A Study of Comparison of Efficacy and Safety of Intravenous Iron Sucrose with and Without Erythropoietin Versus Blood Transfusions in Patients with Severe Iron Deficiency Anemia.

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ABSTRACT

Objective: This study was undertaken to compare the efficacy and safety of intravenous iron sucrose with and without erythropoietin versus blood transfusions in raising the hemoglobin level in patients with severe iron deficiency anemia.

Study Design: Sixty patients with severe iron-deficiency anemia were randomly assigned to receive intravenously iron sucrose plus recombinant human erythropoietin or iron sucrose alone thrice weekly. Target hemoglobin value was 11.0 g/dL. Efficacy measures were reticulocyte count, increase in hematocrit, and time to target hemoglobin level. Safety profile and cost of therapy was also evaluated.

Results: Both regimens were effective, but with adjuvant recombinant human erythropoietin the reticulocyte counts were higher from day 4 (P<.01), increases in hematocrit were greater from day 4 (P <.01), and the median duration of therapy was shorter, with more patients reaching the target hemoglobin earlier. The groups did not differ with respect to adverse effects during therapy.

Conclusion: Adjuvant recombinant human erythropoietin safely enhanced the efficacy of iron sucrose in the treatment of severe iron-deficiency anemia but increased the cost of therapy.

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Introduction
Anemia is defined as a reduction in the number of circulating erythrocytes. It is a common manifestation of primary bone marrow disorders (resulting in impaired production of erythrocytes), primary abnormalities of erythrocytes (resulting in an increased rate of destruction), immunologic disorders, nutritional deficiencies, and a broad spectrum of systemic diseases that secondarily result in anemia\(^2\). Iron deficiency occurs as a late manifestation of prolonged negative iron balance and its progression can be divided into 3 stages-Negative iron balance, iron-deficient erythropoiesis and iron-deficiency anemia\(^3\).

Iron deficiency anemia (IDA) is considered to be among the most important contributing factors to the global burden of disease\(^3\). Globally, the most significant contributor to the onset of anemia is iron deficiency so that IDA and anemia are often used synonymously. It is assumed that 50% of the cases of anemia are due to iron deficiency, but the proportion may vary among population groups. Nearly half of the pregnant women in the world are estimated to be anemic: 52% in non-industrialized - as compared with 23% in industrialized countries. In India, for example, up to 88% of pregnant and 74% of non-pregnant women are affected\(^4\).

Definitive diagnosis requires laboratory tests\(^5\). Measurement of hemoglobin or hematocrit is the most cost efficient and commonly used method to screen for anemia. A low serum ferritin (<15 ug/L), in addition to a low hemoglobin or hematocrit, confirms the diagnosis of iron deficiency anemia. However, ferritin levels may be normal or elevated when iron deficiency and infection, chronic inflammation, malignancy or conditions causing organ or tissue damage (e.g., arthritis, hepatitis) occur simultaneously. An elevated serum transferrin receptor concentration (TfR) (>8.5 mg/L) is an early and sensitive indicator of iron deficiency. It is, however, also raised in Thalassemia and hemolytic anemias\(^6\). Severe anemia is diagnosed when hemoglobin concentration is less than 7.0g/dl\(^7\).

Treatment: The traditional approach to anemia has been oral supplementation or blood transfusions. Oral iron therapy, although effective in most cases\(^8\), may be limited in many cases due to dose dependent side effects, lack of compliance and insufficient duodenal absorption \(^9, 10\). Hence, parenteral iron therapy becomes important. Iron-Dextran is the most stable, allowing the total dose to be given at one time\(^11\). However, there is a small but significant incidence of anaphylaxis associated with it, which has convinced many practitioners to use either of two alternative preparations –sodium ferric gluconate\(^12\) and iron sucrose\(^13\). Rare anaphylactic reactions have been reported with iron sucrose, but they appear to be less frequent than those with iron dextran. The total dose is calculated from the following formula:

\[
\text{Iron to be injected (mg) = weight (kg) x } \frac{\text{normal hemoglobin}}{2.4} + 500mg
\]

Value – actual hemoglobin value (g/dl) x 2.4 + 500mg

Blood transfusions are usually that last resort in treatment of iron deficiency anemia but are frequently used in symptomatic patients. There are no definitive guidelines but according to the available literature, usual threshold hemoglobin level for it is 6-7 gm/dl\(^14\). Each unit of Red Blood Cells contains approximately 147-278 mg of iron. Hemoglobin equilibrates in 15 minutes after RBC transfusion\(^15\). One unit will increase the Hb level in an average-sized individual by approximately 1 g/dl and the Hct by 3%.

