Iron sucrose with or without recombinant erythropoietin for treatment of moderate and severe anemia in late third trimester

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Abstract

Aim: This trial was undertaken to evaluate the efficacy and safety of intravenous infusion of iron sucrose (ISC) with adjuvant recombinant human erythropoietin (rhEPO) versus ISC alone, in correction of moderate and severe iron deficiency anemia (IDA) during late third trimester.

Patients and methods: Forty two pregnant women with gestational age ≥ 32 weeks with IDA resistant to oral iron therapy alone were randomly assigned to intravenously ISC plus rhEPO or ISC alone 72-96 hour a part. Target hemoglobin value was 11 g/dl. Primary outcome were hematological respond to treatment by increase in hematocrit and reticulocyte count while the secondary outcomes were other hematological parameters, serum ferritin, patient's symptoms.

Result: Both regimens was safe and effective but in ISC + rhEPO group the reticulocyte count were higher from day 8 (P< 0.0001), rising in hematocrit were greater from day 8 and continued (P 0.01 – 0.0001) and at end of study (day 29) more women in ISC + rhEPO group reach the target hemoglobin of 11 g/dl than in ISC alone group (no = 20 vs no = 16). Both groups did not differ in respect the maternal and fetal safety outcomes parametes.

Conclusion: Intravenous ISC at 300 mg in 300ml NaCl 0.9% infused over 30 minutes is safe and effective, adding rhEPO subcutaneously at low dose 4000 u/ 72-96 safely synergistic the efficacy of ISC in correction of gestational IDA resistant to oral iron therapy.

Keywords: Gestational anemia, deficiency anemia recombinant human erythropoietin, iron sucrose.

Abbreviations:

ID : Iron deficiency
IDA : Iron deficiency anemia.
WHO : World health organization.
rhEpo: Recombinant human erythropoietin
ISC : Iron sucrose.
HB : Hemoglobin.
MCV : Mean corpuscular volume.
MCH : Mean corpuscular hemoglobin
MCHC: Mean corpuscular hemoglobin concentration.
CRP : C-reaction protein
CBC : Complete blood picture.

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Introduction

Iron deficiency (ID) is a leading risk factor for morbidity and mortality worldwide[1]. The world health organization (WHO) estimates a prevalence of iron deficiency anemia (IDA) as 25% in Europe, more than 40% worldwide, with proposed prevalence of ID being two fold higher[2,3].

Maternal effects of ID include increased morbidity and mortality resulting from pregnancy and childbirth in addition to fatigue, dysnea, irritability, poor concentration, low energy and low mood sate[4].

In severe cases, with attendant threat of increased maternal – fetal morbidity and mortality, safe and effective treatment is mandatory. Traditional treatment which based on either oral iron or blood transfusion or both, has had drowbacks. High dose oral iron efficacy was limited by the high incidence of side effects, thus noncompliance, while, allorgenic transfusion are remains a last resort because of patient choice and the risks of infection, immunologic impact and transfusion reactions[5,6].

Recently, alternative strategies, including parenteral administrated iron sucrose and recombinant human erythropoietin (rhEPO) were tried and found to be successful in treatment of postpartum anemia[5,7,8]. Also, found to be safe and effective in treating IDA during pregnancy as rhEPO does not cross the placenta[9,10,11,12,13].

The aim of the present study was to compare efficacy and safety of intravenous iron sucrose with or without rhEPO in treatment of moderate and severe IDA in late third trimester.

Patient and Methods

The present prospective randomized controlled trial was conducted at the department of obstetrics and gynecology of Benha University Hospital, Benha, Egypt between January 2016 and May 2016. Ethical approval was received from the Benha Faculty of Medicine, Ethics committee before beginning of the study. All women provided written informed consent before inclusion in the study. Treatment was started at ≥ 32 weeks gestational age and was continued for 4 weeks or until target hemoglobin (HB) level of 11 g/dl was reached. Women included in this study if gestational age ≥ 32 weeks, with IDA "after failed trial oral iron or noncompliance on oral iron or intolerance to oral iron", diagnosed by complete blood picture (CBC), as HB < 9.5 g/dl for moderate anemia, HB < 7 g/dl for severe anemia and serum ferritin < 30 µg/L[14]. Women with anemia from causes other than ID (e.g. vitamin B12 or folate deficiency), chronic infection, renal failure, history of previous blood transfusions, history of intravenous iron intolerance, history of hematological disease (e.g. thalassemia or sickle cell disease), history of seizures, rheumatoid polyarthritis evidence of hepatic or renal dysfunction, evidence of chronic viral infection (positive hepatitis B virus surface antigen, positive hepatitis C virus antibody), serum transaminase level of greater than 1.5 times the upper limit of normal or serum creatinine level of more than 2mg/dl all were excluded.

