Parenteral iron sucrose as an alternative to packed cell transfusion in moderate to severe anaemia in pregnancy

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ABSTRACT

Introduction: Iron deficiency anaemia remains the most common medical disorder in pregnancy in the developing world, with the burden of disease impacting on both the mother and the new born. Packed cells\blood transfusions are associated with complications like both immune and non-immune mediated reactions and blood borne diseases. The safety of sucrose has been demonstrated in previous studies.

Material and Methods: A prospective, comparative study was conducted in the Department of Obstetrics and Gynaecology, Kakatiya Medical College, Warangal during August 2010 to August 2012. All antenatal women were screened for anaemia and those presenting with moderate to severe anaemia between gestational age of 16-34 weeks were included in the study. These women were randomly selected to study and control groups where for the study group Intravenous Iron Sucrose was given and for control group, packed cell transfusion was given. A detailed history, clinical examination, obstetric examination and investigations were done for these antenatal women and an informed consent was taken.

Results: On an average 80% were in the age group of 15-24 years in both groups. In iron sucrose group, mean Haemoglobin % at baseline 7.1±0.8g/dl, after 1 week 7.9±0.6, after 4 weeks 11±0.5g/dl and at delivery 11.7±0.6 g/dl. Where as in packed cell group, baseline Hb% was 7.0±0.8g/dl, after 1 week 10.2±0.5%g/dl, after 4 weeks 10.3±0.5 g/dl and at delivery 10.2±0.4% g/dl. The mean haematocrit values in iron sucrose group at baseline 20.9±2.5%, after 1 week 25.3±2.2% and 4 weeks 33.6±2.0%. And in packed cell group at baseline 20.8±2.3%, after 1 week 30.0±1.9% and after 4 weeks 30.2±2.0%. The mean ferritin values in Iron sucrose group at baseline and after 4 weeks are 8.9±1.7µg/L and 89.8±6.7µg/L respectively where as in packed cell group, at baseline 8.7±1.8µg/dl and at 4 weeks, 40.1±5.4µg/L. In both groups, with each intervention the improvement in Hb%, haematocrit and ferritin values were statistically significant.

Conclusion: Parental Iron Sucrose is a safe, non-toxic alternative to packed cell transfusion in the management of moderate to severe anaemia complicating pregnancy. Parental iron sucrose therapy has a sustained rise of haemoglobin and haematocrit which persists even after the time of delivery and should be an integral part of management for the patients of moderate to severe anaemia.

Key words: Parenteral Iron Sucrose, packed cell transfusion, anaemia, pregnancy

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INTRODUCTION

Anaemia is a condition of low circulating haemoglobin where the haemoglobin concentration has fallen below threshold, lying at 2 standard deviations below the median of a healthy population of same age, sex and gestational age.[1] As per the world health organization, the cut off values of haemoglobin to diagnose anaemia is as follows: mild anaemia 100-109 (g/l), moderate anaemia 70-99 (g/l) and values lower than 70(g/l) is considered as severe anaemia.[2] The Centre for Disease Control (CDC), defines anaemia as haemoglobin level <

11g/dl during first and third trimester and 10.5 g/dl during the second trimester, taking into account the physiological changes in pregnancy.[3]

According to National Academy of Sciences panel on nutrition and pregnancy, iron deficiency in pregnancy has been defined as ferritin levels lower than 12 ng/ml and it is considered the gold standard for the diagnosis of iron deficiency anaemia in pregnancy.[4]

The Indian Council of Medical Research has provided the classification of iron deficiency anaemia as follows: 8-11 g% as mild, 5-8 g % as moderate and <5 g% as severe anaemia.[5]

Iron deficiency anaemia (IDA) remains the most common medical disorder in pregnancy in the developing world, with the burden of disease impacting on both the mother and the new born (and subsequent child and later adult). And also the dimorphic anaemia due to iron and folic acid deficiency is common in developing countries. The prevalence of Fe-deficiency anaemia in pregnancy in the developing world is 56% (range 35 – 75 %), vs. 18% in the developed world.[6] Without adequate iron supplementation, ferritin falls to subnormal levels towards the end of pregnancy even in the industrialized nations.[7,8]

