

**Rapid versus slow intravenous iron sucrose administration: efficacy, safety and potential cost-savings in an Indian rural pregnant population with iron deficiency anemia.**

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## Structured Abstract

**Background:** The Iron-Folic Acid (IFA) program launched in India some 30 years ago to provide free iron and folate to pregnant women to eradicate iron deficiency anemia (IDA) has failed, since the prevalence of IDA in pregnancy is still in excess of 50%. Intravenous iron sucrose circumvents many of the obstacles that have contributed to the failure of the IFA program, but requires careful and rigorous evaluation in a low resource setting such as India.

**Objectives:** To compare the efficacy, safety and cost of two methods of administering intravenous iron sucrose, the conventional slow intravenous infusion versus the rapid “bolus-push” technique.

**Patient & Methods:** 152 pregnant women with iron deficiency anemia (Haemoglobin < 11g/dl) attending a rural antenatal clinic in India between Nov 2008 and Feb 2009 were randomized to receive two doses of intravenous iron sucrose by one or other of the two methods under comparison. Irrespective of the pre-treatment haemoglobin (Hb), all women received the same total dose of iron sucrose of 400mg divided into two equal doses administered 2-4 days apart at 20-24 weeks gestation. The 75 women randomized to Group A received iron sucrose by the slow infusion (over half an hour) technique, while the 77 women randomized to Group B had the iron sucrose administered by the rapid “bolus-push” technique over 2-5 minutes. Any adverse reactions were recorded after the first injection. Per unit additional costs incurred were calculated for each method.

**Results:** There were no differences in patient demographics or pre-treatment Hb between the two groups. Both groups recorded a statistically significant increase in the mean Hb level in response to treatment (  $p < 0.05$ ), but there were no differences between the two groups. No woman experienced major adverse reactions, but minor reactions were reported in 5 (6.7%) women in Group A and 15 (19.5%) women in Group B ( $p > 0.05$ ). Only two women experiencing minor reactions required intravenous hydrocortisone, and symptoms resolved within 20 minutes in both. Cost analysis revealed that the slow infusion was seven times more expensive than the bolus push technique (200 versus 30 INR)

**Conclusions:** The administration of iron sucrose by the bolus-push technique has similar efficacy to the conventional slow infusion technique, but is seven times cheaper. Although

associated with a higher incidence of adverse reactions, all were minor, and all resolved rapidly. The bolus-push technique may represent a cost-effective approach to the eradication of iron deficiency anemia in pregnancy in low-resource settings.

**Keywords:** Iron deficiency anemia (IDA), iron-folic acid (IFA), Pregnancy, haemoglobin (Hb), iv iron sucrose

## Introduction

Nearly 30 years after the initiation of the iron-folic acid (IFA) program to provide free iron-folic acid supplementation to all pregnant women commencing from the second trimester until 3 months of lactation, studies show that the prevalence of iron deficiency anemia (IDA) in pregnancy in India is rising<sup>1</sup>, being quoted in the range 50-60%<sup>2</sup>. The IFA program has therefore failed, and this for a variety of reasons including partial coverage of the population, inadequate dosing of the iron supplement, short supplies, defective absorption because of intestinal infestations, diets which contain high levels of iron chelators, problems with formulation, inadequate consumption or poor compliance by the beneficiaries, failure to replenish the stocks at the beneficiary level, and lack of effective health education and supervision<sup>3</sup>. It has become evident that cosmetic initiatives will not overcome the failings of the IFA program, and fresh thinking is required. In the developed world it has long been documented that intravenous (iv) iron supplementation is highly effective in treating IDA in a variety of settings, including pregnancy. There is irrefutable evidence that compared to oral iron, iv iron sucrose results in a much more rapid resolution of IDA<sup>4, 5</sup>, has minimal side-effects, and because it is administered intravenously, it circumvents many of the problems that bedeviled the IFA program, including problems of compliance. Unlike intravenous dextran iron, anaphylactic reactions are virtually unknown with iron sucrose. We recently conducted a small prospective cohort study and found that as little as two doses of 200mg of iv iron sucrose given to pregnant women with moderate anemia significantly increase haemoglobin (Hb) levels within 4 weeks, suggesting that a full-dose regimen could eradicate IDA. There were no major adverse reactions, and only a tiny minority of women experienced minor adverse reaction, and all women stated that they found the treatment acceptable to them (Divakar et al, submitted).

