



## Comparison of Effect of Oral Iron Ascorbate Therapy versus Intravenous Iron Sucrose Therapy on Maternal and Fetal Outcomes in Anaemic Pregnant Women: A RCT

Authors

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### Introduction

Anaemia is defined as a condition in which the number of red blood cells or their oxygen-carrying capacity is insufficient to meet the physiologic needs, which vary by age, sex, altitude, smoking, and pregnancy status<sup>1</sup>. According to WHO, the overall mean global figure for the incidence of gestational anemia is 25%, an average 56% in the developing world and 18% in industrialized countries. In developing countries the prevalence of anemia among pregnant women averages 56%, ranging between 35 to 100% across different regions of the world. Various studies from different regions of the country (India) have reported the prevalence of anaemia to be between 33 and 100%.<sup>2</sup>

Iron deficiency anemia is the most common form of anemia the world over and also the most common nutritional disorder in the world.<sup>3</sup>

The single most important cause for the widespread iron deficiency anemia in our country is inadequate iron intake in the diet combined with the poor bioavailability of dietary iron.<sup>4</sup>

In India, anemia is the second most common cause of maternal deaths, accounting for 20% of total maternal deaths. Anaemia affects mainly the

women in child bearing age group, young and adolescent girls.<sup>5</sup>

However, adverse maternal and fetal outcomes due to anaemia in pregnancy can be controlled and monitored by good antenatal care and appropriate action, including referral in accordance to the level of severity of the anaemia.<sup>6</sup>

### Review of Literature

In a study by Abhilashini et al 100 women with gestational age between 30 and 34 weeks with established iron deficiency anaemia with Haemoglobin-6-8g/dL were randomised to receive either oral ferrous sulphate 200 mg thrice daily or required dose of intravenous iron sucrose 200 mg in 200 ml NS on alternate days. Haemoglobin, haematocrit, mean corpuscular volume, reticulocyte count were measured at recruitment and on 2nd week, 4th week and at 37 weeks. They concluded that Intravenous iron sucrose treated iron deficiency anaemia of pregnancy faster and more effectively than oral iron therapy and with no serious adverse drug reactions like gastrointestinal side effects which are a major problem with oral iron.<sup>7</sup>

Shafi et al conducted a randomized experimental study at K. J. Somaiya Hospital involving 200

pregnant women with iron deficiency anemia. In the intravenous group iron dose was calculated from: Total iron dose required (mg) =  $2.4 \times \text{weight in kg} \times \text{target hemoglobin} - \text{actual hemoglobin}$  g/dl + 500. Target hemoglobin was set at 12 g/dl. In the oral group patients received 200 mg oral ferrous ascorbate daily. Hemoglobin and serum ferritin were reviewed at 2, 4, and 6 weeks. Paired and independent t test was applied. They established that Intravenous iron more efficaciously elevated hemoglobin and restored iron stores faster than oral iron, with no severe adverse reactions.<sup>8</sup>

In a study by Asma et al, this study aimed to evaluate the therapeutic effectiveness, safety and cost of intravenous iron sucrose therapy. 453 patients diagnosed with iron deficiency anaemia, who received intravenous iron sucrose between 2004 and 2008 were reviewed. The improvement of hematologic parameters and cost of therapy was well tolerated. Although the cost of intravenous iron sucrose therapy may seem high, side effects including gastrointestinal irritation seen during oral iron therapy were not experienced during intravenous therapy.<sup>9</sup>

Study by Ragip A et al established that iron sucrose is a safe and effective alternative to oral iron in treatment of iron deficiency anaemia of pregnancy. It restores blood stores more rapidly and a prompt increase in haemoglobin may be achieved.<sup>11</sup>

In a study by Al momen et al, 52 women treated with intravenous sucrose and 59 women treated with 300 mg of oral iron sulphate. It was found that intravenous therapy resulted in higher haemoglobin levels in shorter periods compared with oral therapy group. They concluded that iron sucrose is safe and effective in the treatment of iron deficiency anaemia during pregnancy. No serious adverse events were noted with iron sucrose while 6% of patients who could not tolerate oral ferrous sulfate were excluded from the study.<sup>12</sup>

In a study by Bayoumeu F et al, an open study involving 50 patients with haemoglobin levels

between 8 and 10g/dl and a ferritin value of <50mg/dl. The oral group received 240mg of iron sulphate per day for 4 weeks. Treatment efficacy was assessed by measurement of haemoglobin and reticulocytes on days 8, 15, 21 and 30 and at delivery and of ferritin on day 30 and at delivery. They concluded that iron sucrose appears to be a treatment without any serious side effects hence indicated in correction of pregnancy anaemia or iron stores depletion.<sup>13</sup>

In their study by Divakar et al it is evident that 40% of women who took oral iron showed an increase in Hb of upto 0.5 gm% , whereas 53% in the IV iron sucrose group showed a greater improvement of 0.6 -0.9gm% . In the IV iron sucrose group, 17% of pregnant women showed an increase in Hb of greater than 2gm% , whereas such a rise was seen in only 3% of the oral iron group . The superiority of IV iron sucrose, even when given at suboptimal doses over oral iron is unquestionable.<sup>17</sup>

### Aim and Objectives

Proposed study has following aim and objectives:

1. To assess the efficacy and acceptability of intravenous iron sucrose when compared to oral iron in treatment of anaemia in pregnancy.
2. To compare the overall pregnancy outcome with respect to changes in the -  
A . Haemoglobin level  
B. Serum ferritin level
3. To compare which therapy restores iron stores faster and more effectively; oral iron ascorbate or parenteral iron therapy
4. To compare which route of administration of iron improves maternal and fetal outcome; oral iron ascorbate or intravenous iron sucrose therapy