According to World Health Organization around 500,000 maternal death cases per year and 20,000,000 morbidity cases per year are related to iron deficiency anaemia.[9]

Nearly half of the global total number anaemic women live in the Indian sub-continent and in India alone the prevalence of anaemia during pregnancy may be as high as 88% according to ICMR.[10] The NFHS-2 (National Family Health Survey, 1998 - 1999) data using hemocue system reported prevalence of anaemia as 49.7 percent in pregnant women; 56.4 percent in breastfeeding non pregnant women; and 50.4 percent among non pregnant non breastfeeding women.[11]

Pregnancy causes a state of plethora. The RBC mass increases by 30%, whereas the plasma volume increases by 40-50%, resulting in erythrocyte dilution by 5-15% and decrease in haemoglobin concentration by approximately 2 g/dl. The picture on peripheral smear however remains normocytic and normochromic. This phenomenon is regarded as "physiological anaemia of pregnancy".[12] The requirements of iron are 4 mg/day (2.5 mg/day in early pregnancy, 5.5 mg/ day from 20- 32 weeks and 6-8 mg/day from 32 weeks onwards).[13]

Anaemia is estimated to contribute 20 % of all maternal deaths and 9 times higher risk of perinatal mortality.[14] Mild anaemia may not have much effect on pregnancy except for low iron stores. Moderate anaemia may cause increased weakness, fatigue and poor work performance. Women with severe anaemia may have palpitations, tachycardia, breathlessness, increased cardiac output leading into cardiac stress, which can cause decompensation and congestive cardiac failure which may be fatal.[13]

Increased incidence of pre-term labour (28.2%) and pre-eclampsia (31.2%)) have been associated with anaemia. Similarly anaemia and iron deficiency in pregnancy are associated with large placental weight and a high ratio of placental weight to birth weight (placental ratio),[15] both of which are predictors of adult hypertension.[16]

This study is necessitated because the majority of the primary and referral hospitals (tertiary hospitals) are using routinely packed cell\blood transfusions in cases of anaemia that are haemodynamically stable and they are associated with complications like both immune and non-immune mediated reactions and blood borne diseases. Therefore there is a need for an alternative modality of treating severe anaemia in pregnancy without much side effects.

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.[17] Therefore many of the physicians opt for blood transfusions in both moderate to severe anaemia even when the subject's general condition is stable leading to unnecessary exposure to blood transfusion reactions. The reported transfusion rate in obstetrics, varies from 0.16% to 2.6% with abnormal labours and deliveries.[18]

The safety of sucrose, demonstrated in previous studies, somewhat reduced the anxiety that was associated with other parental iron preparations, namely iron dextran and gluconate. This shows that there is still some need of an alternative modality to tackle this problem. Iron sucrose given parenterally fulfills the criteria and therefore there is a need for this study. The present study was undertaken with the objectives to study the efficacy of iron sucrose in moderate to severe anaemia in pregnancy and to compare the efficacy of iron sucrose with packed cell transfusion and evolve the protocol, based on the study and to establish whether iron sucrose could be an alternative to packed cell transfusion for the management of moderate to severe anaemia complicating pregnancy remote from term.

MATERIAL AND METHODS

Study design and Setting: A prospective, comparative study was conducted at Govt. Maternity Hospital, Hanamkonda in the Department of Obstetrics and Gynaecology, Kakatiya Medical College, Warangal during August 2010 to August 2012.