Could iv iron sucrose be the Holy Grail in the eradication of IDA in pregnancy in a low-resource setting such as India? There are huge potential, although not insurmountable, challenges. Firstly, conventional practice requires that iron sucrose be administered by slow intravenous infusion in divided doses administered over several days or weeks. Each such infusion requires a hospital bed and other paraphernalia, significantly adding to the cost of the treatment. Since the vast majority of women in India embark on pregnancy with mild to moderate anemia, these women would require multiple infusions, which in turn would necessitate several visits to the hospital. Long standing experience shows that despite educational

campaigns, and other measures to take up treatments, there is almost always poor uptake when a treatment requires several hospital visits. This would be particularly true of the treatment of IDA, where the women do not necessarily have any overt symptoms.

The challenge is therefore to develop and/or evaluate treatment regimens that are efficacious, safe and cost-effective. To this end we have conducted a prospective randomized trial in which we have compared the efficacy, safety and cost of providing intravenous iron sucrose via a “bolus push” technique over 2-5 minutes versus the conventional slow intravenous infusion which is administered over about 30 minutes.

## Patients and Methods

**Study subjects:** Women were invited to participate if they were anemic (Hb <11g/dl) and were pregnant at gestational age of 20 – 24 weeks. All the women were recruited from two rural antenatal clinics in southern India between Nov 2008 and Feb 2009. Written informed consent was obtained from all participants.

**Sample size:** We have previously reported a 69.4% prevalence rate of iron deficiency anemia in rural settings in India in a recent study (Divakar et al, 2009; submitted). Anemia was defined as Hb less than 11 g/dl (Indian Council for Medical Research). Using this prevalence rate the sample size to assess the two modalities of parenteral iron sucrose therapy was calculated using n-master software®, with a relative precision of 12% and  $\alpha$  error at 5 % (95% confidence interval). We calculated that 60 women would be required in each arm. To allow for dropouts, we aimed to recruit 160 women in total, but in the event managed to recruit 152.

**Study design:** Randomized controlled trial

**Methodology:** All women were de-wormed with two tablets of Mebex Plus (Mebendazole and Pyrantel Pamoate - Cipla India Pvt Ltd) prior to commencement of treatment. Each woman received a total dose of 400mg intravenous iron sucrose divided into two equal (200mg) doses administered 2-4 days apart, regardless of her pre-treatment Hb (ie no specific calculations were conducted to tailor iron sucrose dose to the woman's pre-treatment Hb, as is done in conventional therapy). Women were randomized to receive a slow intravenous infusion of iron sucrose in 100ml saline over 30 minutes (Group A, n = 75), or to receive the iron sucrose as a rapid intravenous bolus-push over 2-5 minutes, administered through a venous butterfly cannula once correct positioning in the vein had been tested with normal saline (Group B, n = 77). No test dose was given, and all women were closely observed for up to 30 minutes for adverse reactions such as nausea, burning sensation at infusion site, local pain, rashes and breathlessness during or immediately after the injection. If an adverse reaction occurred and did not settle in 15-20 minutes, one vial of Hydrocortisone (100mg) was given intravenously. The women were also advised to contact the unit if they developed any subsequent symptoms. Hb was measured at 4 weeks post treatment.

**Economic analysis:** The costs involved in the infusion method included the cost of 100 ml of 0.9 % normal saline, intravenous set, cannula and infusion charges and bed occupancy charges for one hour (30 minutes infusion + 30 minutes observation). The push method considered the costs of 10ml 0.9% saline and syringe.

**Statistical analysis:** Data was analyzed using SPSS version 11 (Statistical Package for Social Sciences). The paired t-test was used to estimate the significance of difference between the mean change in Hb within each group and between the two groups of women. The student t-test was used to test the significance of differences between mean Hb of the two groups at baseline and at 4 weeks. The tests were considered to be significant at 95% level of significance ( $p < 0.05$ ).

