

Management of iron deficiency anaemia in gynaecological patients at Jinnah Postgraduate Medical Centre, Karachi

Ayesha Nasir, Haleema Yasmin, Razia Korejo

Department of Obstetrics and Gynaecology, Jinnah Postgraduate Medical Centre, Karachi.

Abstract

Objective: To determine the efficacy and safety of subcutaneously administered recombinant human erythropoietin in combination with intravenous iron sucrose for the management of iron deficiency anaemia in gynaecological patients in Jinnah Postgraduate Medical Centre Karachi.

Methods: It was an interventional quasi experimental study carried out in the department of Obstetrics /Gynaecology, at JPMC from 1st Nov 2007 to May 2008. All patients with indications for major Gynaecological surgery with iron deficiency anaemia having a mean haemoglobin level of 7gm/dl were selected and the target haemoglobin was 11gm/dl.

Patients who were symptomatic, had chronic bleeding, renal failure or had signs of anaemia other than iron deficiency were excluded from the study.

All investigations were done on day one before the start of therapy, and then treatment was initiated with recombinant human erythropoietin in a dose of 5000 IU subcutaneously and injection Iron Sucrose 200mg in 100cc NaCl intravenously on 3 alternate days. The parameters checked in succession on day 4 and day 10 included increase in haemoglobin level, haematocrit, reticulocyte count, and time required to reach the target haemoglobin.

Results: Twenty three patients fulfilled the inclusion criteria and were selected for the study. At the end of 10 days of starting therapy increase in haemoglobin was on an average of 2.8gm/dl, increase in mean corpuscular volume was 4fl, Serum Iron increased by 99.86ug%, total iron binding capacity decreased by 30.86%, transferrin saturation increased by 15.5%. There were no serious reactions to Erythropoietin or Iron sucrose.

Conclusion: It is concluded that recombinant erythropoietin along with iron sucrose safely increased the haemoglobin level in 10 days to the target level thus rendering the patients fit for surgery and, none of the selected patients needed blood transfusion.

Keywords: Iron deficiency anaemia, Erythropoietin, Iron sucrose, Blood transfusion (JPMA 61:998; 2011).

Introduction

The production of red cells involves the interaction between bone marrow which produces red cells and the kidney which produces the hormone erythropoietin. Hypoxia of the kidney prompts synthesis and release of erythropoietin which travels to the bone marrow via the blood circulation and activates new red blood production. Erythropoietin therefore is part of a finely-tuned feedback circuit that controls red blood cell levels.

Erythropoietin is a glycoprotein hormone, synthesized predominantly in the kidney, that promotes the differentiation of erythroid progenitor cells and therefore it regulates the production of red blood cells. In addition, it stimulates the synthesis of haemoglobin.¹

In recent years, recombinant human erythropoietin (r-HuEPO, Epoetin Alfa) has become readily available and has been recommended for the treatment of anaemia. Epoetin Alfa has been shown to accelerate erythropoiesis

and reduce the requirement for blood transfusion in patients undergoing gynaecological surgery.²

This study was undertaken to determine the efficacy and safety of subcutaneously administered recombinant human erythropoietin along with intravenous iron sucrose in the management of iron deficiency anaemia in patients awaiting elective gynaecological surgery.

Patients and Methods

It was an interventional study carried out in the department of Obstetric/Gynaecology at Jinnah Postgraduate Medical Centre, Karachi, from 1st Nov 2007 to May 2008.

All those patients with indications for major Gynaecological surgery having a mean Haemoglobin level of 7gm/dl with iron deficiency anaemia confirmed by low Serum Ferritin and increased Iron binding capacity were selected after informed consent. They were all admitted for correction of anaemia prior to surgery and the target

haemoglobin was 11gm/dl.

Patients who were symptomatic, had chronic bleeding, renal failure or signs of anaemia other than iron deficiency were excluded from the study.