Subjects: All antenatal women were screened for anaemia and total 100 women who fulfilled

inclusion criteria were recruited in this study. Purposive sampling was used owing to the limited resources. The antenatal women presenting with moderate to severe anaemia i.e., Hb% <8g/dl, heamatocrit <25 and serum ferritin <12 µg/L between gestational age of 16-34 weeks were included in the study. All antenatal women below 16 weeks and more than 34 weeks of gestational age, women with very severe anaemia who were haemodynamically unstable, known allergy to parental iron and women with haemoglobinopathies were excluded from the study. These women were randomly selected to study and control groups where for the study group Intravenous Iron Sucrose was given and for control group, packed cell transfusion given. A semistuctured questionnaire was used to assess the socio-demographic characteristics. Detailed history, clinical examination, obstetric examination and investigations were done for the antenatal women and an informed consent was taken. In study group i.e., the iron sucrose group, haemoglobin deficit was calculated and total dose of iron sucrose required was calculated by the following formula and rounded up to the nearest multiple of 100 mg.

Total dose of iron required (mg) = weight (Kg) × (target Hb-actual Hb in g/dl) × 2.4 +500

In the formula, weight represented patient's weight before pregnancy, 2.4 represented the correction factor .The factor 2.4 is derived from blood volume i.e., 7% of body weight and iron content of Hb i.e., 0.34% so 0.24 = 0.07 × 0.0034 × 1000 (conversion from gram to mg). The additional 500 mg is given in order to restore the iron stores.

Mean requirement of iron sucrose for moderate anaemia was1100 mg and for severe anaemia it was 1300 mg.Mean requirement of packed cells for moderate anaemia was 3 units and for severe anaemia 4-5 units.

The total dose of iron sucrose was administered at a dose of 200 mg in 200 ml of 0.9% Normal Saline over a period of 40-50 minutes on alternate days. No test dose was required. Facilities for cardio-pulmonary resuscitation made available nearby. Monitoring during infusion was done at every 10 minutes and at the end of infusion. Any signs and symptoms of adverse reactions were looked for. All the ethical guidelines were followed while conducting the study.

In the same way in the control group the subjects were given packed cell transfusion on alternate day depending on the Hb deficit (calculated on the basis of improvement of Hb% by 1.3-1.5g/dl with transfusion of packed cells). Monitoring was done same as for iron sucrose infusion. Outcome: The outcome measured was haemogram done at 1 week, 4 weeks after the transfusion and at the time of delivery to look for improvement in Hb% and haematocrit. Serum ferritin levels were measured 4 weeks after the transfusion. And at the time of delivery, maternal haemoglobin, baby birth weight and NICU admissions were noted to know both maternal and fetal outcome.

Statistical analysis: The data recorded from the questionnaire was subjected to statistical analysis using the SPSS and NCSS 8 software. All significant tests were two- tailed with an alpha level of 0.05.

RESULTS

Table 1 describes the baseline characteristics of respondents across both the groups. The study group and the control group had 50 subjects each. On an average 80% were in the age group of 15-24 years in both groups. In Iron Sucrose group, 54% were primi-gravida and 46% were multi-gravida whereas in packed cells group 60% were primi and 40% were multi-gravida.

In Iron sucrose group, 56% were between gestational age of 28-34 weeks and 44% between 16-27 wks and in packed cells group, 68% were between gestational age of 28-34 wks and 32% between 16-27 wks.In both groups, on an average 85% were with moderate anaemia (6-8g/dl) and 15% were with severe anaemia.(<6g/dl)

Table 1: Baseline characteristics of respondents

Variable		Iron Sucrose		Packed cell	
		Number	Percentages	Number	Percentages
Age in years	15-24	40	80	41	82
	More than 25	10	20	9	18
Gravida	Primi gravida	27	54	30	60
	Multi gravida	23	46	20	40
Gestational age (weeks)	16-27	22	44	16	32
	28-34	28	56	34	68
Severity of anaemia (Hb%)	Moderate	43	86	42	84
	Severe	7	14	8	16
Total		50	100	50	100

Haemoglobin values in both the groups before and after intervention are depicted in table 2. In iron sucrose group, mean Haemoglobin % at baseline 7.1±0.8g/dl, after 1 week 7.9±0.6, after 4 weeks 11±0.5g/dl and at delivery 11.7±0.6 g/dl. By paired T test (two tailed), the p values were significant with respect to baseline Hb% values.