## Results

### **(i) Characteristics of participants:**

A total of 152 women consented to participate in the study. There were 75 women in Group A (40 primigravidae and 35 multigravidae) and 77 in Group B (37 primigravidae and 40 multigravidae). The mean age of the women in group A was 22.31 years (SD 2.52) and mean weight was 45.85kg (SD 5.50). While the mean age of the women in group B was 22.30 years (SD 2.52) and mean weight was 46.73kg (SD 5.50). In Group A 19 (25.33%) and in Group B 22 (28.57%) women were lost to follow up after administering the first dose of intravenous iron sucrose. [Table 1]

### **(ii) Hb changes in response to intravenous iron sucrose:**

Both groups had comparable pre-treatment Hb levels. Group A mean Hb was 9.34 g/dl (SD 0.82) and Group B 9.2 g/dl (SD 0.70). Both groups showed a statistically significant ( $p < 0.05$ ) rise in Hb at 4 weeks as compared to baseline, with a mean Hb of 10.20 g/dl (SD 0.80) in Group A 10.29g/dl (SD 0.74). The mean increase in Hb for the whole group was 1.02 g/dl. [Table 2]. The differences in changes in mean Hb between the groups following treatment were found to be non-significant.

### **(iii) Change in severity of anemia in response to intravenous iron sucrose:**

Prior to iron therapy in Group A 3.6% women fell into the severe anemia category, but at four weeks there were none. In the same group 76.8% had moderate anemia, and this prevalence had dropped to 19.6 % at 4 weeks; while women in the category of mild anemia had increased from 19.64% to 66%,; 14.3% of previously anemic women in this group were rendered non-anemic. The corresponding changes in Group B were as follows: there were no women with severe anemia at baseline; the prevalence of moderate anemia fell from 81.8% to 18.2%, while mild

anemia increased from 18.2% to 67.3%, and 14.5% of previously non-anemic were rendered non-anemic. [Figure 1 a, b, c]

**(iv) Adverse reactions to intravenous iron sucrose:**

In Group A, 5 (6.7%) women experienced minor adverse reactions while 15 (19.5%) did so in Group B [Figure 2].

Two women in group B required intravenous hydrocortisone 100 mg when they developed rashes and GI symptoms lasting more than 20 minutes, and all symptoms and signs resolved within 20 minutes of administering the hydrocortisone. No woman experienced any major side effects and none required hospitalization.

Of the 19 women lost to follow up in group A, 2 had adverse reactions, while among the 22 patients lost to follow up in group B, 4 had adverse reactions after the first dose. There was no correlation between loss to follow up and the development of adverse reaction.

**(v) Cost comparison between slow intravenous infusion and the bolus push technique:**

The costs involved in the infusion method included the cost of 100 ml of 0.9 % normal saline, intravenous set, cannula and infusion charges and bed occupancy charges for one hour (30 minutes infusion + 30 minutes observation) amounting to 200 INR per injection in Group A. The push method per injection cost is 30INR (Group B). Thus the slow infusion was seven times more expensive than the bolus push technique

## Discussion

The case for establishing supplementation programs that can effectively eradicate IDA in pregnancy in the developing world cannot be over-stated. In India, where maternal mortality is still as high as 350 - 450/100,000 live births (a figure similar to that found in Europe 200 years ago<sup>6,7</sup>), anemia is estimated to contribute 20 percent of all maternal deaths<sup>8</sup>. The often unrecognized consequence of maternal IDA is the impact on the fetus, newborn, child and subsequent adult. Anaemia and iron deficiency in pregnancy are associated with large placental weight and a high ratio of placental weight to birth weight (placental ratio)<sup>9</sup>, both of which are predictors of adult hypertension<sup>10</sup>. In the newborn, IDA is associated with poor performance in the Bayley Mental Development Index<sup>11</sup>. While nutritional factors may be contributory, it seems more than likely that IDA in infancy and early childhood is largely secondary to maternal iron deficiency during pregnancy. Thus to address the problem of iron deficiency in infancy and early childhood is to close the proverbial stable door after the horse has bolted. The definitive solution is to eradicate iron deficiency during or even before pregnancy. The rising prevalence of IDA in pregnancy thirty years after the initiation of the IFA program is an indictment of the failure of this program, and the urgent need to explore alternative approaches.