### Materials and Methods

**Study site:** Obstetrics and Gynaecology department (both inpatient and outpatient) of eastern railways Kolkata, a tertiary care hospital offering referral services to pregnant women

**Study population:** Patients were selected mainly from population of Kolkata and adjacent area.

**Sample size:** The number of subjects for this study was 106.39 ~ 106 with power 83%. (According to the National Family Health Survey (2005–2006) incidence of anemia in pregnant women in India is 56.8 % on an average based on urban and rural areas) <sup>6</sup>. The formula used for sample size calculation was as follows:-

$$n = \frac{4pq}{L^2}$$

Where

n= Required sample size

p= Incidence of anemia in pregnant women in India [as per National Family Health Survey (2005–2006)].

q = 1 - p

L = Loss % (Loss of information)

### Statistical Analysis

Statistical Analysis was performed through Epi Info (TM) 3.5.3 which is a trademark of the Centers for Disease Control and Prevention (CDC).

Descriptive statistical analysis was performed to calculate the means with corresponding standard deviations (s.d.). With the help of this software, basic cross-tabulation and frequency distributions were prepared.  $\chi^2$  test was used to test the association between different study variables under study. Corrected  $\chi^2$  test was used in case of any one of cell frequency was found less than 5 in the bivariate frequency distribution.

Test of proportion (Z-test) was used to test the significant difference between two proportions. t-test was used to test the significant difference between means.

Also One Way Analysis of variance (ANOVA) followed by *post hoc* Tukey's Test was performed with the help of Critical Difference (CD) or Least Significant Difference (LSD) at 5% and 1% level of significance to compare the mean values.  $p \leq 0.05$  was considered statistically significant.

**Sample design:** This was randomized controlled trial (RCT) comparing effectiveness of oral iron ascorbate or intravenous iron sucrose therapy in reduction of maternal anemia. Recruited sample of 106 pregnant women volunteers were randomly assigned to 2 therapy arms using a computer generated random numbers before starting the trial. Group 1 comprised of women receiving oral iron and group II comprised women receiving intravenous iron.

Definition of anemia for this study was: ' a haemoglobin concentration of less than 10 gm/dl when the peripheral blood is examined.

**Study duration:** Duration of the study was one year i.e from September 2014 – August 2015

**Study design:** Randomized Controlled Trial (RCT)

### Study techniques

#### Criterion for case selection

- Primigravida and multigravida between 26 and 34 weeks of gestation
- Pregnant women with haemoglobin level between 6 and 10gm%
- Women with established iron deficiency anaemia
- Women with no prior history of blood transfusions
- Women who are not on any therapeutic iron therapy
- MCV < 100fl and a ferritin level < 50 microgram/l

#### Criterion for case exclusion:

- Women with history of any haematological disease
- Women with multiple pregnancy
- Intolerance to iron derivatives
- Recent administration of iron therapy
- Women with risk of preterm labour
- Women with medical complications like tuberculosis, diabetes, renal and hepatic disorder

**Parameters studied**

The study protocol had been approved by the Institutional Ethics Committee. Written, informed consent was sought from the study participants. A sample of 106 volunteer pregnant women were selected randomly, who fulfilled the inclusion and exclusion criteria and then were randomly allocated to either oral iron ascorbate (n=53) or intravenous iron sucrose (n=53) therapy arm. Both maternal and fetal condition were assessed at baseline, after 3 weeks and after 8 weeks. Study subjects had freedom to discontinue their participation in the study any time and their rights to get treatment in the hospital were not influenced by their choice to participate or not in the study. They were advised regarding diet and were asked to take iron tablets after meals and not take coffee or tea before and after taking tablets. They were explained about repeating investigations during follow up visits after 3 weeks and 8 weeks respectively.

**VISIT 1**

Information regarding patients name, address, age, and history of amenorrhoea were obtained and results of general examination, maternal weight and obstetrical examination were noted. Investigations included estimation of hemoglobin value, serum ferritin level and peripheral smear examination to note the type of anemia. Haemoglobin estimation was done by Sahli's method which is more practical, cost effective and commonly used.

Iron tablets along with folic acid, vitb12 and tab Albendazole 400mg were given to the oral iron group. Women were instructed to take two tablets (ferrous ascorbate with 100 mg of elemental iron per day with 1.1 mg of folic acid) twice daily throughout the pregnancy.

The iron sucrose group were also administered folic acid and vit b12 and tab Albendazole 400mg along with therapy and were advised to avoid oral iron during iron sucrose therapy and thereafter. The total iron dose in mg was calculated from the following formula:

$$2.4 \times \text{weight} \times (\text{target} - \text{actual Hb}) \text{ in g/dl} + 500 \text{ mg}$$

Rounded up to nearest multiple of 100.

In the formula since the patient's pre pregnancy weight was not known, the weight at the time of the first visit was considered in kilograms. Target hemoglobin in g per dl was set at 11 g/dl

In each infusion the maximum total dose administered was 200 mg elemental iron in 100 ml of normal saline infused over 20–30 min, given on alternate days. Each ampoule was of 2.5 ml containing 50 mg of elemental iron. The ampoules were diluted with normal saline immediately before the infusion. No test dose was given. Treatment was completed after administration of the calculated dose.

They were advised to report any adverse side effects immediately. They were explained about repeating investigations during follow up visits after a period of 3 weeks and 8 weeks respectively.

**VISIT 2 after 3 weeks**

After a period of 3 weeks the pregnant women were examined clinically and maternal weight was noted. Haemoglobin and serum ferritin estimation was done in both groups to note the improvement in values.

The side effects volunteered by the women were noted and they were advised to continue tablets in the oral iron group. The iron sucrose group were advised to continue folic acid and to avoid oral iron.

On subsequent visits general and obstetrical examination was done and maternal weight and adverse side effects if any were noted.