In packed cell group, mean Haemoglobin % at baseline 7.0±0.8g/dl, after 1 week 10.2±0.5%g/dl, after 4 weeks 10.3±0.5 g/dl and at delivery 10.2±0.4% g/dl. By paired T test the p values were significant with respect to baseline Hb% values. *P* value was significant at 1 week showing immediate rise in Hb% with packed cells.

The mean rise of Hb % at 1 week in iron sucrose group is 0.8±0.2g/dl and in packed cell group, it is 3.2±0.6%g/dl. By Kolmogirov smirnov test , p-value is < 0.001 which is statistically significant in favour of packed cell transfusion.

The mean rise of Hb% from 1 week to 4 weeks in Iron Sucrose group is 3±0.5g/dl where as in packed cell group it is 0.3±0.3.By equal variance T test p value is <0.001, which is statistically significant in favour of Iron sucrose.

The mean rise of Hb% by delivery from baseline is 4.6±0.6g/dl and 3.2±0.7g/dl in iron sucrose and packed cell groups respectively. By equal variance T test, p value < 0.001, which is statistically significant.

Table 2: Haemoglobin values in both the groups before and after intervention

Groups	Variables	Mean Hb(g/dl)	SD	CI (95%)	P
Iron sucrose group	Baseline Hb%	7.1	0.8	6.9 - 7.3	--
	After 1 week	7.9	0.6	7.7 -8.1	0.01
	After 4 weeks	11	0.5	10.8 -11.1	0.001
	At delivery	11.7	0.6	11.5 – 11.9	0.001
Packed cell group	Baseline Hb%	7	0.8	6.7 - 7.2	---
	After 1 week	10.2	0.5	10.1 – 10.4	0.0001
	After 4 weeks	10.3	0.5	10.2 – 10.5	0.001
	At delivery	10.2	0.4	10.0 – 10.3	0.001

Haematocrit values in both the groups before and after intervention are shown in table 3. The mean haematocrit values in iron sucrose group at baseline 20.9±2.5%, after 1 week 25.3±2.2% and 4 weeks 33.6±2.0%. By paired T test (two tailed) , the p values were significant with respect to baseline haematocrit values.

The mean haematocrit values in packed cell group at baseline 20.8±2.3%, after 1 week 30.0±1.9% and after 4 weeks 30.2±2.0%. By paired T test (two tailed), the p values were significant with respect to baseline haematocrit values.

Mean rise of haematocrit from baseline to 1 wk in iron sucrose and packed cell groups were 4.4±1.3% and 9.1±2.0% respectively. By Mann-Whitney U test p value=0.0001. It is statistically significant in favour of packed cell transfusion.

Mean rise of haematocrit from baseline to 4 weeks in iron sucrose and packed cell groups were 12.7±2.1% and 9.3±2.3% respectively. By equal variance T test p value=0.001. It is statistically significant.

Table 3: Haematocrit values in both the groups before and after intervention

Groups	Variables	Mean Haematocrit	SD	CI (95%)	P
Iron sucrose group	Baseline Hb%	20.9	2.5	20.1-21.6	--
	After 1 week	25.3	2.2	24.7-25.9	0.01
	After 4 weeks	33.6	2.0	32.9-34.2	0.001
Packed cell group	Baseline Hb%	20.8	2.3	20.1-21.5	---
	After 1 week	30	1.9	29.3 – 30.5	0.0001
	After 4 weeks	30.2	2.0	29.5 – 41.7	0.001

Table 4 describes the Ferritin values in both the groups before and after intervention. The mean ferritin values in Iron sucrose group at baseline and after 4 weeks are 8.9±1.7µg/L and 89.8±6.7µg/L respectively where as in packed cell group, at baseline 8.7±1.8µg/dl and at 4 weeks, 40.1±5.4µg/L. In both groups, with each intervention the improvement in ferritin values were statistically significant by paired t test.

