

Comparison of Intravenous Iron Sucrose alone Versus Intravenous Iron Sucrose Along With Erythropoietin for Management of Anemia for Gynecological Patients Waiting for Surgery

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ABSTRACT

Background: Anemia is a common in underdeveloped countries and is associated with poor quality of life. The transfusion of blood is a relatively common component in the management of gynecological patients. As blood transfusion is not free of risks, Iron sucrose and recombinant human erythropoietin is an attractive

Aim: To compare the efficacy and safety of subcutaneously administered recombinant human erythropoietin in combination with intravenous iron sucrose versus intravenous sucrose only for the management of iron deficiency anemia in gynecological patients waiting for surgery to avoid blood transfusion, in JPMC Karachi.

Study design: Randomized clinical trial.

Setting: Department of Gynecology and Obstetrics, Ward-8 Jinnah Postgraduate Medical Centre, Karachi.

Duration with dates: One year, from 1st January 2010 to 31st December, 2010.

Methods: Three hundred and thirty four women, fulfilling the inclusion criteria were included. All patients with indications for major gynecological surgery like fibroid uterus, adenomyosis, endometriosis, dysfunctional uterine bleeding with iron deficiency anemia having a mean hemoglobin level of 7gm/dl were selected and the target hemoglobin was 11gm/dl. Patients, who were symptomatic, had chronic bleeding disorder and uncontrolled hypertension was excluded from the study. Sample population was equally divided in two therapeutic groups and then treatment was initiated.

Results: Three hundred and thirty four women fulfilling the inclusion criteria were included in this study. 167 women were included in each group. There was no statistically significant difference in age, weight and pre treatment hemoglobin level of both groups ($p>0.05$), however mean hemoglobin level at day 14 of women given only iron sucrose was 10.59 ± 1.21 gm/dl and of women given iron sucrose with erythropoietin was 11.9 ± 0.62 gm/dl ($p<0.05$). Student's t-test was applied to compare increase in hemoglobin level in two groups. It was found that increase in hemoglobin level of group who received injection erythropoietin plus sucrose was more and this difference was statistically significant. No adverse effects were noticed while giving erythropoietin injections.

Conclusion: The combination of recombinant human erythropoietin and parenteral iron is more effective in stimulating erythropoiesis and in treating iron deficiency anemia in women especially of reproductive age group as compare to only parenteral iron therapy.

Key words: Iron deficiency anemia, Intravenous iron sucrose, Erythropoietin

INTRODUCTION

Worldwide most common reason for anemia is iron deficiency anemia. However the magnitude of the problem in developing countries is enormous due to malnutrition, high parity and poverty and is associated with low quality of life. Most of the patient presenting in Gynae OPD due to abnormal uterine bleeding are anemic. Pre operative blood transfusion is common in such patients, which is associated with risks like longer hospital stays, incompatibility reactions and transmission of viral load^{1, 2}. New products are developing nowadays to correct anemia without blood transfusion. Iron sucrose and recombinant human erythropoietin therapy has changed the management of anemia and established its utility as an alternate to blood transfusion in several specialties. Iron sucrose has already been used in treating anemia due to iron deficiency. Parenteral iron sucrose has several advantages because it is associated with low incidence of severe side effects such as anaphylactic reactions but addition of erythropoietin stimulating agent further

enhances the effects of iron in treating iron deficiency anemia in short duration. The introduction of recombinant human erythropoietin has revolutionized the treatment strategies for patients suffering with anemia of chronic renal disease and chronic heart failure and to improve chemotherapy induced anemia.³ However, its use in gynecological patients presenting with iron deficiency anemia due to blood loss is limited. The major clinical benefits of erythropoiesis stimulating agents are effective treatment of anemia and avoidance of blood transfusion risk.⁴ Erythropoietin is a growth factor that stimulates the production of red blood cell in Iron deficiency anemia. Iron is an essential element for the production of new red blood cells and erythropoietin is the accelerator for the process. These are two basic and mandatory components for production of new red blood cells. Iron deficiency anemia results when either of these two is deficient. Both of these factors are complementary for efficient erythropoiesis. Absence of one of the component makes the process inefficient. Even when both components are available, they must be delivered to the bone marrow coordinately for proper action. There are several different types of erythropoietin like Procrit, Epogen. and Aranesp. The major