Erythropoietin (EPO): During the last decade many new and exciting functions have been attributed to EPO and many of these are related to non-erythropoietic effects\(^16\). Several functions i.e. inhibition of inflammation and apoptosis, anti-oxidant effects and stimulation of angiogenesis, may be of potential use. Along with potentially beneficial effects attributed to EPO, there are reports indicating that the mortality and morbidity rates are increased in some patient groups\(^17, 18, 19\). rhEPO has a direct action on the endothelium increasing the reactivity of the underlying extra- cellular matrix towards platelets, effect that may be the cause of its thrombogenic potential\(^20\).

The main mechanism for the increase in hematocrit was long thought to rely exclusively on augmentations in red cell mass, but it was demonstrated that EPO also decreases plasma volume\(^21\). The clinical response to IV iron may be attributed to the effect of EPO therapy on iron mobilization from the reticuloendothelial system into RBC precursors\(^22\). The success of EPO therapy in correcting the anemia of chronic renal failure has led to substantial clinical experience in iron therapy and erythropoiesis in this setting\(^23\). IV iron administration is used commonly in hemodialysis patients undergoing EPO therapy\(^24\).

Various controlled studies in the past have investigated the efficiency of intravenous iron sucrose with or without erythropoietin in patients of renal failure, pregnant females and cancer associated anemias. In the present study, we will investigate the efficacy of intravenous iron sucrose with or without erythropoietin in patients of severe iron deficiency anemia. The measures of efficacy will be reticulocyte count, increase in hematocrit, time to target hemoglobin and we will evaluate the safety profile and cost of I.V. iron, erythropoietin and blood transfusion.

\[\text{http://www.pacificejournals.com/aabs}\]
Materials And Methods
The study population included 60 patients of both sexes attending the indoor of the Department of Medicine, Acharya Shri Chander College of Medical Sciences and Hospital, Sidhra, Jammu. The subjects were aged between 17 and 62 yrs. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Criteria For Selection:
1. Hemoglobin concentration < 7 g/dl
2. PBF showing a microcytic hypochromic picture
3. Serum ferritin < 12 mcg/dl

Exclusion Criteria:
1. History of allergy to iron
2. Patients of anemia due to acute blood loss
3. Patients of chronic renal failure
4. Pregnant anemic females
5. Other causes of microcytic hypochromic anemia
6. Leukemias/Plasma call disorders/Cancers
7. Withdrawal of consent
8. Thalassemia minor

After evaluation of all inclusion, exclusion criteria and informed consent, eligible patients entered a randomized parallel group study and were assigned to three treatment groups. The first group received intravenous iron sucrose at a dose of 200 mg thrice weekly for 2 weeks followed by switch to oral iron tablets of 100 mg daily. The second group received iron sucrose as above plus recombinant human erythropoetin in the dose of 6000 IU subcutaneously thrice weekly for two weeks. As above these patients were also switched to oral iron in the same dose after two weeks. The third group received whole blood transfusions on alternate days for 5 times.

Patients in the group 1 and 2 were assessed before the start of treatment, then at day 4 and then once weekly, till the target hemoglobin was reached. Reticulocyte counts were measured on day 4, 7 and 14. Hemoglobin and hematocrit were measured on day 4 and then once weekly till the target hemoglobin (11g) was reached. Serum ferritin levels were measured at the baseline and the end of treatment. In group 3 hemoglobin and hematocrit values were checked on alternate days.

Data are presented as mean ± 1 S D or percentage when appropriate. A “p” Value of < 0.05 was considered significant. Mean values for individual groups were determined by pooling the results of individual patients and dividing it by 20 (no. of observations).

Statistical Analysis: It was done using ANOVA (analysis of variance) and p values were determined. A “p” value < 0.05 was considered statistically significant, <0.01 highly significant, <0.001 very highly significant and <0.0001 extremely significant.

Results
Out of 60 patients, 26 (43%) were males, 34 (57%) were females. In group 1 there were 9 (45%) males and 11 (55%) females. In group 2 also 45% males and 55 % females and in group 3, 8 (40%) were males and 12 (60%) were female patients.

