Recombinant human erythropoietin in mildly anemic women before total hysterectomy

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Summary

The purpose of this study was to investigate the efficacy of preoperative recombinant human erythropoietin (rHuEPO) treatment in a group of mildly anemic women.

Methods: This randomized controlled study included 50 healthy, mildly anemic women who underwent total hysterectomy for leiomyomas. The study group (Group A) included 23 women who received rHuEPO 600 U/kg once weekly for three weeks, plus iron supplementation. The control group (Group B) included 27 women who received only iron supplementation. Blood samples were obtained on days -14, -7, 0, +3, +7 and +14.

Results: An increase in preoperative mean hemoglobin concentration was noted in both groups; however, the increase was significantly higher in Group A throughout the study period. Mean reticulocyte count was also significantly higher in this group, whereas mean ferritin level was significantly lower. No postoperative transfusion was needed in Group A, whereas five women were transfused in Group B.

Conclusion: Rapid and persistent improvement of hematologic parameters makes the use of rHuEPO for preoperative treatment of mildly anemic women with benign uterine pathology a very interesting approach.

Key words: Hysterectomy; Leiomyoma; Erythropoietin; Anemia.

Introduction

Hysterectomy is one of the most frequent surgical procedures performed. In a Danish cohort study, the life-time prevalence of hysterectomy was 10.4%, with 40-year-old women having the highest rate (7.9 per 1,000) [1].

The most common indication for hysterectomy is benign uterine pathology, mainly uterine leiomyomas. Many of these patients have a history of abnormal uterine bleeding and present with low preoperative hematocrit levels. Moreover, a mean blood loss of approximately 800 ml is usually anticipated in a total hysterectomy for leiomyomas [2]. Preoperative blood management in such cases can be done either with allogeneic blood transfusions, or with autologous blood donations or recombinant human erythropoietin (rHuEPO) treatment.

Allogeneic blood transfusion has been associated with several risks, so preoperative autologous blood donations and rHuEPO therapy have become favorite alternatives in recent years. However, autologous blood donations can lead to development of anemia [3, 4], which can be a drawback in cases of women who already have decreased hematocrit levels. Preoperative treatment with rHuEPO can facilitate the collection of a sufficient amount of autologous blood in a short period of time without causing severe anemia [5].

This study was carried out in order to investigate whether preoperative rHuEPO treatment without an autologous blood transfusion could fulfill regular perioperative blood needs in a group of mildly anemic women with benign uterine pathology.

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Materials and Methods

This prospective clinical trial included 50 healthy women who, before they underwent abdominal total hysterectomy because of uterine leiomyomas, were randomly allocated into two grours: Group A (study group), who were treated with rHuEPO plus iron supplementation, and Group B (controls), 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 600 U/ml SC once weekly for three weeks (preoperative days -14, -7 and the morning before the operation). Iron supplementation was given throughout the study period. Randomization was done by using a random number generator and both operators and patients were unaware of their grouping; controls were given similarly looking subcutaneous injections with normal saline on the same days. All women were extensively informed about the purposes of the study and gave their consent.

Eligibility criteria included absence of major medical illness (including hemoglobinopathies, other blood disorders and malignancies), age between 30 and 60 years, baseline hemoglobin level ≥ 9 and < 12 g/dl, body weight between 50 and 80 kg, ferritin > 50 ng/ml and uterine leiomyomas demonstrated by means of ultrasonography. Baseline laboratory examinations were done on day -14 and they were repeated on days -7, 0, +3, +7 and +14. Baseline investigations included a complete blood count, reticulocyte count, ferritin, transaminases, blood urea nitrogen, creatinine, glucose, electrolytes and lactate dehydrogenase. Complete blood count, reticulocyte count and ferritin levels were also measured thereafter. Intraoperative blood loss was estimated by weighing suction content and surgical tampons before and after surgery.

Outcome measures included need for blood transfusion, hemoglobin, reticulocyte and ferritin levels, as well as length of postoperative hospitalization.

Statistical analyses were conducted in SPSS (SPSS, Inc., Chicago, IL) and in StatXact-3 (Cytel Software Corporation, 1993).

Results

Fifty women were included in the study; 23 received rHuEPO (Group A), whereas 27 received only iron supplementation (Group B). None of the women had received GnRH analogues preoperatively.

Descriptions of the two groups of women are presented in Table 1.

Baseline laboratory investigations did not show any differences between the two groups. Both rHuEPO plus iron supplementation and iron supplementation alone induced an increase in mean Hgb levels in the corresponding groups until the time of operation. However, a more profound increase of Hgb concentration was observed in Group A, and there was a significant difference in mean Hgb levels between the two groups throughout the study period. On day 3, mean Hgb concentration had fallen in both groups, followed by a gradual increase. Mean Hgb concentration at the end of the study was higher than baseline in Group A and lower than baseline in group B ($p < 0.001$ in both instances). Alterations in mean Hgb levels are presented in Figure 1.

