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# THE EFFICACY OF PRE-OPERATIVE ERYTHROPOIETIN THERAPY

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## ABSTRACT

*Objective:* **To determine whether a single weekly low dose of erythropoietin (EPO), haematenics and antimalarials is effective in increasing the pre-operative haemoglobin of patients coming for potential blood losing surgery.**
*Design:* **A prospective observational study.**
*Setting:* **The Korle-bu Teaching Hospital, Accra, Ghana.**
*Subjects:* **Thirty one patients with low haemoglobin scheduled for potential blood losing surgery.**
*Results:* **A mean weekly dose of EPO administered of 10,840 ± 640 IU raised the haemoglobin by 2-5g% above baseline levels in 28 (90.3%) of the patients. Twenty five (81%) of the patients had an uneventful normovolaemic haemodilution during their surgery.**
*Conclusion:* **A single weekly dose of 150 ug/kg of EPO, haematenics, chloroquine (anti-malarial) and a high protein diet is efficacious in raising the pre-operative haemoglobin in Ghanaian patients.**

## INTRODUCTION

Erythropoietin (EPO) is a glycoprotein hormone produced by the renal tubular, peritubular and mesangial cells that causes committed stem cells to be converted to red blood cells. Since 1989 recombinant human erythropoietin (rHuEPO) has been used for the treatment of anaemia of chronic renal failure (1). Recently EPO has been used pre-operatively to increase the red-cell mass and to allow blood to be harvested for autologous blood transfusion in patients including Jehovah's Witnesses (JW's) (2-4). The increasing incidence of HIV, hepatitis B and hepatitis C has created an awareness of dangers of blood transfusion and also blood conservation (5). It is also known that allogenic blood transfusion increases the recurrence of cancer by immunomodulation (6). Ghanaian patients are now aware that under certain circumstances they can be transfused with their own blood during surgical procedures and that the use of EPO will increase their chances of autologous blood transfusion. Haemoglobin augmentation and treatment of anaemia at the Korle-Bu hospital is usually done using ferrous sulphate and chloroquine is added to prevent malaria-associated haemolysis (7,8). EPO has recently been introduced in the Korle-Bu Teaching Hospital for haemoglobin augmentation. This study was undertaken because the effectiveness of EPO in increasing the pre-operative haemoglobin, and therefore reducing the need for allogenic blood, has not been studied in Ghana.

## MATERIALS AND METHODS

This was a prospective observational study carried out from 1st January 2001 to 30th June 2002 at the Korle Bu Teaching Hospital, Accra. Enrolled into the study

were patients with low haemoglobins (Haemogloin <12 g%), including Jehovah's Witnesses, being prepared for surgery and who opted for autologous blood transfusion. In the Jehovah's Witnesses being prepared for open heart surgery a haemoglobin of less than 13g% was considered to be low. Excluded were patients with strokes, varicose veins and previous deep vein thrombosis. Also excluded were patients whose systolic blood pressures were above 160 mmHg and diastolic pressures greater than 110 mmHg. After checking the pre-operative haemoglobins patients were given subcutaneous injections of 150ug/kg of EPO (RECORMON[R]) for a period of three to four weeks. The haemoglobin was subsequently checked weekly and also changes in the blood pressure of the patients. The injections were stopped if the checked haemoglobin was more than 15.0g%. The patients were also given iron supplements in the form of ferrous sulphate 50mg and 200mg three times daily for the child and adults respectively. Weekly chloroquine of 300mg for adults and 60mg for the two year old, and a high protein diet of fish, meat and beans were also given. The blood pressure of all our patients were taken weekly during the study. The lower limbs of the patients were examined for swelling, redness or pain to exclude venous thrombosis. Data were collected to ascertain the number of patients who had autologous blood transfusion. All the patients completed the study.

The cost of 2000iu of EPO was ascertained from the hospital pharmacy. The data were quantitatively analysed and the standard deviation calculated for most of the variables.