The mean rise in ferritin values from baseline to 4 weeks in both groups is 80.9±6.7µg/L and 31.4±4.9µg/L respectively in iron sucrose and packed cell group. By Mann-Whitney U test, p value <0.0001 which is statistically significant.

Table 4: Ferritin values in both the groups before and after intervention

Groups	Variables	Mean Ferritin	SD	CI (95%)	P
Iron sucrose group	Baseline	8.9	1.7	8.4-9.4	--
	After 4 weeks	89.8	6.7	87.9-91.7	0.001
Packed cell group	Baseline Hb%	8.7	1.8	8.3-9.3	---
	After 4 weeks	40.1	5.4	38.6 – 41.7	0.001

Table 5 reveals the birth weight of the baby and NICU Admission. The mean baby birth weight at delivery in iron sucrose and packed cell groups are 3.1±0.4kg and 2.6±0.2kg respectively. By Kolmogorov-smirnov test p value=0.0001 which is statistically significant.

There were 2 cases in iron sucrose group and 9 cases in packed cell group, admitted in NICU. However this association was statistically not significant (Fisher´s exact test, p = 0. 051).

Table 5: Birth weight of baby and NICU Admission

Variables	Iron sucrose group	Packed cell group	P
Birth weight ±SD (in Kg)	3.1 ± 0.4	2.6 ± 0.2	0.0001
NICU Admission	2	9	0.051

In the context of the adverse effects, in Iron Sucrose group there were 3 cases with pain at canula site, 1 case with arthralgia, 2 cases –vomitings,1 case-hypotension and 1 with abdominal cramps. None of the subjects discontinued the transfusion.

The adverse effects in packed cell group noted were febrile reaction-6 cases, dyspnoea-2 cases, urticaria-4 cases, vomiting-2 cases, hypotension-5 cases and jaundice 1 case. 3 subjects discontinued the transfusion.

DISCUSSION

We had a total number of 50 subjects in each Iron Sucrose group and packed cell group. More than 80% of the subjects were in the age group of 15-24 years in both the groups. Primi and multigravidas were in the average of 55% and 45% respectively. In the Iron Sucrose group and packed cells group the average percentage of subjects in the gestational age of 28-34 weeks were 56% and 68% respectively. In our study on an average 82% of subjects in both groups presented with moderate anaemia i.e., 6-8 gm/dl and on an average 15% of both the groups presented with haemoglobin less than 6 gm/dl i.e., severe anaemia.

In our study the mean base line value of haemoglobin % in the Iron Sucrose group in moderate anaemia was 7.4%g/dl which increased to 8.1% g/dl after 1 week, 11 g/dl after 4 weeks and 11.8g/dl at delivery. In the severe anaemia group i.e., with Hb% less than 6 g/dl, the mean baseline values of Hb% was 5.5g/dl which increased to 6.7g/dl after 1 week, 10.1 g/dl after 4 weeks and 10.9g/dl at delivery. From these figures it is very obvious that Iron Sucrose gives a steady increase in the Hb% which is more perceptible after 4 weeks and up to the delivery. Also this is an objective measurement which can be quantified to measure the efficacy of the drug.

The study done at Zurish Obstetrics Clinic in the year 2005 demonstrated a significant rise of Hb% from the mean baseline haemoglobin of 9.1g/dl to 11g/dl by the end of day 25. This study demonstrated high efficacy and safety of parenteral iron in subjects < 9 gm/dl which is in conformity with our study.[19]

Also Al-Momen et al, in the study demonstrated an average rise of Hb% of 7.5gm/dl to 12.8 gm/dl in an average period of 6.9 weeks.[20] And another study done by Gravier et al, showed a Hb rise of 3.8 gm/dl after 14 days, thus showing improvement of Hb% with Iron Sucrose in 2 weeks.[21]

In comparison to packed cells group i.e., control group, the rise in Hb% is observed immediately after one week i.e., 3.2 gm/dl but beyond that there is no demonstrative increase in Hb% rise at 4 weeks and at delivery , after giving packed cell transfusion. The Hb% levels show a plateau after 1 week. This is in contrast to Iron Sucrose which shows a steady rise up to 4 weeks and till delivery. We conclude from these findings that Iron Sucrose gives a steady Hb rise which is maintained up to delivery in contrast to packed cells which shows immediate improvement but shows a plateau after that. This is clinically and statistically significant.