Sample size was calculated based on findings on study by **Breymann et al.**[13] where after 28 day follow up during pregnancy (after 21 week gestation), patient mean corpuscular volume (MCV) increased to (91.1 ± 4.3 FL) following treatment with ISC with rhEPO and increased to 84.8 ± 6.3 FL in women who received treatment of ISC without rhEPO. With study power of 95% and an alpha – error of 5%, it was calculated that 19 participants were necessary in each treatment arm. The decision was made to enroll 21 women in each group to account for a dropout rate of 10%.

Continuous variables were expressed as mean ± SD (range) unpaired student t test was use to compare mean between the two groups while paired student t test was use to compare mean between pretreatment parameter to that of after therapy. Statistically analysis was done by Medcalc easy – to – use statistical software for windows desktop (www.medcalc.org). Medcalc software bvba 2016.

Primary outcome were hematological respond to treatment measure by increase in hematocrit and reticulocyte count while secondary outcomes were other hematological parameters, ferrtin status, women's anemia related symptoms improvement.

Participants were recruited on consecutive and prospective basis from antenatal clinic. Forty two women were randomly assigned to two treatment groups of 21 patients each by means of closed envelopes method. Total iron deficit was calculated for each women using the Gauzoni formula[15].

Total iron deficity (mg) =

Patient weight (Kg) × (Target HB – actual HB) g/L × 0.24 + depot iron.

For women in this study, target HB was 11 g/dl (110 g/l) and depot iron was 500 mg.

After calculating the total iron deficit, women in group (A) (group of ISC + rhEPO) received ISC intravenously at 300 mg on 300 ml sterile NaCl

0.9% (3 Ample, Euronemia, each ample 100 mg iron sucrose on 5ml solvent "EUROPEAN EGYPTIAN, PHARMACEUTICAL INDUSTRIES, ALEXANDRIA – EGYPT) over 30 minutes and subcutaneous rhEPO 4000 U (Epoetin 4000 IU, South Egypt Drug industries CO. "SEDICO" 6 October city, Egypt), this was givin at day 1, 4, 8, 11, 15, 18 "Saturday and Tuesday every week". While women in group (B) (group of ISC without rhEPO), only intravenous ISC was given in the same fashion but without given subcutaneous rhEPO. Thus, the maximum dose of intravenous ISC does not excised 600 mg per week as recommended by manufacture but, the total single dose had been exceed that was recommended by manufacture which is 200 mg. This was decided to gain more patients compliance and that has been proven to be safe. Subcutaneous route for rhEPO was choiced to delay its clearance, so prolonged exposure to its enythropoiesis stimulation growth effect.

Blood sample were taken at baseline and at day 8, 15, 22, 24 (Saturday / week) (in ethyleneddiaminetetraacetic acid treated tubes) for CBC while serum ferritin and CR were measured only at baseline and day 29. All parameters were measured after sampling, hematologic parameters were measured by (Advia analyzer, Bayer diagnostics, lever Kusen, Germany). Ferritin was determined by immunochemical- imminsence (Elecsys systems, Roche AG, Switzerland) and CRP was evaluated by immunoprecipitation.

Results

Twenty of 42 women reported having used iron tablets since early second trimester and compliant, while remaining were noncompliant either they did not like oral tablets or oral tablets was resulting in gastrointestinal size effects hence uncompliance. Before treatment with intravenous ISC with or without rhEPO, IDA (ferritin < 30 Mg/l)(14) was confirmed in all women and all contraindication for intravenous ISC where excluded. The groups did not differ in baseline hematological characteristics, ferritin status or time of treatment initiation as shown in table (1).

Both groups showed an immediate reticulocyte response and continuous increase in hematocrit. Group A (ISC with rhEPO) had higher reticulocyte counts than group B (ISC without rhEPO) from day 8 of treatment and had greater increased in hematocrit from day 8 and continued up to day 29 as shown in table (2).

By day 22 of therapy in group A, only 5 women didn't reach the target HB of 11 gm/dl while in group B 11 women didn't reach the target HB of 11 gm/dl. At day 29 of therapy, only 1 women in group a had not reached the target HB level, whereas 6 patients in group B had not done so with HB values ranging from 9.6 - 10.5 g/dl.