Data from this study corroborates previous reports from resource-rich countries on the safety and efficacy of intravenous iron sucrose in pregnancy<sup>12</sup>. The challenges posed by attempts to use iron sucrose as a vehicle for the mass eradication of IDA in resource-poor areas include the cost of the drug and the method of its administration, the sheer logistics of administering several infusions of the drug to women who need it most, compromising compliance, and potential concerns about adverse reactions and how they might be handled in such settings. We have sought to evaluate ways in which these impediments might be overcome. If iron sucrose could be used on a mass scale, this would eventually drive down the cost of the drug, especially if generic formulations could be developed. This is a challenge for governments and the pharmaceutical industry. The use of the bolus-push technique has potential for cost savings because of the avoidance of the need for a hospital bed and other paraphernalia associated with the conventional infusion technique currently used in the administration of iron sucrose. Our study shows that this is indeed a feasible approach, with similar efficacy to the conventional, and thereby

corroborating the report by Macdougall et al<sup>13</sup> who demonstrated the safety of iron sucrose 200 mg as a 2 minute push in a total of 2297 injections. They found, as we did, a higher incidence of adverse reactions with the bolus-push technique, but all the reactions fell into the minor category, and we have also corroborated this finding. From the point of cost, our finding that the bolus-push technique is seven times cheaper than conventional slow intravenous infusion raises the possibility that its use could render iron sucrose affordable for use on a mass scale.

Even in this small study, the rate of loss to follow up was very high. We were concerned whether this might have been related to adverse reactions, but found no correlation between the incidence of adverse reactions and rates of loss to follow up. Thus we can only conclude that this high loss rate reflects what really does happen in practice – there is a high failure to complete treatment courses or comply with treatment. This has major implications for any program designed to use iv iron sucrose to eradicate IDA in pregnancy, since the women who need replacement most (Hb < 9 g/l) are the ones who would need several visits if the iron sucrose were to be administered by several divided doses as per current convention. A key potential solution might be to evaluate the use of a single dose of iv iron sucrose administered by the bolus-push technique.

At present 200mg is the maximum iv iron sucrose dose considered safe for administration at one sitting. Current practice is that the required iron dose is calculated for each woman based on the woman's Hb deficit and her pre-pregnancy weight. Data from this study gives an indication of the potential doses that could be used. If we assume, based on our own experience, that the mean Hb for most women entering pregnancy in the rural setting is 9.0 g/dl, and that the mean weight of these women is 47.0 kg, calculations indicate that a single dose of 200mg iron sucrose would raise the woman into the non-anemic range ie Hb > 11g/dl. It is generally stated that in pregnancy an additional 500mg iron are required to replenish stores<sup>14</sup>. We gave an additional 200mg of iron sucrose, although this would be insufficient to replenish the stores. By so doing, we treated the women's anemia, leaving some spare albeit inadequate amount of iron for stores. Thus if the 400mg dose (or higher) could be safely administered in a single bolus-push, the woman would not need to return for several infusions, compliance no longer becomes an issue, and efficacy would be virtually guaranteed, while costs are substantially reduced. Such an approach would go a long way to eradicating IDA in pregnancy in low-resource settings.

**Conclusion:** The bolus-push technique for the administration of intravenous iron sucrose may represent a cost-effective approach to the eradication of iron deficiency anemia in pregnancy in low-resource settings. Further studies are required on optimal iron sucrose dose regimens that could be administered as single total dose infusions.

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**Author Contributions:** Dr Hema Divakar had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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*Drafting of the manuscript:* Drs. Divakar H, Manyonda IT

*Critical revision of the manuscript for important intellectual content:* Drs. Divakar H, Manyonda IT

*Statistical analysis:* Divakar H, Manyonda IT, Tyagi S

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*Study supervision:* Divakar H,

