Administration of recombinant human erythropoietin in patients with gynecological cancer before radical surgery

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Summary

The purpose of this prospective study was to investigate the efficacy of preoperative administration of recombinant human erythropoietin in patients with gynecological cancer.

Methods: The study included 38 women with gynecological cancer who were divided randomly in two groups. Study group A included 20 women with gynecological cancer who received recombinant human erythropoietin (rHuEPO) plus iron supplementation for ten days before surgery and five days postoperatively. Group B (controls) included 18 patients who received only iron supplementation for the same time period. Blood samples were obtained on days -10, -3, 0, +3, +5, +10.

Results: The mean hemoglobin level was significantly higher in group A than in group B on the day of the operation and remained significantly higher postoperatively while an inverse relationship was observed for mean ferritin values in the two groups.

Conclusion: Preoperative administration of rHuEPO in patients with gynecological cancer seems to be effective in the blood management of these patients.

Key words: Gynecological cancer; Anemia; Erythropoietin.

Introduction

Preoperative blood management in cases of gynecologic cancer with significant anticipated perioperative blood loss is traditionally done either with allogeneic blood transfusions or with autologous blood donations. Allogeneic blood transfusion, apart from the widely recognized risks of reactions and transmission of blood-born diseases, also exerts an immunosuppressive effect, which could be detrimental for cancer patients. Indeed, allogeneic blood transfusion has been associated with an increase in postoperative infection risk and a deterioration in survival in cancer patients [1-3]. However, preoperative recombinant human erythropoietin (rHuEPO) treatment has recently been shown to be a cost-effective alternative. Pre- and perioperative administration of erythropoietin has been effective in contemplating perioperative blood loss in both benign and malignant gynecologic conditions.

The aim of this randomized controlled trial was to assess the efficacy of this medication in women being operated on for gynecological cancer with radical operations, to control for toxicity of the drug in women with a weak immune system, to assess the impact of this regimen in reducing surgical waiting time, and finally to evaluate the impact of rHuEPO in the rate of blood transfusions.

Material and Methods

This prospective clinical trial included 38 women with gynecological cancer who underwent radical abdominal surgical methods. The participants were randomly allocated into two groups: Group A (study group) included 20 patients who were treated with rHuEPO plus iron supplementation, and Group B (controls) included 18 patients who were given only iron supplementation. Iron was given to all women at a dose of 200 mg/d, whereas women in Group A additionally received rHuEPO 200 U/kg body weight (BW) daily for ten days preoperatively and five days postoperatively. Iron supplementation was given throughout the study period. Randomization was accomplished by using a random number generator and both operators and patients were unaware of their grouping; controls were given similarly looking subcutaneous injections of only water on the same days. The rHuEPO or placebo syringes were contained in sealed, opaque envelopes. Administration of the syringes and blood sampling took place at the tertiary institute or local hospitals by personnel not directly involved in the study. All women were extensively informed about the purposes of the study and gave their consent.

Laboratory monitoring included full blood count, reticulocytes, transaminases, electrolytes, creatinine, iron, and folic acid level, three times preoperatively and three times postoperatively (on days -10, -3, 0, +3, +5 and +10, where day 0 is the day of the operation). Arterial blood pressure was monitored twice daily and all women were administered low molecular weight heparin thromboprophylaxis.

Intraoperative blood loss was estimated by measuring the amount of blood aspirated and weighing the gauze pads.

Pyrexia, thrombotic events and need for blood transfusion were recorded in all women.

Statistical analyses were carried out by SPSS (SPSS, Inc., Chicago, IL) and StatXact-3 (Cytel Software Corporation, 1993).

Results

Nineteen women were operated on for cervical cancer, nine for ovarian and ten for endometrial cancer. The mean age of women was similar in both groups. The preoperative hemoglobin levels and intraoperative blood loss were also similar; however, mean hemoglobin in group A

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was significantly higher than that of group B on the day of surgery and remained significantly higher thereafter (Table 1 and Figure 1). An inverse relationship was observed for mean ferritin levels in the two groups (Table 1).