In group A mean age was 37.2 ± 13.5 years and in group B and group C it was 36.45 ± 11.6 and 38.85 ± 11.79 years respectively. The difference in age was nonsignificant (p-value 0.883) between these groups. The difference in baseline parameters was not significant (p-value > 0.05) between these groups. In both the groups hemoglobin levels increased significantly from day 4 (p value < 0.0001). The increment in hemoglobin values continued in both the groups till the end of therapy. However, hemoglobin values were higher in group 2 compared to group 1 on all the days (day 4, 7, 14, 21, 28, 35, and 42). As compared to group 1, group 2 patients had significantly higher increments in hemoglobin throughout the duration of therapy. The difference between two groups was very highly significant (p value < 0.001) at day 7 and highly significant (p value < 0.01) on rest of the days. Reticulocyte count started increasing in both the groups as early as day 4 of therapy. However as compared to group 1, group 2 patients had significantly higher counts (p value < 0.0001) i.e. extremely significant at day 4, day 7 and day 14 of therapy (Table 1). In both the groups hematocrit levels increased significantly from day 4 (p value < 0.0001). The increment in hematocrit values continued in both the groups till the end of therapy. However, hematocrit values were higher in group 2 compared to group 1 on all the days (Table 2). As compared to group 1, group 2 patients had significantly higher increments in hematocrit throughout the duration of therapy. The difference between two groups was extremely significant (p value < 0.0001) at day 4, 7, 14, 21, 28 and 35 and significant (p value < 0.01) at day 42. At the end of the treatment there was a significant rise in serum ferritin values in both the groups (p value < 0.0001) and serum ferritin values came in the normal range in both the groups. There was no statistical difference (p value > 0.05) in the serum ferritin values at the baseline or at the end of treatment among the two groups.
Mean cost of treatment in group 1 was Rs. 1295 ±32.19, in group 2 it was Rs. 6693 ± 28.63 and in group 3 Rs. 5240 ± 35. There is a significant difference (p value < 0.0001) in the cost of treatment among the three groups (Table 3). In group 1 only 1 patient (5%) reported an adverse reaction to treatment, while in group 2 and group 3, 10 & 20 % of patients had some adverse effect as a result of treatment (Table 4). It took 43.3 ± 5.5 days in group 1 to reach the target hemoglobin of 11 g / dl while it required 36.6± 3.1 days in group 2 to reach the target hemoglobin level. Time to reach the target hemoglobin was significantly less (p value < 0.001) in group 2 compared to group 1 (Table 5).

Table 1: Reticulocyte counts (mean ± SD) in % at day 0, 4, 7 and 14

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
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<th>Group 2</th>
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<th>P value</th>
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<tr>
<td>Day 0</td>
<td>1.63</td>
<td>0.44</td>
<td>1.59</td>
<td>0.44</td>
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<td>Day 4</td>
<td>2.50</td>
<td>0.28</td>
<td>3.09</td>
<td>0.44</td>
<td>&lt; 0.0001</td>
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<tr>
<td>Day 7</td>
<td>3.41</td>
<td>0.31</td>
<td>5.30</td>
<td>0.47</td>
<td>&lt; 0.0001</td>
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<tr>
<td>Day 14</td>
<td>3.54</td>
<td>0.37</td>
<td>4.69</td>
<td>0.45</td>
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</table>

Table 2: Mean hematocrit values (%) ± SD at day 0, 4, 7, 14, 21, 28, 35 and 42

<table>
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<tr>
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<th>Group 2</th>
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<tr>
<td>Baseline</td>
<td>18.67</td>
<td>1.47</td>
<td>18.73</td>
<td>1.33</td>
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<td>1.93</td>
<td>22.77</td>
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<tr>
<td>Day 7</td>
<td>22.66</td>
<td>2.13</td>
<td>26.47</td>
<td>2.29</td>
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<tr>
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<tr>
<td>Day 14</td>
<td>26.29</td>
<td>2.40</td>
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<td>Day 21</td>
<td>27.38</td>
<td>2.27</td>
<td>31.03</td>
<td>2.40</td>
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<tr>
<td>P value</td>
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<td>Day 28</td>
<td>29.42</td>
<td>1.92</td>
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<tr>
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<td>Day 35</td>
<td>31.20</td>
<td>1.67</td>
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<tr>
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<tr>
<td>Day 42</td>
<td>32.48</td>
<td>1.73</td>
<td>34.50</td>
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<tr>
<td>P value</td>
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Table 3: Total cost of treatment (Rs. ± SD)

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<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
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<td>Group 1</td>
<td>1295</td>
<td>32.19</td>
</tr>
<tr>
<td>Group 2</td>
<td>6693</td>
<td>28.63</td>
</tr>
<tr>
<td>Group 3</td>
<td>5240</td>
<td>35</td>
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</table>

Table 4: Incidence of side-effects

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<th>No. of patients reporting side-effects</th>
<th>% of total (20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Group 2</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Group 3</td>
<td>4</td>
<td>20</td>
</tr>
</tbody>
</table>

