

Managing anemia in gynecologic surgery with postoperative administration of recombinant human epoetins

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Summary

Objective: To investigate whether postoperative administration of erythropoietin can safely augment in the rapid restoration of hemoglobin (Hgb) values following major gynecologic surgery.

Methods: Thirty-three women were enrolled. They had all undergone gynecologic surgery due to malignant or non-malignant reasons. Because of chronic blood loss, many of these patients were iron depleted. Examinations of hematology, serum chemistry and urinalysis values were obtained. Subcutaneous administration of r-HuEPO, in a dosage of 40,000 IU was initiated on the first postoperative day. One additional injection of 40,000 IU was given on the fourth day after surgery. Contemporarily the patients received orally a polysaccharide-iron complex.

Results: During the early postoperative period three patients that were transfused due to severe anemia and one more that was lost in follow-up were excluded from the study analysis. The remaining 29 patients showed a considerable rise in Hgb counts that reached a median value of 1.9 g/dl within a 20-day period.

Conclusion: The postoperative administration of r-HuEPO in gynecologic surgery in patients where autologous blood transfusions can be avoided is challenging, since it can guarantee an uneventful postoperative period with rapid resuscitation without posing the patient to the well-established risks of transfusions.

Key words: Hematocrit; Hemoglobin; Recombinant human epoetin alpha; Gynecologic surgery; Postoperative administration; Recovery; Quality of life.

Introduction

Perioperative anemia is a common complication of gynecologic surgery, and in recent years various articles have proven conclusively that the preoperative administration of Recombinant human epoetin alpha – in different protocols – is efficient in avoiding perioperative blood transfusion [1, 2].

Blood transfusion is associated with well recognized, inherent and unavoidable risks, such as infectious disease transmission, adverse immunologic reactions, sensitization to histocompatibility antigens, fluid overload, emerging infections, prolonged hospital stay and a possible immunosuppressive effect; besides stored blood is often of limited accessibility [2].

Other treatment approaches except red blood cell (RBC) transfusion are hematinic supplementation (iron, folates, vitamin B₁₂), GnRH agonists and recombinant human erythropoietin (r-HuEPO).

Despite the fact that the vast majority of gynecological surgery is elective, another, large proportion is performed under urgent circumstances, thus not allowing strategies of preoperative correction of anemia. Hemoglobin levels correlate inversely with transfusion requirements. A considerable number of patients, with borderline RBC count and hemoglobin values may also become anemic after surgery.

The aim of our study was to define the effectiveness of postoperative administration of recombinant human erythropoietin in the rapid rise of hemoglobin levels.

Materials

We conducted a prospective study at the Gynecologic Department of Patras University Hospital between January 2003 and February 2004. We recruited patients with a normal or anemic preoperative hematology status who underwent gynecologic surgery that resulted in the onset or deterioration of previously established anemia. Thirty-three patients were initially recruited. The ages varied between 24 and 73 years, the median value being 52 years old. Enrollment stopped when an arbitrarily preset one-year period expired.

Of the 33 patients, five had malignant disease and 28 benign. Four women with endometrial cancer underwent total abdominal hysterectomy, and one with ovarian cancer total abdominal hysterectomy plus bilateral salpingo-oophorectomy and omentectomy. In the group of benign pathology, five women with dysfunctional uterine bleeding underwent abdominal hysterectomy, three with uterine prolapse underwent vaginal hysterectomy, two with endometriosis underwent excision of the endometriotic lesions, one with an adnexal mass underwent total abdominal hysterectomy plus bilateral salpingo-oophorectomy, while from the vast majority of the remaining 17 patients with myomas, five underwent myectomy, and 12 total abdominal hysterectomy.

Initial hematocrit and hemoglobin counts varied widely. Median values of preoperative hematocrit and hemoglobin were 11.1 g/dl and 34.2%, respectively.