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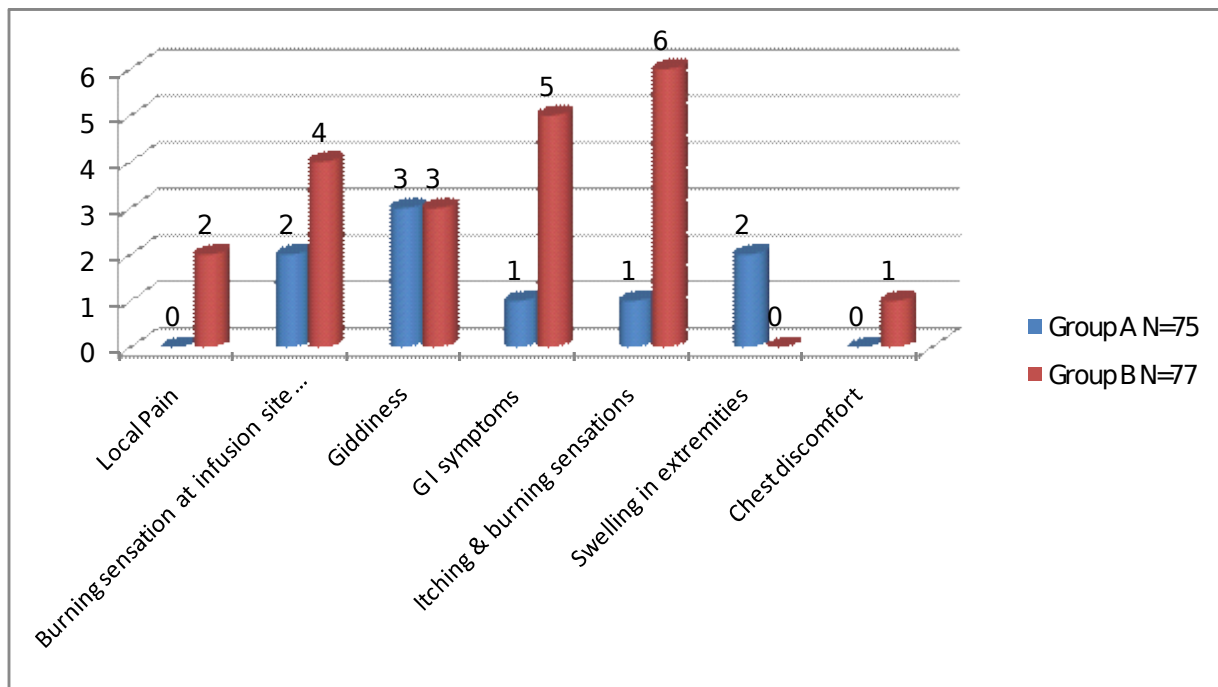
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**1: Changes in category of severity of anemia:**

Anemia was categorized according to the criteria established by the Indian Council of Medical Research (ICMR) as follows: <4g/dl = very severe anemia; 4 - 6.9 g/dl = severe anemia; 7-9.9g/dl = moderate anemia; 10-10.9g/dl = mild anemia; and >11g/dl = non-anemic

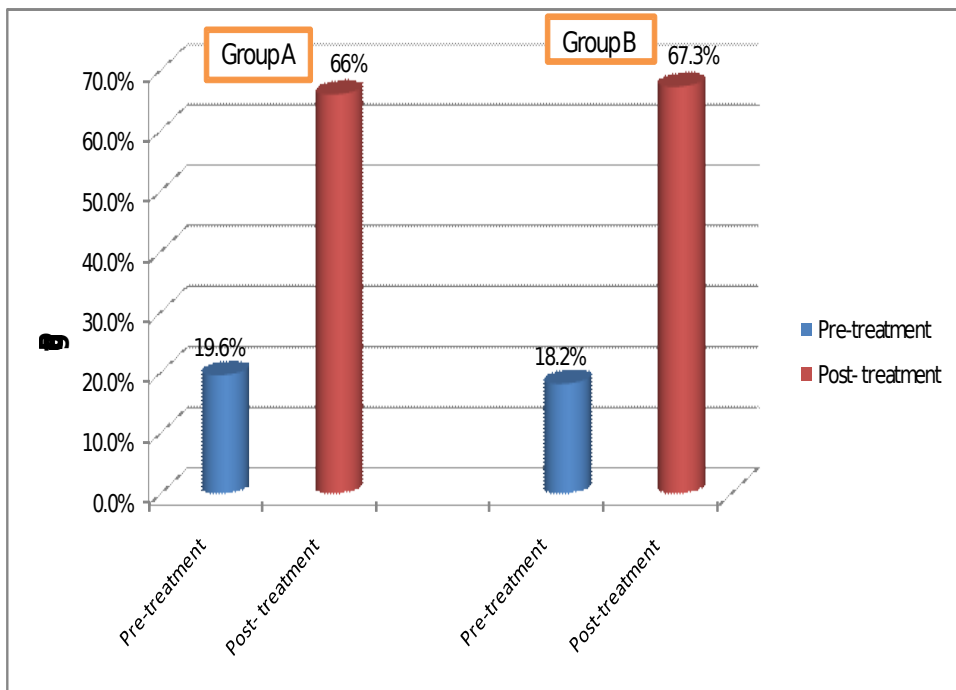
**Fig 1a: Percentage of pregnant women rising into the non-anemic category at 4 weeks following 400mg of intravenous iron sucrose.**