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difference between Procrit ,Epogen and Aranesp is that Aranesp is given less often than Procrit. Otherwise, all three agents work equally well in the treatment of anemia. Erythropoiesis stimulating agents (ESA) are generally well tolerated ad structurally and biologically, are similar to naturally occurring protein, erythropoietin. These agents are used to maintain hemoglobin around required level to minimize both blood transfusions as well drug related possible adverse effects. Although role of erythropoietic agents has been appreciated in literature for correction of anemia in gynecological patients but there is limited data available about comparative studies comparing intravenous iron alone versus intravenous iron plus erythropoietin. We conducted this study to compare both theses group to find out, if combination is better than intravenous iron alone or not .The primary aim of study is to increase preoperative hemoglobin levels with rapid recovery of anemia. Results of the study would be applied on patients awaiting elective surgeries because of low hemoglobin levels secondary to iron deficiency anemia to increase hemoglobin and to make them fit for surgery without blood transfusion.

MATERIAL AND METHODS

It was a randomized clinical trial and was conducted in department of Gynaecology and Obstetrics, Jinnah Postgraduate Medical Centre, Karachi for one year from 1st January 2010 to 31th December 2010.The patients attending, Jinnah Postgraduate Medical Centre, out-patient department with iron deficiency anemia and inclusion criteria were enrolled in the study after taking informed consent. Inclusion criteria were age between 25-50 years, mean hemoglobin level 7gm/dl, non-obstetrical patient, no history of blood transfusion and parenteral iron infusion in last 30 days. Exclusion criteria were patients with uncontrolled hypertension, previous history of thromboembolism, allergy to iron sucrose, symptomatic patients and those having ongoing hemorrhage requiring blood transfusion. Sampling technique was by non-

probability purposive sampling. They were counseled regarding purpose, treatment dosage, effects and follow up. Patients were simply randomly assigned to two groups by computer generated list. Hemoglobin and reticulocyte count before starting therapy were recorded in both groups. Group A received 200mg intravenous iron sucrose therapy on three alternate days after test dose and group B, received 200mg intravenous iron sucrose after test dose along with subcutaneous 5,000i.u erythropoietin on three alternate days. Hemoglobin and reticulocyte count were measured on day 4th and final outcome on day 14th. Information was then entered in proforma by the researcher. After collection of data the data entry and analysis were conducted by using statistical package for social science (SPSS) software version 16. Mean ± standard deviation was calculated for age, weight, baseline hemoglobin level & hemoglobin level at day 14.

T- test was applied to see, if the difference between two groups is statistically significant or not. P value of <0.05 was considered significant. The effectiveness of therapy was measured by the increase in hemoglobin following therapy.

RESULTS

Three hundred and thirty four women fulfilling the inclusion criteria were included in this study.167 women were included in each group. Both groups were compared for demographic features like weight and age. Mean age of patients in group (A) was 36.0±5.1 years as compare to group (B), 37.7± 5.7 years (p-value 0.389). Mean weight of patients in Group (A) was 65±5.2 kg as compare to group (B), 64.90±5.3kg (p-value 0.402).Preoperative hemoglobin in group (A) was 7.99±1.1gm/dl while hemoglobin in group (B) was 8.131±1.1gm/dl (p-value 0.345). Hemoglobin level at day 14 in group (A) was 10.5±2.1 while in group B it was 11.9±0.6 (p-value <0.05). No adverse effects were noticed while giving erythropoietin injections.

Comparison of mean age, weight, pre &post therapy hemoglobin level between two groups

Group	Age (yrs)	Weight (Kg)	Baseline hemoglobin (Gm/dl)	Hemoglobin at day 14 (Gm/dl)
Iron sucrose only Group A (n=137)				
Mean	36.09	65.32	7.99	10.59
Std. Deviation	5.19	5.29	1.18	1.21
Iron sucrose with erythropoietin Group B (n=137)				
Mean	37.75	64.90	8.13	11.93
Std. Deviation	5.75	5.35	1.11	0.62
P value	0.389	0.402	0.354	<0.05

Data given as mean± SD, n= Number of cases

DISCUSSION

Anemia due to heavy menstrual bleeding is one of the most common causes of iron deficiency anemia leading to general tiredness, weakness in patients. Prevalence of iron deficiency anemia in Pakistan is up to 53%.⁵ Large number of patients planned for elective surgery having anemia are women. ⁶ Blood transfusion has been traditionally the fastest method to treat anemia and to make patient fit for surgery, in spite of all its associated risks, like longer hospital stays, incompatibility reactions and transmission of viral load.^{1,2} To avoid blood transfusion iron sucrose has been used to increase hemoglobin level for last few

decades.⁷ However it has been seen that iron alone takes longer time to have an effect and its effect is weaker than when combined with erythropoietin. Preoperative correction of anemia is emerging as a possible alternative to blood transfusions. Iron sucrose and recombinant human erythropoietin is an attractive and safe alternative combination for the management of anemia. Erythropoietin is synthesized in the kidney and to a minor degree in the liver, erythropoietin is the primary regulator of human erythropoiesis. Erythropoietin is a glycoprotein hormone.⁸ Tissue hypoxia causes release of erythropoietin into plasma where it binds with receptors which are located on

red blood cell precursors located in bone marrow .Erythropoietin induces proliferation and differentiation of precursors of red cells ⁹.