Similarly, there were differences in reticulocyte count patterns between the two groups. A significant difference between the two groups appeared on day -7 ($p < 0.001$) and it persisted until the 14th postoperative day. The alterations in reticulocyte count of the two groups are shown in Figure 2.

In Group A, a constant decrease in ferritin levels was observed throughout the study period, resulting in significantly lower mean concentrations than observed in Group B, despite the fact that both groups were receiving the same regimen of iron supplementation. Ferritin alterations during the study period are shown in Figure 3.

Mean intraoperative blood loss was approximately 600 ml and it did not differ between the two groups. Mean length of postoperative hospitalization did also not differ between the two groups.

Table 1. — *Results of the study.*

Parameter	Group A	Group B	95% CI of the difference of the means
Mean age (yrs)	48.2 [4.1]	49.2 [4.7]	
Mean Hgb on day -14 (g/dl) [SD]	10.3 [4.1]	10.4 [4.6]	
Mean Hgb on day -7 (g/dl) [SD]	11.2 [0.7]*	10.5 [0.6]*	0.3 to1.1
Mean Hgb on day 0 (g/dl) [SD]	11.9 [0.7]**	10.7 [0.7]**	0.8 to 1.6
Mean Hgb on day +3 (g/dl) [SD]	10.3 [0.8]**	8.8 [0.7]**	1.9 to 2.0
Mean Hgb on day +7 (g/dl) [SD]	10.7 [0.8]**	8.8 [0.7]**	1.4 to 2.3
Mean Hgb on +14 (g/dl) [SD]	10.8 [0.2]**	9.1 [0.7]**	1.3 to 2.1
Mean rcc count on day -14 (%) [SD]	1.96 [0.17]	2.00 [0.22]	
Mean rcc count on day -7 (%) [SD]	4.00 [0.45]**	1.96 [0.21]**	1.80 to2.20
Mean rcc count on day 0 (%) [SD]	4.90 [0.45]**	2.04 [0.24]**	2.66 to 3.06
Mean rcc count on day +3 (%) [SD]	5.26 [0.44]**	2.31 [0.21]**	2.66 to 3.06
Mean rcc count on day +7 (%) [SD]	4.92 [0.39]**	2.55 [0.20]**	2.71 to 2.53
Mean rcc count on day +14 (%) [SD]	4.47 [0.32]**	2.53 [0.20]**	2.11 to 2.52
Mean ferritin on day -14 (ng/ml)	65.2 [14.7]	68.5 [11.6]	
Mean ferritin on day -7 (ng/ml)	55.0 [13.9]*	68.4 [11.7]*	-6.1 to -20.7
Mean ferritin on day 0 (ng/ml)	43.7 [11.1]**	68.3 [10.4]**	-18.4 to -30.8
Mean ferritin on day +3 (ng/ml)	36.4 [10.4]**	62.5 [10.1]**	-20.1 to -31.9
Mean ferritin on day +7 (ng/ml)	33.4 [9.6]**	59.1 [9.6]**	-20.2 to -31.1
Mean ferritin on day +14 (ng/ml)	29.8 [8.7]**	54.7 [9.8]**	-19.6 to -30.2
Mean intraoperative blood loss (ml) [SD]	645 [116]	593 [130]	
Mean postoperative hospitalization (d) [SD]	7.6 [0.5]	7.8 [0.9]	

Hgb: hemoglobin, rcc: reticulocyte, SD: standard deviation.
*Significant at the level of 0.001; *Significant at the level of < 0.0001.

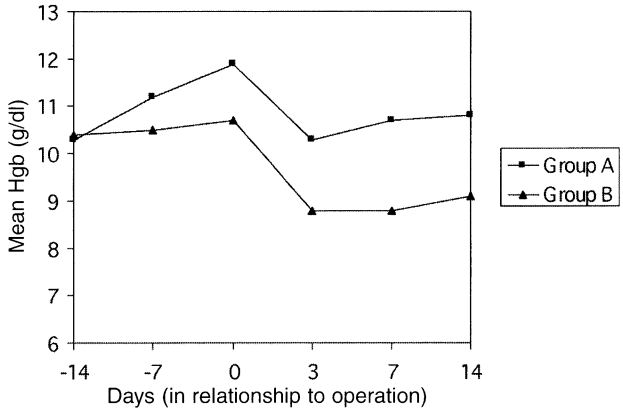

Figure 1. — Mean Hgb concentration.

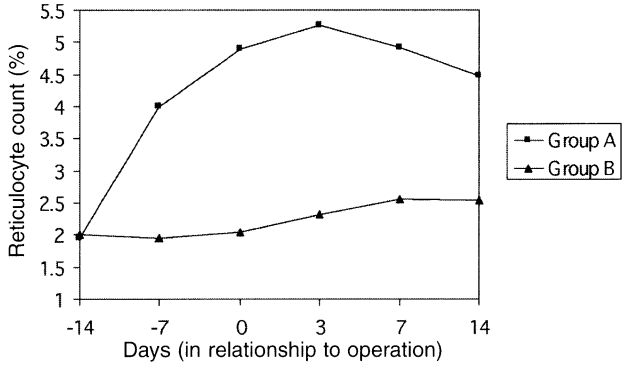

Figure 2. — Mean reticulocyte count.