14.3% of previously anemic were rendered non-anemic in Group A and 14.5% in Group B



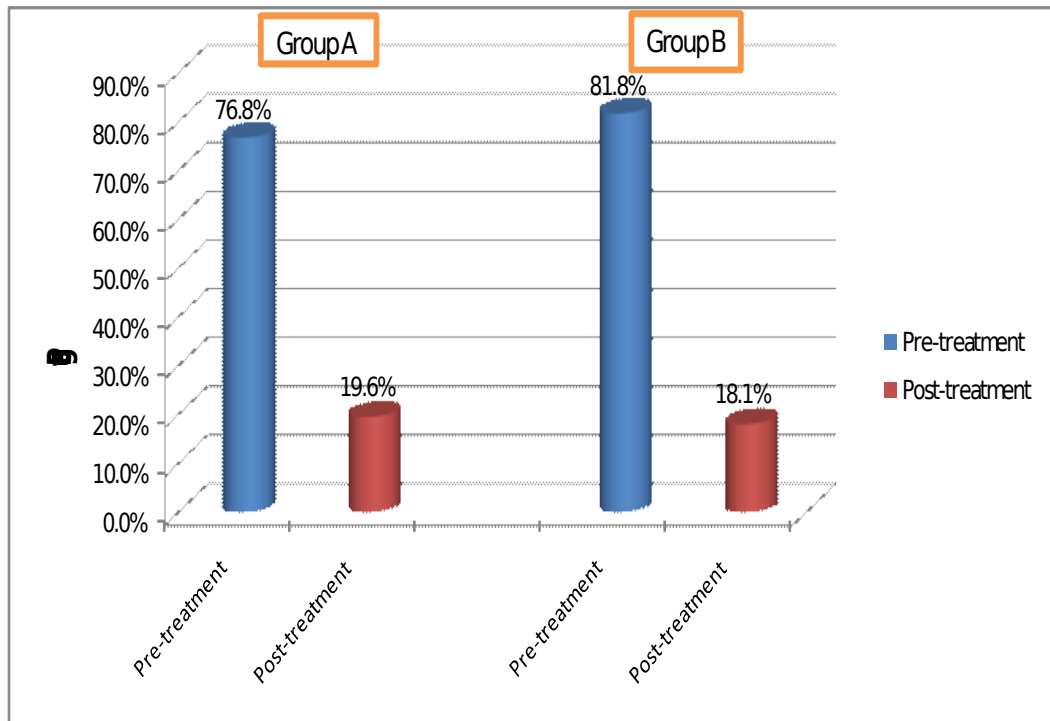
**Fig 1b: Percentage of pregnant women with mild anemia before and at 4 weeks after administration of 400mg of intravenous iron sucrose. The rise in the incidence represents a shift from the moderate to the mild anemia categories.**

Prior to iron therapy in Group A the group with mild anemia had increased from 19.6% to 66%. The changes in Group B were similar, where the mild anemia group increased from 18.2% to 67.3%.



