent and target Hb was met by the seventh week. After the fourth week, 29 women were still left in the control group to reach their target Hb. So, t value could not be compared after 4 weeks as there was no comparison group. In both the groups, 29/30 patients responded to the therapy (one patient in each group had a reaction) and none of the patients required blood transfusion. A much greater rise in the reticulocyte count was observed after the first week of therapy in the case group as compared to the control group (The rise was significant at 0.01).

In the case group, a mean rise of 1.3gm/dl in the Hb was noted per week, while in the control group the mean Hb increased only 0.85gm/dl per week. Rise in the case group was found to be significantly more ($p < 0.01$) as compared to the control group. In the case group, the improvement of Hb concentration was obvious as early as the first week of treatment. The corresponding increase in the control group was much less and became apparent only after the second week (Table 3).

In the case group, the target Hb of 11 gm % was met in 21.7 ± 4.5 days, however in the control group target Hb was met in 34.4 ± 5.8 days (Table 4). This difference was also found to be significant ($p < 0.01$).

Table 5: Represents the adverse effects in both groups.

Group	N	Infusion reactions	Preterm labour	Need for blood transfusion	Non responders
Case group	29	1	1	Nil	Nil
Control group	29	1	2	Nil	Nil

In our study, 29/30 enrolled women in each of the two groups responded sufficiently to the therapy. One woman in each of the two groups had a reaction to the therapy. So, treatment had to be stopped. However the rest 29 responders in each group had correction of their anemia with no major adverse effects. One patient in the case group and two in the control group went into preterm labour around 36 weeks, after the completion of therapy, however, without neonatal complications. The pregnancy outcome was good in all the other cases. There were no signs of any adverse effect on neonates possibly associated with the therapeutic protocol (Table 5).

Hence, both regimens were effective, but with adjuvant recombinant human erythropoietin, the increases in Hb were greater after 1 week of treatment and this treatment was found to be significant ($p < 0.01$), and the median duration of therapy was shorter (22 versus 34 days), with more patients reaching the target hemoglobin level by 4 weeks of treatment in the case group as opposed to 7 weeks in the control group and the average rise in Hb/week was much more in the case group versus the control group. The groups did not differ with respect to

maternal and fetal safety parameters. None of the women needed additional antepartum or postpartum blood transfusion.

DISCUSSION

This study was conducted to determine the safety and efficacy of IV administered iron sucrose with recombinant erythropoietin in the treatment of moderate or severe iron deficiency anemia in the third trimester of pregnancy. Recent literature suggests that EPO has been successfully used to treat non-renal obstetric anaemia, postpartum anemia, end stage renal disease, as well as anemia of pregnant women with chronic hematological disorders.⁹⁻¹⁷ Retrospective data suggests that combination of adjuvant EPO with parenteral iron sucrose is safe and effective in treatment of iron deficiency anemia in pregnancy.

In a randomized trial of 40 patients (20 case group, 20 control group) with Gestational anemia, Breyman et al, compared the efficacy and safety of intravenously administered iron sucrose with and without adjuvant

recombinant human erythropoietin for the treatment of resistant iron deficiency anemia during pregnancy.¹⁸ To the case group Inj iron sucrose and Inj EPO was administered whereas only Inj iron sucrose was administered to the control group. He found both regimens to be effective, but with adjuvant recombinant human erythropoietin the reticulocyte count and hematocrit levels rose faster. Also, more patients reached the target hemoglobin (11g/dl) by 4 weeks of treatment in the combination group than in the group treated only with intravenous iron sucrose.

In another study by Sifaki et al, the efficacy and safety of rHuEPO combined with iron sucrose was tested in 26 pregnant women with iron deficiency for a period of 4 weeks.¹⁹ Results of this study also favoured the use of rHuEPO with parenteral iron sucrose. This study further discusses issues related to the safety and efficacy of rHuEPO treatment during pregnancy, the attitudes of pregnant women toward treatment options, financial burden of therapy as well as side effect profile of rHuEPO and parenteral iron.

Our study also showed similar results with both groups showing good therapeutic response. However the case group showed remarkable enhancement of erythropoiesis as proved by the significant increase in Hb noticed from as early as the first week of therapy and target Hb (11gm%) was achieved in all the patients in case group by 4 weeks of therapy where as patients in the control group took around 7 weeks to reach the target Hb.

As parenterally administered iron sucrose is safe and effective, the combination of the two substances increases the efficacy of anemia therapy by stimulating erythropoiesis at the same time that it delivers enough iron for hemoglobin synthesis and iron stores. It is now generally accepted that r HhEPO should be combined with parenterally administered iron, especially when iron stores are empty before therapy.^{20,21}

Literature has shown that with the administration of high doses of EPO, secondary iron deficiency due to the stimulation of erythropoiesis may result, and this may mask the beneficial effects. Hence, supplementation with iron preparation is imperative.

In the study conducted by Breymann et al on 40 patients, mean Hb at the start of therapy was 9.0 ± 0.7 in group 1 and 9.2 ± 0.6 in group 2, mean duration of therapy was 18 days in case group and 25 days in control group. However in our study with 30 patients each in both groups, mean Hb at the start of therapy was 6.69 ± 0.63 in the case group and 6.72 ± 0.74 in the control group. Mean duration of therapy in the case group was 22 days and 34 days in the control group.