In our study .mean hemoglobin level at day 14 of women given only iron sucrose was 10.59 ± 1.21 gm/dl and of women given iron sucrose with erythropoietin was 11.93 ± 0.62 gm/dl ($p < 0.05$) It was found that there was statistically significant difference in hemoglobin level of group who received injection erythropoietin plus sucrose (p value < 0.05). The current study also found that there was rapid rise in reticulocyte on day 4 in group B showing efficient process of erythropoiesis. Ayesha Nasir, et al. ¹⁰ locally conducted a study to determine the efficacy and safety of subcutaneously administered recombinant human erythropoietin in combination with intravenous iron sucrose for the management of iron deficiency anemia found that at the end of 10 days of starting therapy increase in hemoglobin was on an average of 2.8gm/dl .The study concluded that recombinant erythropoietin along with iron sucrose safely increased the hemoglobin level.

Consistent with our study, Francesco Sesti et al reported the effect of rhEPO on reducing the need for blood transfusion in patients undergoing gynecologic surgery. ^{11,12,13} Erythropoietin is also gaining popularity as a therapeutic option during pregnancy and the postpartum period. Krafft A, Breyman C et al in their study compared efficacy and safety of intravenously administered iron sucrose with and without adjuvant recombinant human erythropoietin for the treatment of iron-deficiency anemia during pregnancy. ^{14,15} Forty patients with iron-deficiency anemia were randomly assigned to receive intravenously iron sucrose plus recombinant human erythropoietin or iron sucrose alone twice weekly .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 11($P < .01$), and the median duration of therapy was shorter (18 vs 25 days), with more patients reaching the target hemoglobin level by 4 weeks of treatment.

Breyman C , in another study found that iron sucrose plus rhEPO was more effective in correcting pregnancy anemia than was iron sucrose alone, as estimated by the increases in reticulocyte count, hematocrit, and hemoglobin level. Patients who received rhEPO reached the target hemoglobin level earlier ^{16, 17}.

Current study results confirm the findings of prior studies regarding the increase in level of hemoglobin with highly statistical significance ($p < 0.05$).

All the patients in our study showed increase in hemoglobin to target value. All the patients commented on an overall improvement in the quality of life from 3rd day of therapy and increased reticulocyte count on day 4. Another study was conducted by _Abd El Raheem Mostafa_ to compare the effect of recombinant human erythropoietin and iron or iron alone on blood transfusion requirements in elective myomectomy patients. There was a significant increase in Hb (g/dL) and Hct % ($p < 0.0001$) in group who received iron plus erythropoietin as compared to group with only iron and control group ¹⁸.

Our patients were followed up for 3 months after surgery and did not report any serious drug related adverse effects. However, an associated increased risk of blood

clots has been reported in some recent studies ^{19,20} .This risk can be reduced by avoidance of predisposing factors like prolonged period of bed rest , encouraging mobilization and with use of blood thinner as a prophylactic measure in high risk patients who are being treated with(ESA) erythropoiesis stimulating agents.

Administration of only intravenous iron for correction of anemia is never associated with increased risk of thromboembolic complication because it never leads to supra-physiological increase in Hb level & thrombocytosis, as can happen with high doses of erythropoiesis stimulating agents.²¹ However it has been seen that iron alone takes longer time to have an effect and its effect is weaker than when combined with erythropoiesis stimulating agents. Besides thromboembolic complications other possible adverse effects associated with ESA therapy are flu-like symptoms, headache, tachycardia, nausea, vomiting, diarrhea, pain at the site of the injection. ESA use is contraindicated in patients with preexisting uncontrolled hypertension. However we didn't notice any adverse effect due to injection except few patients' complained of pain at the site of injection. Therapy with an ESA should be individualized to achieve and maintain hemoglobin levels within the range of 10 to 12g/dl in order to avoid a blood transfusion while limiting risk of adverse event. Further studies are needed to evaluate their use in older patients with higher risk for thrombosis and hypertension.

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