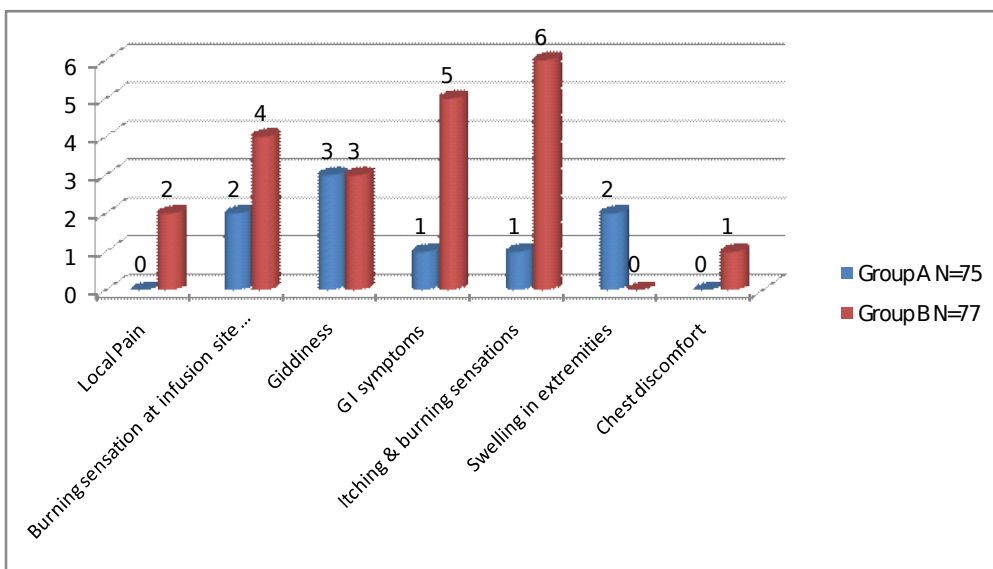
**Fig 1c: Fall in the percentage of women with moderate anemia at 4 weeks following treatment with 400mg intravenous iron sucrose.**

Prior to iron therapy in Group A 76.8% had moderate anemia, and this prevalence had dropped to 19.6% at 4 weeks; the corresponding changes in Group B were: the prevalence of moderate anemia fell from 81.8% to 18.2%.



**Fig. 2. Adverse reactions following the first dose of iv iron sucrose:**

Overall, there were no major adverse reactions, but minor adverse reactions (which included Giddiness, GI symptoms like nausea, burning at the infusion site and itching) occurred in 6.7% among the women in Group A and 19.5% of women in Group B.



**Table 1. Baseline characteristics of study participants**

A total of 152 pregnant anaemic (Hb < 11g/dl) women consented to participate in the study, and 75 were randomized to Group A and 77 to Group B. The parity, mean age and weight of the women were comparable.

<u>Variables</u>	<u>Group A</u>	<u>Group B</u>
<u>Total patients</u>	<u>75</u>	<u>77</u>
<u>ParityPrimigravidae</u>	<u>40</u>	<u>37</u>
<u>Multigravidae</u>	<u>35</u>	<u>40</u>
<u>Age [yrs,mean (SD)]</u>	<u>22.3 (SD2.87)</u>	<u>22.3 (SD2.17)</u>
<u>Weight [kgs, mean (SD)]</u>	<u>45.8</u>	<u>46.7</u>

**Table 2. Response to intravenous iron- sucrose**

Women were given two doses of intravenous iron sucrose (200mg each) on two separate occasions 2-4 days apart. In Group A (n=75) the iron sucrose was administered as a slow intravenous infusion in 100ml saline over 30 minutes, while in Group B (n=77) it was administered as a rapid intravenous bolus-push over 2-5 minutes. Hb was re-checked at 4 weeks following treatment. The two groups had comparable pre-treatment Hb, and both showed a statistically significant (p<0.05) rise in Hb at 4 weeks as compared to baseline.

<u>Variables</u>	<u>Group A</u>	<u>Group B</u>
<u>Pre-treatment Hb (Baseline) g/dl</u>	<u>9.34</u> <u>(SD)</u> <u>(n= 75)</u>	<u>9.2</u> <u>(SD)</u> <u>(n=77)</u>
<u>Post-treatment Hb (4 weeks) g/dl</u>	<u>10.2</u> <u>(SD)</u> <u>(n= 56)</u>	<u>10.3</u> <u>(SD)</u> <u>(n=55)</u>
<u>P value</u>	<u>P &lt; 0.05</u>	<u>P &lt; 0.05</u>