All investigations including blood complete picture, reticulocyte count, Total iron binding capacity (TIBC), Transferrin saturation (TSAT) were drawn on day one, before the start of therapy. Treatment was given with a dose of 5000 IU recombinant human erythropoietin subcutaneously and injection Iron Sucrose 200mg in 100 cc NaCl intravenously.

This was repeated on successive 3rd and 5th days thereby a total of 3 doses on 3 alternate days were given. The parameters checked in succession on day 4, and day 10 included increase in haemoglobin level, haematocrit, reticulocyte count, and the time required to reach the target haemoglobin of 11gm/dl.

Results

Twenty three patients who fulfilled the criteria were selected and admitted for correction of anaemia but the results could be analyzed for twenty two patients as one had to be excluded due to severe bleeding and needed blood transfusion. At the end of 10 days of starting therapy all patients responded positively with a mean increase in Haemoglobin being ± 2.8 gm/dl. The changes in other parameters were also satisfactory (Table).

The highest rise in haemoglobin was 6.8gm/dl in one

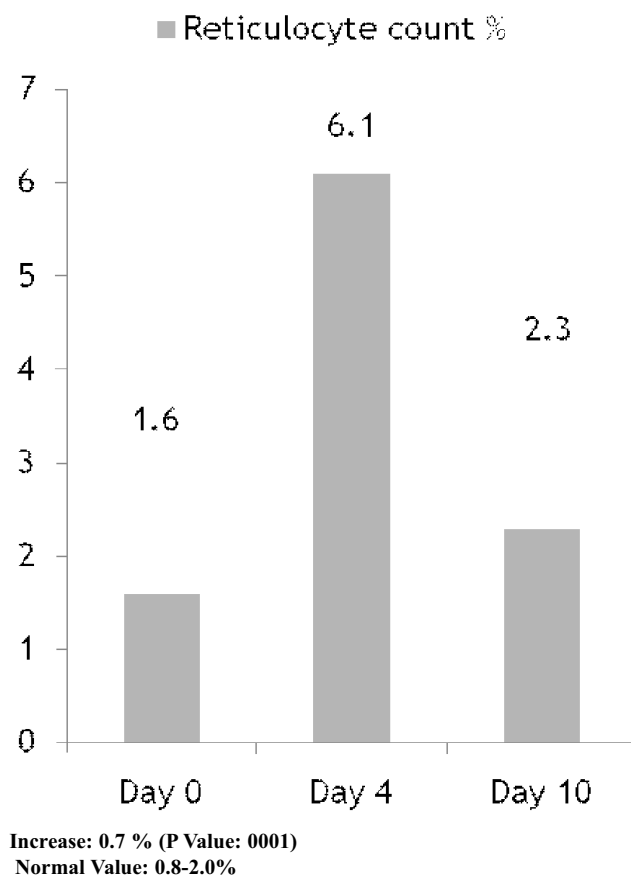


Figure: Changes in reticulocyte count.

Table: Change in findings following epo administration.
Mean $\pm$ SD values of HB, PCV, MCV, Reticulocyte count and transferrin saturation with duration.

Parameter	Day 0 (Mean) (SD)	Day 4 (Mean) (SD)	Day 10 (Mean) (SD)	Increase after 10 days	P- values
Hemoglobin gm/dl	7.3 $\pm$ 1.93	8.2 $\pm$ 2.08	10.1 $\pm$ 1.86	2.8	0.024*
Packed cell volume	26.7 $\pm$ 7.06	29.1 $\pm$ 6.26	34.1 $\pm$ 4.76	7.4	0.031*
Mean corpuscular volume fl	70.7 $\pm$ 9.78	72.9 $\pm$ 7.68	80.4 $\pm$ 6.52	9.7	0.028*
Reticulocyte count%	1.6 $\pm$ 0.71	6.1 $\pm$ 3.98	2.3 $\pm$ 2.30	0.7	0.023*
Transferrin saturation%	11 $\pm$ 21.05	27 $\pm$ 26.92	24 $\pm$ 14.34	13	0.021*

Mean Age: (years): 42.7 $\pm$ 10.1 years.
Mean Body weight(Kgs): 66.6 $\pm$ 12.1 kgs.
*Significant
-Chi Square.

patient and 6.0gm/dl in two patients where Haemoglobin was raised from 6.4 to 13.2 gm and from 4 to 10gm/dl respectively (Figure).