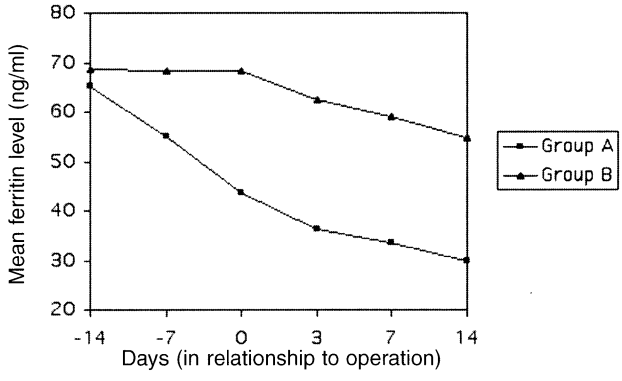

Figure 3. — Mean serum ferritin concentration.

None of the women in the study group needed a blood transfusion, whereas five controls received two units of packed red cells each. Application of Fisher's exact test yielded a significant difference between the two groups ($p < 0.05$).

There were no adverse instances during the postoperative period that could be attributed to rHuEPO administration. Local adverse reactions did not occur and subcutaneous injections of rHuEPO were generally well tolerated. There was also no difference in febrile episodes between the two groups (two per group and transient in all cases). No major postoperative complications occurred in either group.

Discussion

Our results show that administration of subcutaneous rHuEPO together with iron supplementation improves hematological indices in mild preoperative anemia and maintains a better postoperative Hgb than iron supplementation alone. rHuEPO causes a rapid increase in mean reticulocyte count and mean hemoglobin levels, and this effect is already profound at the time point of operation.

The haematopoietic influence of rHuEPO in treated patients is reflected in the higher reticulocyte counts in this group, compared to the corresponding values of the study group. It is of interest that the difference in mean reticulocyte count between the two groups persisted throughout the study period.

Another feature of treatment with rHuEPO is that improvement in haematological indices is accompanied by a decrease in ferritin levels [6]. In our study, mean ferritin levels were already decreased on preoperative day 7, and this decrease was significantly greater in the study group than in controls, despite adequate iron supplementation in both groups. Data coming from patients with chronic renal insufficiency indicate that rHuEPO therapy results in low ferritin values because of iron incorporation for erythropoiesis, and iron deficiency limits the effectiveness of rHuEPO therapy [7]. In the chronic renal failure population, functional iron deficiency is the most common cause of inadequate response to rHuEPO and it has been hypothesized that functional iron deficiency may also occur in cancer patients receiving rHuEPO and may account for the lack of response in up to half of those patients (for a review see Galspy and Cavill) [8].

Recombinant HuEPO can be administered either subcutaneously or intravenously, in single or multiple doses. There are studies suggesting that lower doses of rHuEPO may be required to achieve a target hematocrit when the hormone is administered subcutaneously compared with intravenously. The possible mechanisms for this include sustained stimulation of the erythroid progenitor cells, diminished inhibition of erythropoiesis by proinflammatory cytokines, and prevention of neocytolysis with subcutaneous administration (for a review see Kaufman) [9]. Thus the cost of epoetin is reduced substantially when administered subcutaneously [10]. Several dosing regimens have been tried. Among them, administration of 150 U/kg three times a week and administration of 600 U/kg SC once weekly for four weeks have shown similar favorable effects on hemoglobin levels. We chose the second regimen because of its simplicity. No adverse effects, either local or systematic (e.g. hypertension) were reported during treatment, indicating that this regimen seems to be safe in this population of patients.

There are data showing that preoperative treatment with rHuEPO has favourable effects in cases of urologic [11-13], gynaecologic [5, 14-16] and orthopedic [17] surgery. In a previous study addressing preoperative administration of rHuEPO in anemic women scheduled to be operated on for leiomyomas, rHuEPO was shown to effectively increase preoperative Hgb levels compared to iron supplementation only [9]. However, in contrast to these results, the present study demonstrated a persistent difference in mean Hgb levels throughout the study period, together with a persistent difference in mean reticulocyte count and ferritin levels. However, the dosing regimen was different between the two trials, which could, at least partially, account for these discrepancies.

Given the costs and potential dangers from blood and blood component use, transfusion policy tends to become more strict during the last years [18]. There are several cost-effectiveness analyses, concerning mainly patients with end-stage renal disease and malignancy, yielding various results. In a cost-effectiveness analysis concerning surgery for non-malignant disease (coronary artery bypass graft surgery), the authors conclude that if allogeneic blood-related infections were to be considered, epoetin would be an acceptable intervention [19]. Moreover, rHuEPO therapy is comparable in cost to preoperative autologous blood donations and offers patients greater convenience and less of a time commitment [12].

Conclusion

Rapid and persistent improvement of hematologic parameters, together with reduction in need for transfusion, makes the use of rHuEPO for preoperative treatment of mildly anemic women with benign uterine pathology a very interesting approach.

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