Hypochronic red blood cell count remained elevated from before treatment until the end of treatment in both groups but it was significantly elevated in group A with rhEPO than in group B without rhEPO.

Mean corpuscular volume (MCV) increased in both groups but it was higher in group A with rhEPO than in group 2 without rhEPO from day 8 and continued to the end of therapy (day 29) as shown in table (2).

There were no serious reactions to intravenous iron sucrose at that dose 300 mg in 300 ml saline 0.9% over 30 minutes infusion duration. Also there were no major side effects related to given rhEPO subcutaneously. Also there were unnoticed effect on white blood counts and C reactive protein level in both groups throughout study period.

There were no hypotensive or hypertensive response during or after therapy. Also there were no thromboembolic complications, while platelet counts were increase in all patients during correction of anemia but remained in upper normal range in both groups. Mean maximal platelet counts (103 cells /L) were 271 ± 54 × 103 cells/L in group A and 230 ± 25 ×105 cell/L in group B.

Pretreatment maternal morbidities included frequent nausea (12/42), tiredness (11/42), premature contractions (7/42), postural hypotension (5/42), frequent headach (4/42), all of which improved in response to correction of anemia. Mean blood pressure increased from 72.5 ± 12.2 (55.5 – 94.5) mmHg at initiation of therapy to 78.5 ± 12.5 (60 – 102) mmHg at end of therapy (P = 0.19)*.

Mean gestational age at delivery was 39 ± 1.2 (37 – 41) weeks, mean birth weight was 3288 ± 408 (3120 – 3820). Twenty five women were deviled by elective cesarean section as there was previous ≥ 2 cesarean section. All women had normal antipartum hemoglobin (11.8 ± 1.2) (11.3 – 12.8) g/dl.

Baseline and end of study serum ferritin and c-reactive protein data are shown in table (1 & 2) and there was no statistically significant difference between both groups at treatment initiation and at end of therapy.

Table 1: Baseline characteristics of study participants.

Characteristics	ISC with rhEpo group (no = 21)	ISC without rhEPO group (no = 21)	Reference range*	P value
Age (y)	25.8 ± 3.4 (18 – 38)	27.4±4.6(19-39)		0.25
BMI (kg/m2)	28.3 ± 4.6 (24 – 33)	27.5 ± 3.9 (25-32)		0.52
Gestational age (wk)	34.6 ± 4.8 (32 – 38)	34.2±4.6 (32-38)		0.78
HB (g/dl)	8.2 ± 0.8 (6.2 – 8.9)	8.3±0.6 (6.8-8.8)	>10.5[(1)]	0.64
Hematocrit (%)	26.2 ± 2.3 (23.2 – 28.5)	25.8±2.2(22.8-28)	>32%	0.56
RC (%)	2.1 ± 1.4(0.3-7.0)	1.9±1.2(0.8-6.0)	0-1.5	0.62
HRBCSP(%)	15.5±13.6(1.0-45.1)	18.2±10.2(3.8-40.2)	<2.5	0.47
MCV (FL)	76.4 ± 8.2 (60.3 – 85.2)	75.9±9.2(61.3-86.5)	80-100	0.85
MCH (pg)	19.4 ± 3.7(15.8-24.8)	19.6±3.8(16.5-23.5)	27-32	0.80
MCHC (g/dl)	23.8 ± 2.8(20.5-28.3)	23.1±3.3(21.5-28.9)	31.5-34	0.46
SF (µg/L)	8.5 ± 4.2 (2.6 - 28)	8.3±4.3(3.6-27)	15-200	0.87
CRP (mg/L)	3.3 ± 2.1 (3 – 10)	3.8±2.3(3-10)	< 6	0.46

Abbreviation: ISC with rhEPO: Iron sucrose with recombinant human erythropoietin, **ISC without rhEPO**: Iron sucrose without recombinant human erythropoietin, **BMI**: Body mass index, **HB**: Hemoglobin, **HRBCSP**: Hyothromic red cell proportion(%), **RC**: Reticulocyte count, **MCV**: Mean corpuscular volume, **MCH**: Mean corpuscular hemoglobin, **MCHC** : Mean corpuscular hemoglobin concentration, **SF:** Serum ferritin, **CRP**: C-reactive protein concentration.
- Value were given as mean ± standard deviation (range).
P < 0.05 : Statistically sig nificant.
(1) : 2nd trimester value.

Table 2: Change in hematological parameters serum ferritin in response to treatment.