Day 4 results clearly indicated the high rate of reticulocytosis i.e 6.1 against initial 1.6, and even on day 10 it was 2.3, indicating accelerated erythropoiesis (Figure).

The overall quality of life in all the patients included in this trial improved dramatically from 3rd day onwards. There were no serious reactions to Erythropoietin or iron sucrose.

Discussion

In a developing country such as Pakistan, where poverty, malnutrition and high parity prevails, iron deficiency anaemia is a frequent finding in maximum number of female patients awaiting surgery, which not only delays the surgery but also increases the morbidity as patients resort to transfusions to get fit for surgery.

Other international studies have also indicated that a large number of patients scheduled for elective surgery

having anaemia are women in majority, and a third amongst them have iron deficiency anaemia.³

In Iron Deficiency anaemia, Iron is the required fuel for the production of new red blood cells and Erythropoietin is the accelerator that drives erythropoiesis. When the two are coupled, red cell production moves briskly and efficiently. If one component is absent (e.g. iron deficiency) anaemia results.

Even when both components are available, they must be coordinately delivered to the bone marrow for proper action. For instance, if iron arrives on the scene 6 hours after erythropoietin reaches the bone marrow, red cell production will be suboptimal.

If however high dose of iron is administered the iron deficiency induced upregulation of Erythropoietin will drop due to acute uptake of erythropoietin by shifted erythroid precursors.

From the viewpoint of erythropoietic regulation, the subsequent down-regulation of erythropoietin in the mid to late phases is considered appropriate for the prevention of haemoglobin over production.⁴

Evidence of the interplay between iron and erythropoietin has existed for a number of years. For instance, subjects who needed surgery for GI bleeding but refused transfusion because of religious beliefs sometimes developed extremely low haematocrit due to very severe iron deficiency and responded very dramatically to iron therapy as reported by Dudrick.⁵ Replacement of iron by intravenous infusion dramatically increased blood cell production. In some reports, haemoglobin rose from 3 gm/dl to 9 gm/dl over the course of 14 days.⁵

On the other hand are subjects who have very high iron stores but very low erythropoietin levels. Historically this was seen most clearly in patients with chronic renal failure who required haemodialysis. Because these subjects lacked kidney function, they failed to produce the erythropoietin needed for erythropoiesis and therefore suffered with anaemia of renal failure.

With the cloning of the erythropoietin gene, the drug became available for use in the late 1980's. The haematocrit of anaemic patients with chronic renal failure rose dramatically with erythropoietin treatment.^{6,7}

Iron stores were quite high in these early subjects all of whom had been on maintenance transfusion therapy prior to the introduction of erythropoietin. Iron overload from transfusions had been a serious problem.

Erythropoietin increased both the red cell mass and haematocrit in these subjects and this enhanced cell production which manifested itself as a rise in the plasma iron turnover (PIT) and a decrease in the half-time of iron in the plasma. However, the plasma ferritin level of these patients

dropped substantially despite quite adequate iron stores.

This was the first indication that erythropoietin used in high doses could drive red cell production more rapidly than iron could be delivered to the bone marrow even in subjects with adequate iron stores.⁸

We found in our study population that there was a marked and rapid increase in the Haemoglobin and patients became fit for General anaesthesia and surgery 10 days after the start of therapy.

In a study of patients with gestational iron-deficiency anaemia⁹ forty were randomly assigned to receive intravenous iron sucrose plus recombinant human erythropoietin versus intravenous iron sucrose alone. It was seen that Adjuvant recombinant human erythropoietin safely enhanced the efficacy of iron sucrose in the treatment of gestational iron-deficiency anaemia. Both regimens were effective, but with adjuvant recombinant human erythropoietin the reticulocyte counts were higher from day 4 ($p < 0.01$), increase in haematocrit was greater from day 11 ($p < 0.01$), which is similar to our findings.