**VISIT 3 after 8 weeks**

After a period of 8 weeks haemoglobin and serum ferritin estimation were done to note the improvement in values. Any adverse side effects if any were noted. After delivery birth weight of the baby was noted.

**Statistical Analysis**

Statistical Analysis was performed through Epi Info (TM) 3.5.3 which is a trademark of the Centers for Disease Control and Prevention (CDC).

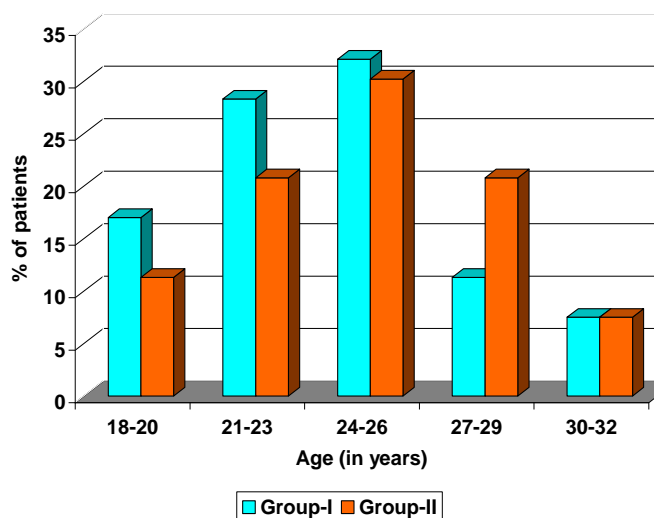
Descriptive statistical analysis was performed to calculate the means with corresponding standard deviations (s.d.). With the help of this software, basic cross-tabulation and frequency distributions were prepared.  $\chi^2$  test was used to test the association between different study variables under study. Corrected  $\chi^2$  test was used in case of any one of cell frequency was found less than 5 in the bivariate frequency distribution.

Test of proportion (Z-test) was used to test the significant difference between two proportions. t-test was used to test the significant difference between the means.

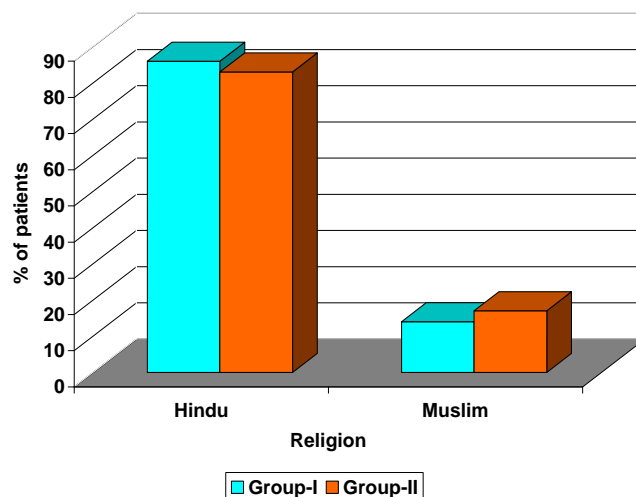
Also One Way Analysis of variance (ANOVA) followed by *post hoc* Tukey's Test was performed with the help of Critical Difference (CD) or Least Significant Difference (LSD) at 5% and 1% level of significance to compare the mean values.  $p \leq 0.05$  was considered statistically significant.

**Results**

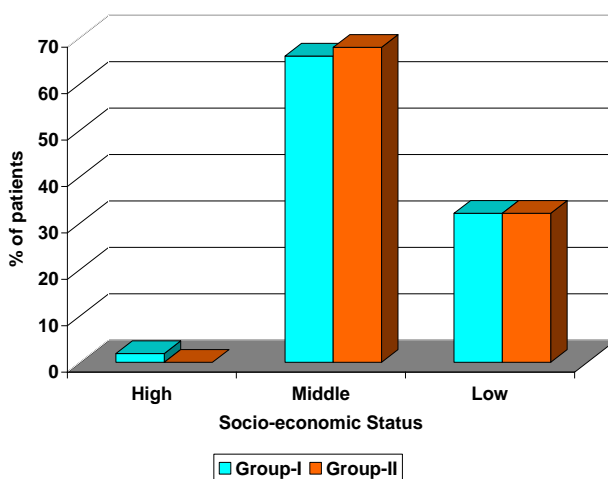
Considering patients who received oral iron therapy as group I and those receiving intravenous iron as group II, the following results were obtained-



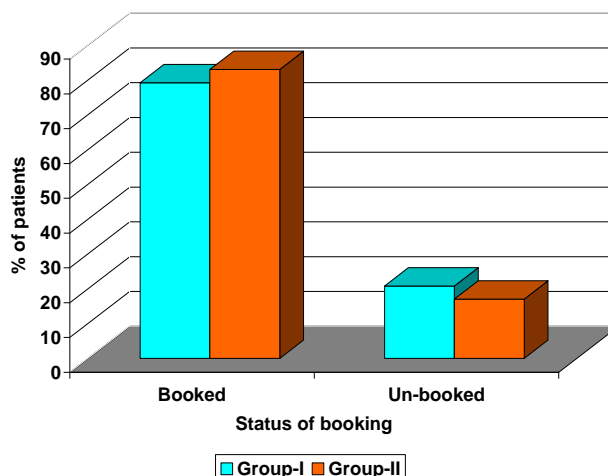
**Graph 1:** showing age distribution of two groups