## RESULTS

Thirty one patients were treated with EPO during the 18-month period. Their mean age was 35.8 ± 4.9 years. The Jehovah's witnesses made up 38.7% (12) of all the patients and five (16.1 %) of them were being prepared for open-heart surgery. Five (16.1%) of the patients were being prepared for general surgery and the rest, 21 (67.8%) were being prepared for gynaecological surgery (Table 1).

The mean dose of erythropoietin given was 10,840 ± 641 iu / week. The average cost of 2000 units of erythropoietin was 170,000.00 cedis (US$ 15.30). Thus the cost of a weekly mean dose of EPO of 10,840iu was about 935,000.00 cedis (US$104.00).

Pre-treatment mean haemoglobin was 10.8 ± 1.0g% with a range of 9.0-13.0g% (Table 2). Nineteen of the patients had a starting haemoglobin of between 9.0-11.0g% and 12 of the patients had haemoglobins above 11.0g%. The post-treatment mean haemoglobin was 13.9 ± 1.1g% with a range of 12.3g%-16.6g%. The highest post-EPO treatment haemoglobin of 16.6g% was in a Jehovah's Witness patient being prepared for open heart surgery.

**Table 1**

*Demographic characteristics, religion and type of surgery*

| Age (year) | JW | Other Christians | Type of surgery | | | | No. (%) |
|---|---|---|---|---|---|---|---|
| | | | General surgery | Open-heart Surgery | Myomectomy | Hysterectomy | |
| 1-10 | 1 | - | 1 | - | - | - | 1 3.2 |
| 11-20 | 2 | - | 1 | 1 | - | - | 2 6.5 |
| 21-30 | 2 | 2 | 1 | 2 | 1 | - | 4 12.9 |
| 31-40 | 4 | 8 | 1 | 1 | 5 | 5 | 12 38.7 |
| 41-50 | 3 | 9 | 1 | 1 | 2 | 8 | 12 38.7 |
| Total No. (%) | 12 (38.7) | 19 (61.3) | 5 (16.1) | 5 (16.1) | 8 (25.8) | 13 (42.0) | 31 100 |

**Table 2**

*Changes in the haemoglobin*

| Haemoglobin (g%) | Pre-EPO No. | (%) | Post-EPO No. | (%) |
|---|---|---|---|---|
| 9.1-10.0 | 6 | 19.4 | – | |
| 10.1- 11.0 | 13 | 41.9 | – | |
| 11.1-12.0 | 7 | 22.6 | – | |
| 12.1-13.0 | 5 | 16.1 | 9 | 29.0 |
| 13.1-14.0 | – | | 3 | 9.7 |
| 14.1-15.0 | – | | 11 | 35.5 |
| 15.1-16.0 | – | | 4 | 12.9 |
| 16.1-17.0 | – | | 4 | 12.9 |
| Total | 31 | 100 | 31 | 100 |

**Table 3**

*Average increase in the haemoglobin*

| Haemoglobin (g%) | No. | (%) |
|---|---|---|
| 2.1-3.0 | 8 | 25.8 |
| 3.1-4.0 | 12 | 38.7 |
| 4.1-5.0 | 8 | 25.8 |
| 5.1-6.0 | 3 | 9.7 |
| Total | 31 | 100 |

The mean increase in the haemoglobin after EPO therapy was about 3.7± 1.0g% with a range of between *2.2-5.8g%* (Table 3). Twenty eight (90.3%) of the patients had an increase of between *2.0-5.0g%*. The highest increase of *5.8g%* was in a JW patient with a low starting haemoglobin of 9.1 g% who was scheduled for open heart surgery.

There was no change in the blood pressure of our patients during the study. There was also no clinical evidence of venous thrombosis in any of the patients during the study.

Twenty five (81%) of the patients had normovolaemic haemodilution during their surgery.

## DISCUSSION

Recently there has been heightened awareness of blood safety and blood conservation methods for religious reasons and also as a result of the increasing incidence of hepatitis B and C and HIV AIDS (5). Alternatives to blood transfusion are being promoted including the use of recombinant human erythropoietin, to reduce dependency on allogenic blood in surgery.