The median duration of therapy was 18 days, whereas in our study the total duration was 10 days where 22 patients reached the target haemoglobin without any need for transfusion.

The introduction of recombinant human erythropoietin (RHUEPO) has revolutionized the treatment strategies for patients suffering with anaemia of chronic renal disease and chronic heart failure. Clinical studies and several observational evidences have demonstrated that RHUEPO is also useful in various non-uraemic conditions including haematological and oncological disorders, prematurity, HIV infection and preoperative anaemia correction.¹⁰

Recombinant human erythropoietin is given after chemotherapy and used in the treatment of solid tumours.¹¹ and has been seen to improve chemotherapy-induced anaemia in children. Erythropoietin has also been used as performance enhancing drug in athletes.¹²

All the patients in our study underwent their respective surgeries and did not need any further blood transfusion. These patients were followed up for 3 months and did not appear to have any serious side effects. All the patients commented on an over all improvement in the quality of life from 3rd day of therapy

Conclusion

It is concluded that recombinant erythropoietin along with iron sucrose safely increased the haemoglobin level in 10 days to the target level thus rendering the patients fit for surgery and, none of the selected patients needed blood transfusion.

Use of this combination therefore seems to be promising in times to come.

References

1. Bieber E. Erythropoietin, the biology of erythropoiesis and epoetin alfa. An overview. *J Reprod Med* 2001; 46 (5 Suppl): 521-30.
 2. Larson B, Bremme K, Clyne N, Nordstrom L. Preoperative treatment of anemic women with epoetin beta. *Acta Obstet Gynecol Scand* 2001; 80: 559-62.
 3. Goodnough LT, Vizmeg K, Sobecks R, Schwarz A, Soegiarso W. Prevalence and classification of anemia in elective orthopedic surgery patients: implications for blood conservation programs. *Vox Sang* 1992; 63: 90-5.
 4. Takahashi Y, Umadome H. Decrease serum erythropoietin level induced by iron replacement therapy in patients with iron deficiency anemia. *Rinsho Ketsueki* 1999; 40: 290-8.
 5. Dudrick SJ, O'Donnell JJ, Raleigh DP, Matheny RG, Unkel SP. Rapid restoration of red blood cell mass in severely anemic surgical patients who refuse transfusion. *Arch Surg* 1985; 120: 721-7.
 6. Eschbach JW, Egrie JC, Dwonig MR, Browne JK, Adamson JW. Correction of the anemia of end-stage renal disease with recombinant human erythropoietin. *N Engl J Med* 1987; 316: 73-8.
 7. Eschbach JW, Haley NR, Adamson JW. New insights into the treatment of the anemia of chronic renal failure with erythropoietin. *Seminars in Dialysis* 1990; 3: 112-21.
 8. Hotta T, Ogawa H, Saito, A, Ito A. Iron balance following recombinant human erythropoietin therapy for anemia associated with chronic renal failure. *Int J Hematol* 1991; 54: 195-200.
 9. Breymann C, Visca E, Huch R, Huch A. Efficacy and safety of intravenously administered iron sucrose with and without adjuvant recombinant human erythropoietin for the treatment of resistant iron-deficiency anemia during pregnancy. *Am J Obstet Gynaecol* 2001; 184: 662-7.
 10. Annieruth Helena D, Jyothsna A, Lakshmi N, Rao P J, Rao GV, Rao KRSS. Therapeutic implications of recombinant human erythropoietin in anaemic related clinical manifestations. *African J Biotechnol* 2006; 5: 2503-9.
 11. Adamson JW, Spivak JL. Physiologic basis for the pharmacologic use of recombinant human erythropoietin in surgery and cancer treatment. *Surgery* 1994; 115: 7-15.
 12. Adamson JW, Vapnek D. Recombinant erythropoietin to improve athletic performance. *N Engl J Med* 1991; 324: 698-9.
-