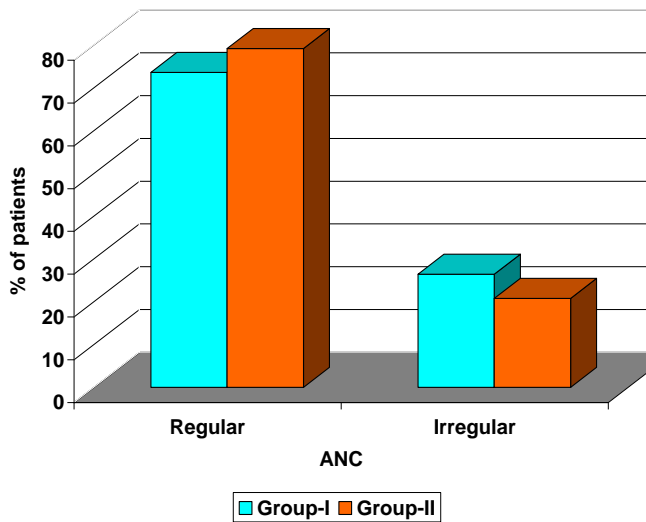
**Graph -2:** Distribution of religion of the patients of the two groups



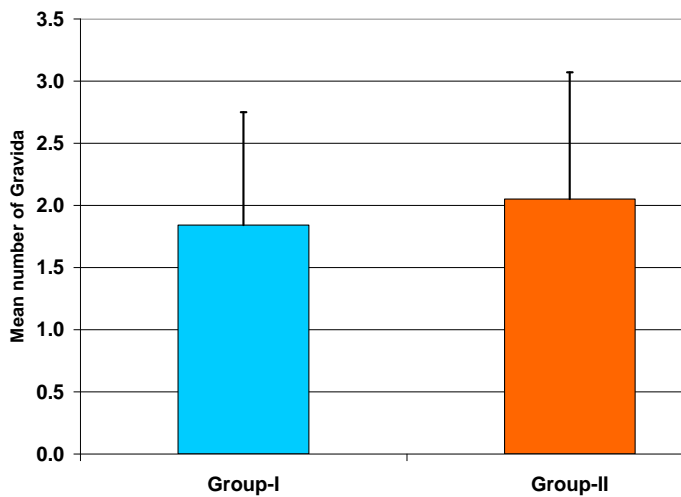
**Graph 3:** Distribution of socio-economic status of the patients of the two groups



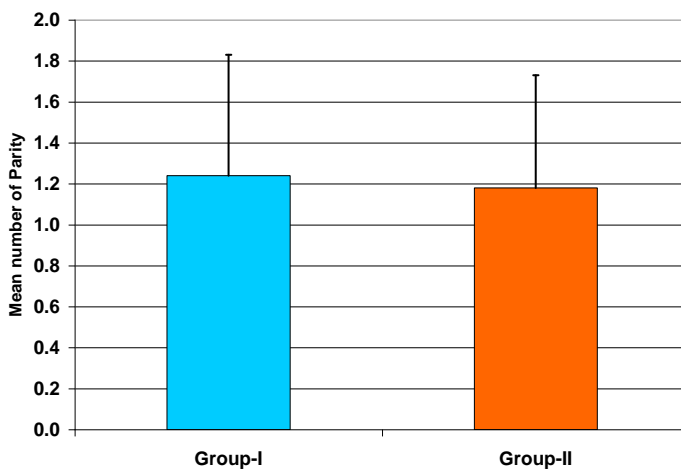
**Graph -4:** Distribution of status of booking of the patients of the two groups



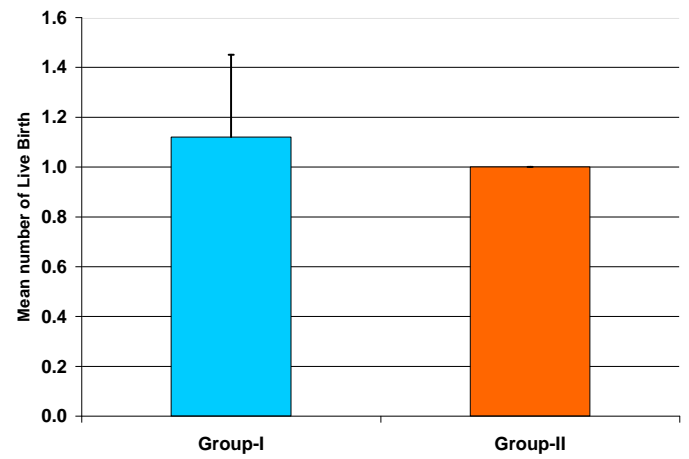
**Graph-5 :** Distribution of ANC of the patients of the two groups



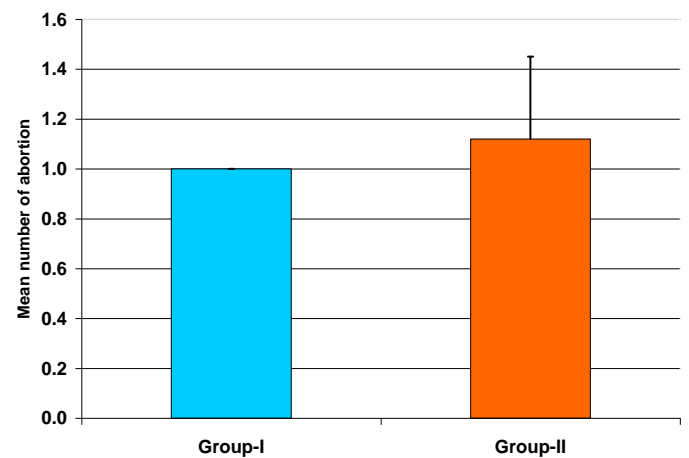
**GRAPH 6 (i):** showing the distribution of obstetric parameter- gravida