The haematocrit values were also taken into consideration in our study. Haematocrit reflects the actual number of circulating R.B.C in the body. Therefore it is more accurate than Hb. A significant rise in mean values of haematocrit from baseline to 1 week in Iron Sucrose and packed cell group were observed in the present study. These values show that the haematocrit values increased by 1 week but further showed a plateau up to delivery in packed cells group. In our study these values prove that the efficacy of Iron Sucrose in having a sustained rise of haematocrit which is maintained up to delivery. These figures are again an objective evidence of the superiority of Iron Sucrose in comparision to packed cells.

Serum ferritin levels were used because they represent the iron stores in the reticulo-endothelial system and also rule out haemoglobinopathies like thalassemia. Improvement of iron stores which is reflected in normal serum ferritin levels is an object to secondary outcome measure. Our study shows that serum ferritin levels almost doubled with Iron Sucrose treatment in contrast to packed cell transfusion. The study done by Khamaiseh et al, which compared the efficacy and safety of IV Iron Sucrose with blood transfusion in postpartum anaemia concluded that IV Iron Sucrose is safe and effective treatment option for postpartum anaemia, which reduces the need for blood transfusion. In this study ,both treatments increased Hb% and haematocrit after 1 week of intervention but more in favour of blood which was due to immediate restoration of RBCs but the increase in S. Ferritin levels were statistically significant in favour of iron group (220% rise) as compared to blood (150%).[22]

In study done by Ragip et al, the serum ferritin values were higher in patients receiving IV iron sucrose throughout the pregnancy.[23] In a study done by Al-momen showed that the serum ferritin levels had increased to 95.5±38.1µg/L from a baseline value of 11.9±5µg/L in a period of 7 weeks with p value less than 0.001 which is statistically significant.[20]

Our study incorporated the fetal outcome viz. baby weight and NICU admissions. There were 2 NICU admissions in Iron Sucrose group and 9 in packed cells group, however this difference was statistically not significant. There may be an improvement in neonatal outcome due to replenishment of maternal iron stores which indirectly improved the nutrition of the fetus. It has also been proved in recent studies that cognitive ability and other neurological functions are affected in iron and folic acid deficiency anaemia especially in the first trimester of the pregnancy. The reason for increased NICU admissions in the control group may be related to neurological deficit caused by lack of storage iron.

Cost wise the economical burden on the subject is equal in modalities of management but iron sucrose has a less toxic profile compared to packed cells and the measurable maternal and neonatal outcome are much superior in terms of objectives measurements viz., clinically and statistically significant. Parenteral Iron Sucrose stands out as an effective alternative to packed cells in the management of moderate to severe anaemia complicating pregnancy which are remote from term gestation.

CONCLUSION

Parenteral Iron Sucrose is a safe, non-toxic alternative to packed cell transfusion in the management of moderate to severe anaemia complicating pregnancy. It is not associated with any major side-effects. Parenteral iron sucrose therapy has a sustained rise of haemoglobin and haematocrit which persists even after the time of delivery as compared to packed cell transfusion. Parenteral Iron Sucrose also improves the storage iron which is depicted by improvement of serum ferritin levels over a period of 4 weeks that in turn improves the fetal and maternal outcomes as compared to packed cell transfusion. Parenteral Iron Sucrose therapy should form an integral part of management for the patients of moderate to severe anaemia remote from term gestation in all hospitals (primary or referral). Depending on the objectively measured outcomes, we can conclude that Parenteral Iron Sucrose is a safe and superior alternative to packed cell transfusion.

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