Parameter		IsG with rhEpo group (no = 21)	ISG without rhEpo group (no = 21)	Δ (95% CI)	P value
HB g/dl	- 8 day	9.4 ± 0.8	8.8± 0.6	-0.6 (-1.04 to -0.15)	0.008
	- 15 day	10.2 ± 0.6	9.5 ± 0.5	- 0.7 (-1.04 to -0.35)	0.0002
	- 22 day	11.2 ± 0.7	10.5± 0.6	-0.7 (-1.10 to – 0.21)	0.001
	- 29 day	11.8 ± 0.9	11.1 ± 0.7	- 0.6 (-1.07 to – 0.12)	0.015
Hematocrit %	- 8 day	29.2 ± 2.3	26.1± 4.8	-3.1 (-5.44 to -0.7)	0.01
	- 15 day	32.8± 2.1	27.8 ± 4.6	- 5 (-7.23 to -2.76)	0.0001
	- 22 day	33.8± 1.8	30.1 ± 4.2	- 3.7 (-5.71 to -1.60)	0.0006
	- 29 day	35.6± 1.8	31.1 ± 4.2	-4.5 (-6.51 to -451)	0.0001
RC %	- 8 day	12.8 ± 2.6	6.8 ± 4.2	-6 (-8.17 to – 3.82)	0.64
	- 15 day	6.8 ± 2.2	4.1 ± 3.8	- 2.7 (- 4.63 to – 0.76)	0.0043
	- 22 day	4.2 ± 2.1	3.9 ± 2.6	- 0.3 (- 1.77 to 1.17)	0.012
	- 29 day	3.8 ± 1.8	3.7 ± 2.1	- 0.1 (-1.49 to 1.29)	0.72
HRBCSP %	- 8 day	17.5 ±13.6	19.2 ± 10.2	1.7 (-5.79 to -9.19)	< 0.0001
	- 15 day	28.5 ± 9.6	18.3 ± 12.1	- 10.2 (-17.01 to -3.38)	0.0075
	- 22 day	27.1 ± 8.6	18.2 ± 13.1	- 8.9 (-15.81 to -1.98	0.68
	- 29 day	15.6 ± 8.7	16.6 ±9.6	- 1.00 (-4.71 to 6.71)	0.88

MCV (FL)	- 8 day - 15 day - 22 day - 29 day	82.8 ± 9.5 85.3 ± 6.5 90.4 ± 5.2 92.6 ± 3.8	76.2 ± 10.5 79.2 ± 8.8 82.6 ± 7.5 85.5 ± 6.3	-6.6 (-12.84 to – 0.35) -6.6 (-12.84 to -0.35) -7.8 (-11.82 to -3.77) - 7.1 (-10.34 to -3.85)	0.038 0.038 0.0003 0.0001
MCH (pg)	- 8 day - 15 day - 22 day - 29 day	23.6 ±2.8 26.8 ± 2.7 28.9 ± 2.2 30.9± 1.8	21.3 ± 4.2 23.8 ± 3.8 25.2 ± 3.2 27.1 ± 2.8	-7.8 (-11.82 to -3.77) -3.0 (-5.05 to -0.94) -3.7 (-5.4 to – 1.9) - 3.8 (- 5.26 to – 2.33)	0.0003 0.0053 0.0001 < 0.0001
MCHC (g/dl)	- 8 day - 15 day - 22 day - 29 day	25.8 ± 2.8 27.7 ± 2.6 29.8 ± 2.2 32.8± 1.8	23.1 ± 4.8 26.2 ± 4.2 27.3 ± 3.8 30.1 ± 3.6	-2.7 (-5.15 to 0.24) -2.5 (-4.67 to -0.32) - 2.7 (-4.63 to – 0.76) - 2.7 (-4.47 to – 0.92)	0.03 0.02 0.0075 0.0038
SF (µg/l)	- 29 day	165 ± 90	175± 80	10 (-43.1 to 63.1)	0.70
RP (mg /dl)	-29 day	4.5 ± 2.3 (3 –10)	4.8 ± 2.1 (3010)	3 (-1.07 to – 1.67)	0.66

Abbreviation: ISC with rhEPO: Iron sucrose with erythropoietin recombinant human, **ISC without rhEPO**: Iron sucrose without erythropoietin recombinant human, **HB**: Hemoglobin, **RC**: Reticulocyte count, **HRBCSP**: Hyothromic red cell proportion(%), **MCV**: Mean corpuscular volume, **MCH**: Mean corpuscular hemoglobin, **MCHC**: Mean corpuscular hemoglobin concentration, **SF**: Serum ferritin, **CRP**: C-reactive protein. **Δ (95% CI)** Mean difference and 95% confidence inter role.
- Value were given as mean ± standard deviation.
- **P < 0.05** : Statistically significant