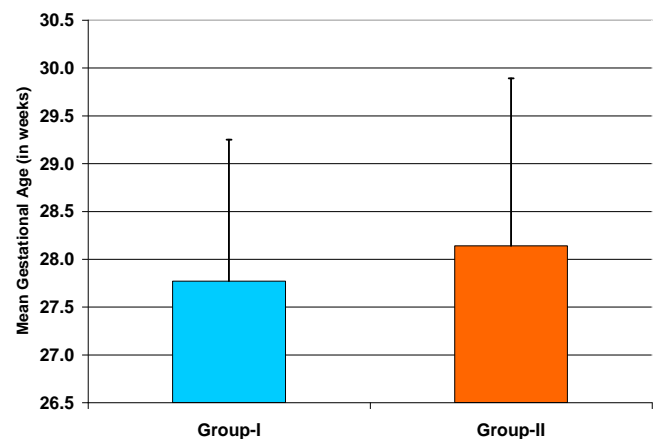
**GRAPH 6(ii):** showing the distribution of obstetric parameter- parity



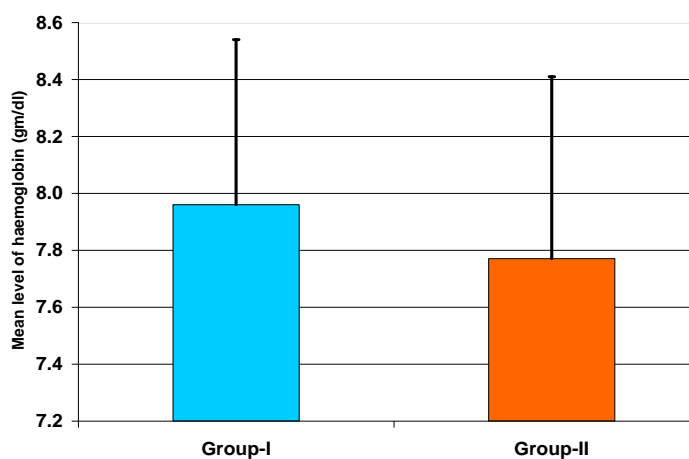
**GRAPH 6(iii):** showing the distribution of obstetric parameter number of live births



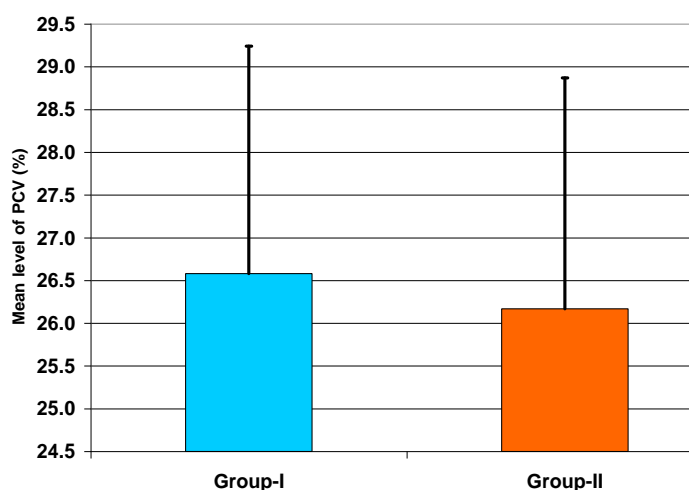
**GRAPH 6 (iv):** showing the distribution of obstetric parameter –number of abortions



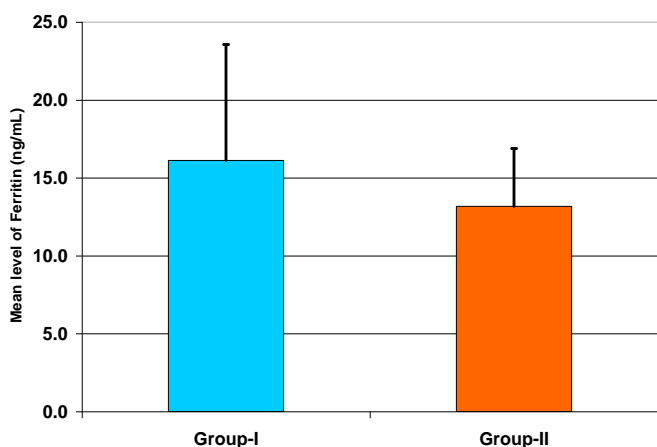
**GRAPH 6(v):** showing the distribution of mean gestational age (in weeks)



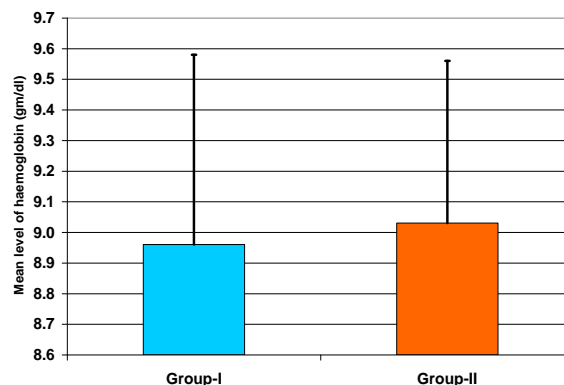
**Graph -7 (i):** showing distribution of levels haemoglobin at first day (Day 0) of the patients of the two groups



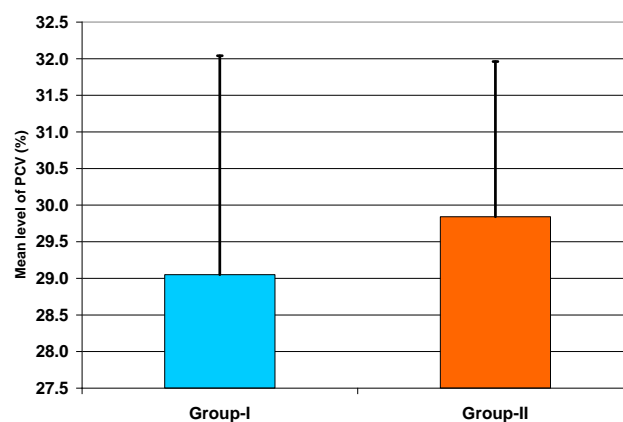
**Graph 7 (ii):** Distribution of levels of PCV at first day (Day 0) of the patients of the two groups