The first three patients who received EPO in the study were all Jehovah's Witnesses who were being prepared for open-heart surgery. Jehovah's Witnesses made up 38.7% of our patients, who, for Bible based reasons refuse allogenic and some forms of autologous blood transfusions. They however accept alternatives to blood, including the administration of EPO, which has been used extensively for JW's throughout the worl d (4,10). The potential of EPO outside treatment of chronic renal failure is just being recognised in Ghana.

Sonzogni *et al* (6) in a previous study administered EPO to children being prepared for open-heart surgery to increase the pre-operative donation of autologous blood. We used EPO for two Jehovah's Witness children aged two and 14 years. Although no autologous blood donation was performed in the two-year-old girl in the study, it allowed hypervolaemic haemodilution and therefore successful surgery. The average age of the patients in this study was however 35.8 ± 4.9 years.

The EPO treatment dose of 150iu/Kg body weight per week was low as compared to earlier studies where doses of 300-600iu/Kg per week were used (2,6,11). The higher doses of EPO used in these studies may have been due to the fact that the pre-donation method of autologous blood transfusion was performed and patients were bled one unit of blood weekly. Most of the patients in the current study however were being prepared for normovolaemic haemodilution and we were able to reach the target haemoglobin with the lower doses of EPO. Milbrink *et al* in their study used a dose of 180iu/Kg / week in divided doses and still had good results with predonation of autologous blood (12).

The cost of a weekly dose of EPO of 10,840iu was about 935,000.00 cedis or US$ 104.00. The lower dose, which gave reasonable results, suits a third world country like Ghana where EPO, although reasonably priced, is not within the reach of most patients. The single weekly dose of EPO was used as compared to most of the other studies who used three divided doses per week for the treatment of their patients (2,6,10,11). The single weekly dose made compliance easier for our patients.

All the patients were prescribed iron supplements in the form of ferrous sulphate as was done in

the other studies (2,3,6,10,11). Patients were also prescribed dietary protein supplementation, antihelminthics to treat potential hookworm infestation and a weekly prophylactic dose of chloroquine to prevent breakdown of the red blood cells by falciparum malaria.

The staple food in Ghana is carbohydrate based and there was the need to advice the patients to increase the protein in their diet to augment haemopoeisis. Falciparum malaria is endemic in the West African sub-region and is known to cause significant anaemia especially in children (7). Frimpong-Boateng *et al* have employed anti-malarial treatment in a previous study for haemoglobin augmentation in Jehovah's Witnesses (8).

EPO of 150iu / week was effective in raising the haemoglobin by an average of 3.7g% ± 1.0. This was comparable to the results an earlier study where an increase of 3.4g% was observed (10). An increase of 3.0g% was recorded with a similar weekly dose of erythropoietin in a Jehovah's Witness patient being prepared for liver tranplantation (13). A few of the patients with low starting haemoglobin's had increases above 4.0g%. The use of EPO would benefit patients with bleeding uterine fibroids as the haemoglobin would increase rapidly and surgery could be done before the next heavy menstrual bleed. The highest haemoglobin was in a JW patient being prepared for open-heart surgery for a defective aortic valve. It is important to note however that EPO was stopped when the haemoglohin was about 15g%. This was to prevent hyperviscosity syndrome with possible intravascular thrombosis, which can occur with very high haemoglobin's and haematocrits (14). There was however no adverse effect associated with the use of EPO in our study.

The use of EPO allows for successful use of all types of autologous blood transfusion, including postoperative blood salvage during surgery (2,3,6,10,11). Twenty five of the patients had successful normovolaemic haemodilution during their surgery.

It is concluded that single weekly doses EPO of 150iu/Kg, together with haematenics, protein supplementation and chloroquine (anti-malarial) is efficacious in raising the pre-operative haemoglobin in Ghanaian patients. The weekly single dose of EPO makes compliance easier. This increase in the haemoglobin improves the chances of autologous blood transfusion and therefore a reduction in the transfusion requirements of allogenic blood.

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