Table 5: Time (Mean ± SD) in days required to reach target Hb

<table>
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<th></th>
<th>Days to reach target hemoglobin</th>
<th>SD</th>
</tr>
</thead>
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<tr>
<td>Group 1</td>
<td>43.3</td>
<td>5.5</td>
</tr>
<tr>
<td>Group 2</td>
<td>36.8</td>
<td>3.1</td>
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Discussion
Effect of Adding Erythropoietin with Iron Sucrose on Hematological Parameters: In the present study, patients in second group were given a combination of iron sucrose and rhEPO. Addition of erythropoietin was associated with statistically significant (p value <0.0001) increase in hemoglobin values from 6.19 ± 0.47 to 7.35 ± 0.54, 8.39 ± 0.62, 9.31 ± 0.55 at day 4, 7 and 14 respectively, which means there was a rise of 2.19 ±0.59 with in first week of treatment. Increase in Hb values at day 14 of treatment was 3.11 ± 0.55. Similar increments have been reported in previous studies25. Significant rise was also seen in hematocrit values, which increased from a baseline value of 18.73 ± 1.33% to 22.7 ± 1, 70%, 26.47 ± 2.29 % and 30.08 ± 2.585 at day 4, 7 and 14 respectively. This mean increase in hematocrit at day 7 of 7.7 ± 2.1% approximates to two blood transfusion units. Reticulocytosis was observed as early as 4th day of treatment with counts on day 7 of therapy being 5.3 ± 0.4% implying a brisk erythropoietin response. Patients were shifted to oral therapy with iron after 14 days of treatment. Target hemoglobin was reached in this group after 36.8 ± 3.18 days.

Effects Of Treatment With Iron Sucrose Alone On Hematological Parameters: Hemoglobin increased from a baseline value of 6.18 ± 0.47 g / dl to 6.91 ± 0.59, 7.52 ± 0.66 and 8.69 ± 0.78 g/dl at day 4, 7 and 14 of treatment respectively. These increments were also consistent with previous studies. Similarly, hematocrit value was also raised to 26.29 ± 2.40% from the initial value of 18.67 ± 1.47% at day 14. Reticulocyte counts also increased during the first 7 days of therapy. It was 3.41 ± 0.31 at day 7 compared to 1.63 ± 0.44% at the start of treatment. Similar to group 2, these patients were also shifted to oral iron after 14 days. It took 43.55 ± 5.53 days to reach target hemoglobin value of 11 g / dl in this group.

Effect on Serum Ferritin Levels: In both group 1 and group2, ferritin levels increased significantly from baseline value (p value < 0.0001). Both the treatments were effective in replenishing the iron stores as evident from normalization of the serum ferritin values by the end of treatment.

Incidence of Adverse Effects: 2 patients experienced urticarial reaction with i.v. iron sucrose which was managed with anti-histamines and 1 patient developed irritation at the site of administration, discontinuation of therapy was not required. rhEPO has thrombogenic potential. Though due to financial constraints, we could not get any specific tests done; but clinically no patient in the rhEPO group developed any thrombotic complication. In the blood transfusion group, 2 patients developed febrile reactions requiring discontinuation of that unit of blood, 2 developed mild urticarial reactions which were managed with antihistamines.

Efficacy Comparison Among Group 1 and Group 2: Rise of Hb and hematocrit in the rhEPO group were more at all days of follow up compared to group of patients receiving iron sucrose alone, difference of rise among the two groups being statistically highly significant (p <0.001 to <0.0001). Reticulocyte responses were also better in rhEPO group with the differences being statistically extremely significant at day 4 and 7 of therapy (p < 0.0001).

Efficacy, Safety and Cost Comparison Among Erythropoietin and Blood Transfusion Group: There was a rise of 2.19 ± 0.59 g/dl within first 7 days of treatment, which is equivalent to rise seen with 2 units of blood transfusion. No adverse effects were attributed to rhEPO in the study while 4 patients in the blood transfusion group developed some adverse reaction.

Cost of Treatment: Cost of treatment incurred on the patient receiving iron sucrose alone was approximately Rs.1295 ± 32.19. In the group receiving rhEPO, total cost of therapy was Rs.6693 ± 28.63. Five units of blood were transfused to each patient in group 3, which resulted in expenditure of approximately Rs.5240 ± 35 per patient.

Conclusion
We conclude that addition of rhEPO to I.V Iron was more effective in correcting anemia as estimated by the increase in reticulocyte count, hematocrit and hemoglobin level. Its use might be limited due to cost but if it can be used as a transfusion alternative, it has the potential to reduce the transmission of HIV, Hep B and Hep C and the risk of allogenic immunization which are responsible for heavy economic burden. It also appears to be an attractive option in patients who are Jehovah’s witnesses. Future studies are required to clearly specify the patients who are most likely to benefit from recombinant human erythropoietin therapy.

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None

Competing Interests
None Declared

References