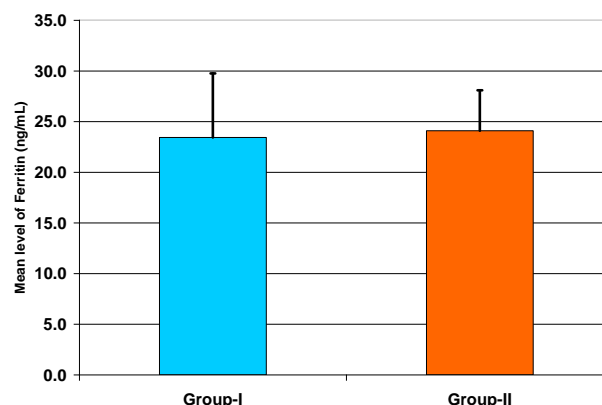
**Graph 7 (iii) :** Distribution of levels of ferritin at first day (Day 0) of the patients of the two groups



**Graph -8 (i):** showing distribution of levels haemoglobin at 3 weeks of the patients of the two groups

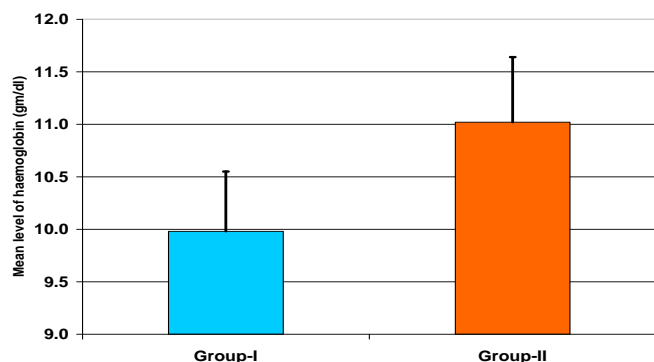


**Graph -8 (ii):** showing distribution of levels of Packed cell volume at 3 weeks of the patients of the two groups

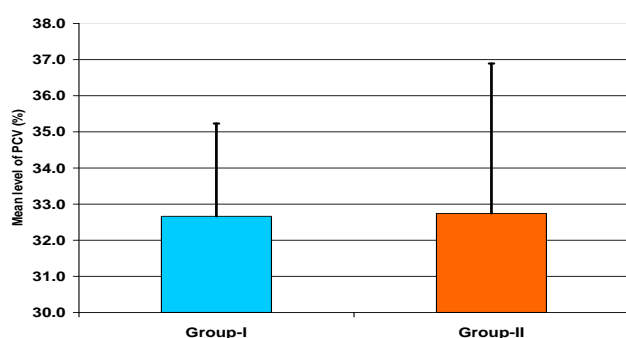


**Graph -8 (iii):** showing distribution of levels of ferritin at 3 weeks of the patients of the two groups

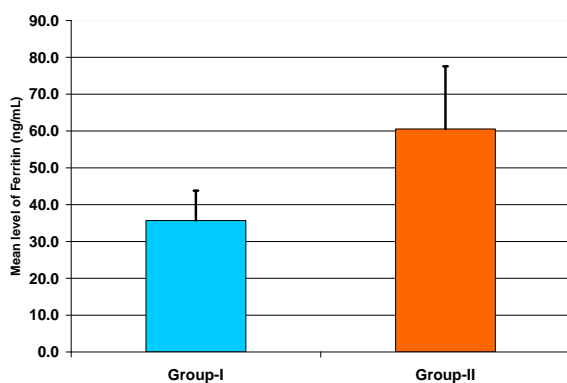
**Table-9:** Distribution of parameters after 8 weeks of the patients of the two groups  
t-test showed that mean level of haemoglobin, ferritin of Group-II was significantly higher than that of Group-I ( $p < 0.01$ ). But no significant difference was found in case of PCV of the two groups ( $p > 0.05$ ).



**Graph -9 (i):** showing distribution of levels of haemoglobin at 8 weeks of the patients of the two groups



**Graph -8 (ii):** showing distribution of levels Packed cell volume at 8 weeks of the patients of the two groups

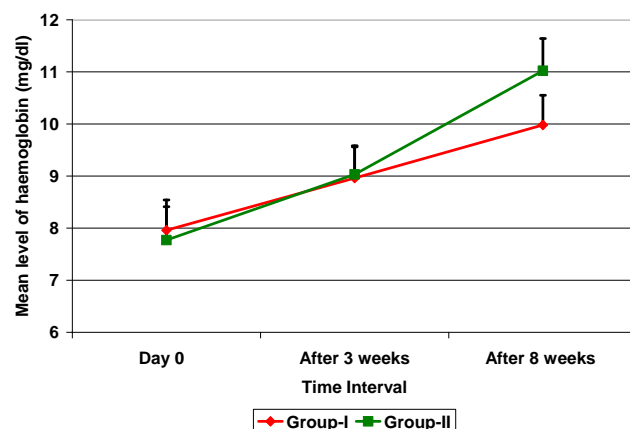


**Graph -8 (iii):** showing distribution of levels of ferritin at 8 weeks of the patients of the two groups

One way ANOVA showed that mean level of haemoglobin increased significantly over time for both the groups.

As per the CD in Group-I there was no significant difference in mean level of haemoglobin at Day 0 and after 3 weeks ( $p > 0.05$ ) but it significantly increased after 8 weeks in comparison with Day 0 ( $p < 0.01$ ).