In the study conducted by Breymann et al, after 4 weeks of therapy only one patient in case group had not reached target Hb of 11gm/dl, whereas 5 patients had not done so

in the control group. In our study, all patients in the case group reached target Hb of 11gm/dl whereas none of the patients in the control group reached the target Hb (11 gm%) in 4 weeks. Time to target Hb was 7 weeks in the control group. In our study just after one wk of therapy, the Hb in the case group rose to 8.06 gms whereas in the control group no significant rise was seen in the first week.

In the case group in our study, a consistent rise in Hb was noted in the weekly follow up and all patients met target Hb in 4 weeks of treatment. However in the control group the initial rise in Hb was noticed only from the second week, after which the rise was consistent and target Hb was met by the seventh week.

In Breymann et al study, case group had higher reticulocyte counts than control group from day 4 of treatment. In our study too, a much greater rise in the reticulocyte count was observed after the first week of therapy in the case group as compared to the control group.

Average rise of 3.17g/dl in Hb concentration during the total period of therapy of 4 weeks was observed in the study by Sifakis et al, with 3g/dl increase within the first 2 weeks.¹⁹ In 5 women (19.2%) there was no significant increase in Hb levels, while in 2 women (7.6%) a further decline in Hb concentration was observed that necessitated a blood transfusion. In our study an average rise of 1.3gm/dl/week was observed in case group and 0.8gm/dl/week in control group. All women responded to the therapy, although the response was slower in the control group.

Despite severe anemia at diagnosis, all patients in the study conducted by Breymann et al, delivered at term with no small for gestational age infants and no blood transfusion requirements.¹⁸ However in our study, 1 case in the case group and 2 in the control group went into preterm labour. However all delivered healthy appropriate for gestational age babies and with no blood transfusion requirements. In the study conducted by Sifaki et al, low frequency of side effects (allergic reactions) and no severe side effects were observed.¹⁹ In our study 2 cases of mild allergic reaction were noted, one each in the case and control group.

The dose of EPO used in earlier studies was much higher than that used by us. We used 2000 IU per dose on alternate days till target Hb was reached. However, in the study conducted by Breymann et al, 18,300IU/kg body wt/dose was used biweekly till target Hb was met, which would roughly come to 18,000IU per dose for a 60kg lady, much higher than the dose used by us. Sifaki et al used 150IU/kg body wt/dose of rHuEPO three times a week, again much more than used by us. Also, with the availability of EPO at an affordable price, the cost of therapy has gone down drastically, thus alleviating the

cost factor which was a major deterrent for its widespread use in trials.

Future studies are needed to select patients who would most likely benefit from rhEPO. There is already evidence that patients with endogenous erythropoietin levels that are lower than proportional to the grade of anemia may benefit more. Cazzola et al have suggested that endogenous erythropoietin levels <100 U/L are disproportionately low for anemia and that such patients should therefore receive erythropoietin supplementation.²²

On the other hand, there are no reference values for anemia-related endogenous erythropoietin levels during pregnancy. The erythropoietin secretory response to anemia may differ between pregnant and non pregnant states, and erythropoietin levels are dependent on various obstetric conditions, as shown previously by Goldstein et al.²³

Breyman et al in his study showed no correlation between endogenous erythropoietin level and hematocrit. This finding agrees with previous observations by Beguin et al, and Fuchs et al, who suggested that erythropoietin secretion is blunted in pregnancy, possibly by inhibitory cytokines such as interleukin 1, interleukin 6, or interferon γ .^{24,25} Levels of these cytokines are elevated in pregnancy by activated immune mechanisms, and they inhibit erythropoietin secretion in vivo and in vitro.

In our study we did not study endogenous erythropoietin levels. So, the correlation between endogenous erythropoietin levels and hematocrit could not be studied. Use of rhEPO till now might have been limited to severe or complicated anemia or cases requiring rapid reconstitution of the red blood cell pool, such as women with placenta previa, Jehovah's Witnesses with anemia, or special subgroups such as those with thalassemia or sickle cell disease.^{11,26,27}

However in recent times rhEPO is being increasingly used as a second line therapy if iron alone fails to increase the hematocrit within a defined interval. Because blood transfusions are a last resort, alternative strategies such as rhEPO plus parenterally administered iron are of considerable interest.

Our study also showed that adjuvant rhEPO combined with an optimized dosage schedule shortens treatment considerably while avoiding the gastrointestinal side effects and associated poor compliance found in as many as 30% of patients receiving oral therapy.

CONCLUSION

To conclude, iron sucrose plus rhEPO is an effective treatment for iron deficiency anemia in pregnancy probably because of a synergistic action, with rhEPO stimulating erythropoiesis and iron sucrose most

effectively delivering iron for hemoglobin synthesis. Further, our findings of rapid restoration of normal Hb levels with rapid correction of anemia in all the patients in the case group as well as the absence of significant side effects suggest that this protocol, can be a solution especially when iron supplementation alone fails or in pregnancy near term, where due to time constraints; we have to resort to life saving measures like blood transfusion, which come with its own set of problems. However, further research and evaluation is required to establish its full place, potential and protocol.

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