Table 1. — *Descriptive data of patients.*

Parameter	Group A	Group B	95% CI in the difference of the means
Mean age (yrs.)	48.6 [7.6]	46.9 7.1 [1]	
Mean hgb on day -10 (g/dl) [SD]	10.6 [0.8]	10.7 [0.7]	
Mean hgb on day -3 (g/dl) [SD]	11.5 [0.8]*	10.9 [0.8]*	0.01 to 1.04
Mean hgb on day 0 (g/dl) [SD]	12.1 [0.6]**	11.2 [0.7]**	0.46 to 1.32
Mean hgb on day +3 (g/dl) [SD]	10.7 [0.7]**	9.8 [0.9]**	0.39 to 1.44
Mean hgb on day +5 (g/dl) [SD]	11.0 [0.7]*	10.5 [0.6]*	0.13 to 0.97
Mean hgb on +10 (g/dl) [SD]	11.9 [0.7]**	10.9 [0.5]**	0.52 to 1.31
Mean ferritin on day -10 (ng/ml)	56.6 [13.9]	61.5 [12.3]	
Mean ferritin on day -3 (ng/ml)	57.2 [13.3]**	72.8 [12.1]**	-23.9 to -7.1
Mean ferritin on day 0 (ng/ml)	52.3 [10.8]**	79.1 [10.6]**	-33.9 to -19.7
Mean ferritin on day +3 (ng/ml)	65.0 [9.9]**	93.6 [10.0]**	-35.2 to 22.0
Mean ferritin on day +5 (ng/ml)	68.8 [8.8]**	96.7 [9.8]**	-33.9 to 21.7
Mean ferritin on day +10 (ng/ml)	113.1 [7.4]**	140.2 [9.8]**	-32.8 to 21.4
Mean intraoperative blood oss (ml) [SD]	565 [121]	538 [140]	
Mean postoperative hospitalization days [SD]	7.9 [0.7]	9.1 [1.0]	

*$p < 0.05$; **$p \leq 0.001$.

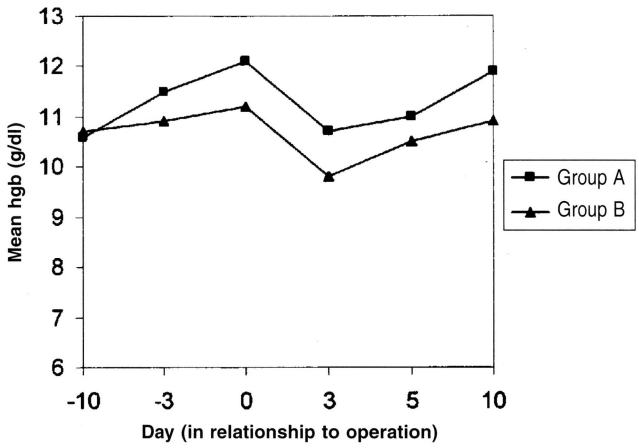

Figure 1. — Mean hemoglobin levels in groups A and B.

Patients who received rHuEPO stayed in the hospital fewer days than the patients in the control group, however this difference was not significant. Blood transfusions were required in three of the patients in group B (two units each), but none in group A.

Postoperative fever was observed in three cases in each group, the highest temperature was < 39°C in all cases and it was resolved in less than 36 hours. No adverse reactions attributed to the drug were recorded.

Discussion

In our study we used a high dose of rHuEPO and administered the drug both pre- and postoperatively to maintain stable blood levels, as the maintenance of these levels is considered to determine its effectiveness.

Administration of rHuEPO was shown to rapidly and significantly increase the mean hemoglobin level, thus ensuring higher hemoglobin at the time of surgery and postoperatively. Moreover, it was associated with a decreased need for blood transfusions and lack of toxicity.

Preoperative treatment with rHuEPO in gynecological cancer patients may be useful in multiple ways. It can be used in cases where transfusions is denied for religious reasons, and it can decrease the need for blood transfusions, which should nonetheless be avoided in oncologic patients as they are adversely associated with prognosis [4-7]. Increased mean hemoglobin level can be beneficial per se, as low hemoglobin concentrations may induce vasculogenesis in malignancies resulting in faster growth and more aggressive behaviour. It facilitates potential postoperative treatment with chemotherapy, radiotherapy or both, and it has been reported to improve quality of life and even prognosis [8-11].

In accordance with our previous findings in a population with benign gynecological disease [12], the increase in hemoglobin concentration in the rHuEPO group was accompanied by a significant drop in ferritin levels. This was attributed to iron incorporation for erythropoiesis [13], and it has been hypothesized that functional iron deficiency may occur in cancer patients receiving rHuEPO and may account for the lack of response in up to half of those patients [11]. This finding underlines the need for sufficient iron supplementation with rHuEPO treatment.

Although we do not have long-term outcomes available, perioperative rHuEPO treatment in gynecological cancer patients seems to be effective in terms of perioperative blood management, eliminates the need for blood transfusions, appears safe and may decrease hospital stay. Moreover, in comparison to autologous blood transfusions, it may offer greater convenience and less time committment for patients [14].

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