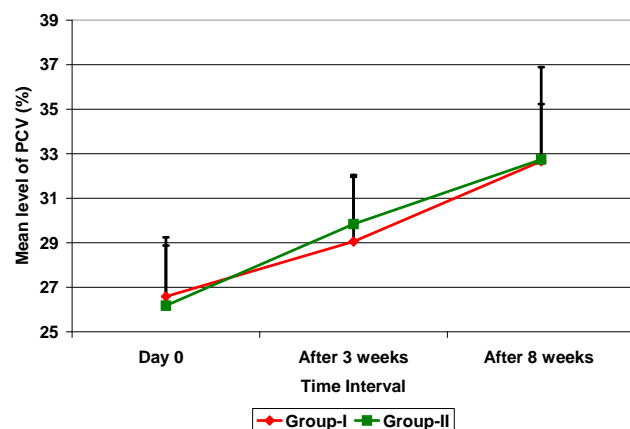
However, as per the CD in Group-II mean level of haemoglobin significantly increased after 3 weeks and 8 weeks in comparison with Day 0 ( $p < 0.01$ ).



One way ANOVA showed that mean level of PCV increased significantly over time for both the groups.

As per the CD in Group-I there was no significant difference in mean level of PCV at Day 0 and after 3 weeks ( $p > 0.05$ ) but it significantly increased after 8 weeks in comparison with Day 0 ( $p < 0.01$ ).

However, as per the CD in Group-II mean level of PCV significantly increased after 3 weeks and 8 weeks in comparison with Day 0 ( $p < 0.01$ ).

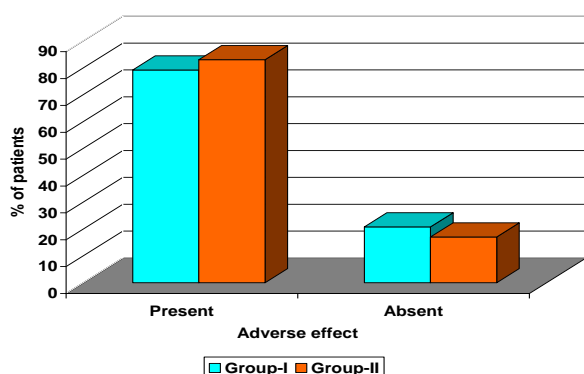
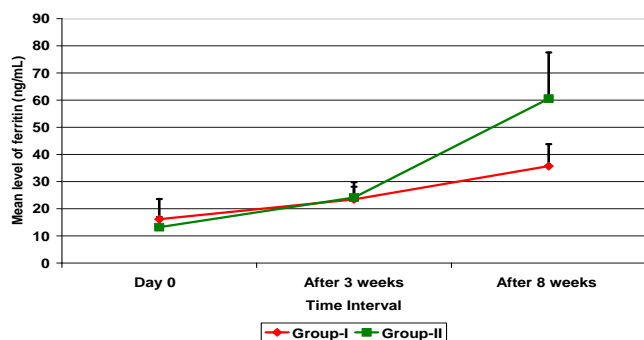




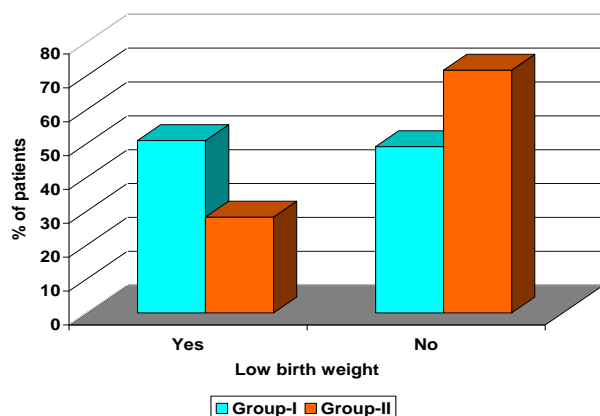
One way ANOVA showed that mean level of ferritin increased significantly over time for both the groups.

As per the CD in Group-I there was no significant difference in mean level of ferritin at Day 0 and after 3 weeks ( $p>0.05$ ) but it significantly increased after 8 weeks in comparison with Day 0 ( $p<0.01$ ).

As per the CD in Group-II there was no significant difference in mean level of ferritin at Day 0 and after 3 weeks ( $p>0.05$ ) but it significantly increased after 8 weeks in comparison with Day 0 ( $p<0.01$ ).



**Graph -13:** Distribution of adverse effect of the patients of the two groups



**Graph -14:** Distribution of low birth weight of the babies of the patients of the two groups

### Discussion

There was no drop out (i.e. non-compliance to treatment) in the two groups of patients in my study. Shafi et al also found that no participants were lost to follow up and there were no dropouts<sup>8</sup> There was no significant difference in the mean age of the patients of the two groups ( $p=0.28$ ). Abhilashini et al also found similar result in their study.<sup>7</sup>

In our study the mean( $\pm$ s.d.) gestational age of the patients of Group-I and Group-II were 27.77 $\pm$ 1.48 weeks and 28.14 $\pm$ 1.75 weeks respectively which was in contrast to study by Abhilashini et al.<sup>7</sup>

There was no significant difference in the parity between the two groups which was similar to study conducted by Abhilashini et al. However, in the study by Ragip et al, 62% of the patients in the iron sucrose group and 42% of the patients of the oral iron group were primigravidas.<sup>11</sup>

At the time of initiation of treatments the mean $\pm$ s.d. level of Hb, PCV%, ferritin of the patients of Group-I were 7.96 $\pm$ 0.58 gm/dl, 26.58 $\pm$ 2.66% and 16.13 $\pm$ 7.43 ng/mL respectively. For Group-II the mean  $\pm$  s.d. level of Hb, PCV%, ferritin of the patients were 7.77 $\pm$ 0.64 gm/dl, 26.17 $\pm$ 2.70% and 13.18 $\pm$ 3.71 ng/mL respectively. Also t-test showed that there was no significant difference of mean level of the parameters of the two groups ( $p>0.05$ ).