Discussion

The current trail shows that iron sucrose intravenously plus rhEPO was more effective in treating moderate and severe IDA during late pregnancy in women whom are not responding to, or intolerant to, or incompliant with oral iron than was iron sucrose without rhEPO, as estimated by increase in reticulocyte count, hematocrit, hemoglobin, and other hematological parameters. Women who received rhEPO were reached the target hemoglobin level (11 g/dl) earlier, iron sucrose without rhEPO was also effective, so the clinical value of statistically differences between giving or holding rhEPO is the time that can be gained when rhEPO is added to iron sucrose.

Several recent trials evaluate the role of rhEPO in correction of non renal anemia during pregnancy[5, 8, 10, 11, 13] and there authors reported both safety and efficacy of rhEPO in treating non renal obstetric anemia.

As intravenous iron sucrose is effective and safe in treating IDA in pregnancy, the adding of rhEPO, increases the efficacy of anemia therapy by stimulating erythoporesis by erythropoiesis stimulation growth factor (rhEPO), at the sametime of supplying enough iron for hemoglobin synthesis and iron stores[13,16,17].

In this trial, despite the pretreatment exsist of functional iron deficiency the treatment with rhEPO doesn't worsen that, during the treatment period, this may be explained by the use of low dose rhEPO(4000 U). Which was given subcutaneously after 300 mg iron sucrose infusion.

Despite that this trial does not measure the serum erythropoietin, the patients in this study get benfities from giving rhEPO, this finding supported by observations of Beguin et al.(18) and Fuchs et al.(19), whom explained that blunted erythropoietin secretion during pregnancy may be due to inhibitory cytokines such as interleukin 1, interleukin 6, or interferon y. This cytokines are increased by activated immune system during pregnancy, and also authors found that cytokines decrease erythropoietin secretion both in vivo and in vitro(20). This trial doesn't measure inflammatory cytokine but evaluate the c - reactive protein and found to be in normal range.

The rhEPO was used by several investigators and found to be effective in severe and complicated cases of anemia, and cases requiring rapid building of red cell pool such as women with placenta previa, or / and placenta percenta(21), Jehovan's witnesses with anemia and special types of anemia such as thalassemia or sickle cell disease[12, 16, 22].

Breymann et al.[13] reported finding like that of this trial, but they used rhEPO intravenously and at high dose of 300 u/kg while giving iron sucrose at dose of 200mg without dilution (10ml solution) 72 – 96h. So, from this trial results, I could concluded that low dose rhEPO (4000 U) subcutaneously givin with ISC 300 mg infusion found to be effective in treating IDA like high rhEPO dose.

Several authors investigated oral iron versus intravenous iron sucrose as **Al Momen et al.**[23], in treating IDA during pregnancy. They found the treatment duration was prolonged as the mean duration was 14.6 week for oral iron against 6.9 week for intravenous iron sucrose. The data in this trial show that adding rhEPO to Intravenous iron at the schedule presented before shortens the treatment duration considerably and at the sametime avoiding gastrointestinal drawbacks of oral iron and also associated with more patients compliance as all our patients complete the planed treatment, this may due to lack of side effects with this schedule, while the compliance with oral iron found to be only 30%[23]. Also **Breymann et al.**[13] reported shortening in anemia treatment duration and improved patients compliance on intravenous ISC with or without rhEPO.

In this study mean number of iron sucrose ampoules was 13.5 ± 3.5 (9 – 18), while mean number of antental clinic visit for giving the treatment was 4.6 ± 1.2 (3 – 6) visit and the total rhEPO vials was 88 in this trial at mean of 4.1 ± 1.2 (3 – 6) vials. There is actual increase in the cost but, the cost of intravenous iron plus rhEPO will be low if blood and blood product was needed. Also the costs of viral infection secondary to infected blood transfusion as HIV, HBV, HCV cloud be eliminated with this policy.

In this trial despite severe anemia at treatment initiation, all women in this trial were delived at term with no intrauterine growth restriction and no need for blood transfusion.

Conclusion:

As shown in this trial, iron sucrose with rhEPO is effective treatment for iron deficiency anemia during pregnancy and iron sucrose at 300mg in 300 ml NaCl 0.9% over 30 minutes is safe and adding subcutaneous rhEPO at dose 4000 U is safe and synergestic the intravenous iron sucrose efficacy.

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