After 3 weeks of treatment the mean  $\pm$  s.d. level of Hb, PCV%, ferritin of the patients of Group-I were 8.96 $\pm$ 0.62 gm/dl, 29.05 $\pm$ 2.99% and 23.44 $\pm$ 6.32 ng/mL respectively. For Group-II the mean  $\pm$  s.d. level of Hb, PCV%, ferritin of the patients were 9.03 $\pm$ 0.53 gm/dl, 29.84 $\pm$ 2.12% and 24.10 $\pm$ 3.99 ng/mL respectively. Also t-test showed that there was no significant difference of mean level of the parameters of the two groups ( $p>0.05$ ).

After 8 weeks of treatment the mean  $\pm$  s.d. level of Hb, PCV%, ferritin of the patients of Group-I were 9.98 $\pm$ 0.57gm/dl, 32.66 $\pm$ 2.57% and 35.68 $\pm$ 8.09 ng/mL respectively. For Group-II the mean  $\pm$  s.d. level of Hb, PCV%, ferritin of the

patients were  $11.02 \pm 0.62$  gm/dl,  $32.74 \pm 4.15\%$  and  $60.53 \pm 17.01$  ng/mL respectively. t-test showed that mean level of haemoglobin, ferritin of Group-II was significantly higher than that of Group-I ( $p < 0.01$ ). But no significant difference was found in case of PCV of the two groups ( $p > 0.05$ ). Shi et al found that significant increases in haemoglobin [mean difference (MD), 0.85; 95% confidence interval (CI), 0.31-1.39;  $p = 0.002$ ] and ferritin levels (MD, 63.32; 95% CI, 39.46-87.18;  $p < 0.00001$ ) were observed in the intravenous group compared with the oral group. As per Shafi et al, an increase in hemoglobin was observed from baseline to 6 weeks in each group, but the increase in hemoglobin in intravenous iron sucrose group was more than oral ferrous ascorbate group at each point of measurement ( $P = 0.000$ ).<sup>8</sup>

Hence our study showed that there was better improvement in haemoglobin and ferritin by administration of iron sucrose as compared to oral iron ascorbate.<sup>7</sup>

Our study showed that (by One way ANOVA) that the mean level of haemoglobin increased significantly over time for both the groups. The mean level of Hb of the patients of Group-I at Day 0, after 3 weeks and 8 weeks of treatment of Group-I were  $7.96 \pm 0.58$  gm/dl,  $8.96 \pm 0.62$  gm/dl and  $9.98 \pm 0.57$  gm/dl respectively. For Group-II The mean level of Hb of the patients at Day 0, after 3 weeks and 8 weeks of treatment were  $7.77 \pm 0.64$  gm/dl,  $9.03 \pm 0.53$  gm/dl and  $11.02 \pm 0.62$  gm/dl.

Similarly one way ANOVA showed that mean level of PCV and serum ferritin increased significantly over time for both the groups.

The mean level of PCV of the patients of Group-I at Day 0, after 3 weeks and 8 weeks of treatment of Group-I were  $26.58 \pm 2.66\%$ ,  $29.05 \pm 2.99\%$  and  $32.66 \pm 2.57\%$  respectively. For Group-II The mean level of PCV of the patients at Day 0, after 3 weeks and 8 weeks of treatment were  $26.17 \pm 2.70\%$ ,  $29.84 \pm 2.12\%$  and  $32.74 \pm 4.15\%$ .

The mean level of ferritin of the patients of Group-I at Day 0, after 3 weeks and 8 weeks of treatment of Group-I were  $16.13 \pm 7.43$  ng/mL,

$23.44 \pm 6.32$  ng/mL and  $35.68 \pm 8.09$  ng/mL respectively. For Group-II The mean level of ferritin of the patients at Day 0, after 3 weeks and 8 weeks of treatment were  $13.18 \pm 3.71$  ng/mL,  $24.10 \pm 3.99$  ng/mL and  $60.53 \pm 17.01$  ng/mL.

Thus the mean level of Hb, PCV% and ferritin of each of the groups had been increasing significantly over time (i.e. at Day 0, after 3 weeks and 8 weeks of treatment ( $p < 0.01$ )).

In 26.4% of the patients receiving oral iron ascorbate were having adverse effect of the treatment which was significantly higher than that of patients receiving intravenous iron sucrose (9.4%). The risk of adverse effect was 3.44 times more among the patients of Group-I as compared to the patients of Group-II [OR-3.44 (1.14, 10.40;  $p = 0.022$ )] and the risk was significant. Shi et al found that there were fewer adverse events in the intravenous group (risk ratio, 0.50; 95% CI, 0.34-0.73;  $p = 0.0003$ ). Also there were no serious adverse drug reactions recorded.<sup>23</sup>

The risk of low birth weight was 2.63 times more among the patients of Group-I as compared to the patients of Group 2. Mean birth weight of the babies of Group-I was significantly lower than that of Group-II ( $t_{104} = 3.37$ ;  $p = 0.0011$ ). However various studies have contradicted this finding. As per Shi et al there was no significant difference in birth weight between the two groups.<sup>23</sup>

### Conclusion

As per the present study intravenous iron sucrose therapy was better tolerated with higher increase in mean haemoglobin and other RBC indices count as compared to oral iron therapy. Also there were no serious side effects with intravenous iron sucrose therapy. Thus intravenous iron sucrose is a good substitute to oral iron therapy in moderate to severe anaemia.

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