Due to heavy menses in the majority of patients resulting in prolonged blood loss, many women included in the study had iron deficiency as defined by a mean serum ferritin below the lower reference value (100 ng/ml) and transferrin saturation less than 15%. Serum ferritin levels serve as a dependable gauge of total iron stores, and a low serum ferritin level is virtually diagnostic of iron deficiency. Ferritin levels are inversely proportional to the duration and intensity of menstrual bleeding, indi-

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cating that anemia is more likely to occur in patients with gynecologic bleeding and may be associated with iron deficiency [3].

Analyses were performed before and after surgery of blood concentrations of folates, hemoglobin, leukocytes, platelets, erythrocyte volume fraction, and reticulocytes. Serum concentrations of folates, vitamin B12, bilirubin, ferritin, haptoglobin, iron, and total iron-binding capacity were measured by standard methods at the central laboratory.

Measurement of aspirated blood volume and the weight of sponges used during surgery were used to estimate blood loss. The estimated intraoperative surgical blood loss ranged from 400-1700 ml.

Four patients (12.12%) received RBC transfusions intraoperatively - two received one unit, one received two units, and the fourth three units. Transfusion was indicated when the hemoglobin level decreased to less than 8 g/dl or if the patient showed clinical signs of hypovolemia.

Methods

Three patients with a hgb < 7.5 g/dl or hct < 24% count immediately post surgery were transfused with one or two units of heterologous RBC's. The two of them had also been previously transfused during surgery. Therefore, all the patients studied had on the first postoperative day a hgb concentration > 7.5 g/dl and a hct value > 24%.

Recombinant r-HuEPO administration was indicated for women with a hemoglobin concentration of < 11.0 g/dl or a hematocrit value > 33.0%.

Baseline hemoglobin and hematocrit counts were considered those of day 1 post surgery, which were correlated with those of the 20th postoperative day.

Treatment with r-HuEPO (*EprexTM*, 40,000 IU Janssen - Cilag, Athens, Greece) subcutaneously was initiated on the first postoperative day (administration of the first dose - 40,000 IU). A second dose (40,000 IU) was administered on day 4 after surgery. In addition these patients received orally a polysaccharide-iron complex corresponding to 200 mg of elemental iron per day.

Iron supplementation started simultaneously with the first dose of recombinant human epoetin alpha and was continued for at least a period of two months.

Pharmacologic prophylaxis for the prevention of deep venous thrombosis was obtained.

The safety and tolerability of r-HuEPO was evaluated by the observed adverse events and laboratory hematology tests.

Results

Erythropoietin therapy was relatively well tolerated. Concerning the major side-effects, mild pyrexia occurred in nine patients (27.27%), nausea in six cases (18.18%), whereas skin reactions at the injection site in five patients (15.15%). One patient (3%) developed thrombocytosis, which could be associated with the administration of r-HuEPO. No thrombotic or vascular events occurred in the study group. No allergic reactions were observed.

Repeat examinations of hematology, serum chemistry and urinalysis values were taken. All tests were analyzed at the central laboratory. A slight increase in platelet concentrations postoperatively was not statistically significant. The variables of iron status (ferritin, transferrin,

haptoglobin, iron, and total iron-binding capacity) showed progressive amelioration. No hemolytic disorders were observed.

The vital signs were constant. Blood pressure measurements did not imply any significant changes.

After the first postoperative day three patients despite the appropriate measures each received two more units of heterologous RBC's (two of them had also been previously transfused immediately post surgery), which accounts for 9.09% of the initially recruited women. These patients were excluded from the interpretation of r-HuEPO efficacy.

Additionally, one patient (3.03% of the total) did not attend the day 20 appointments.

When the remaining 29 patients were examined prospectively on the 10th and 20th postoperative day, they all presented a considerable rise in hemoglobin counts that reached - for the remaining 29 patients a median value of 1.9 g/dl (range 1.6-2.3 g/dl), for this 20-day period. Median hemoglobin concentrations increased for the patients that were subject to analysis from a median value of 8.8 g/dl on the first postoperative day, to a median value of 9.6 g/dl on the 10th postoperative day, to reach a median value of 10.7 g/dl on the 20th postoperative day (Figure 1).

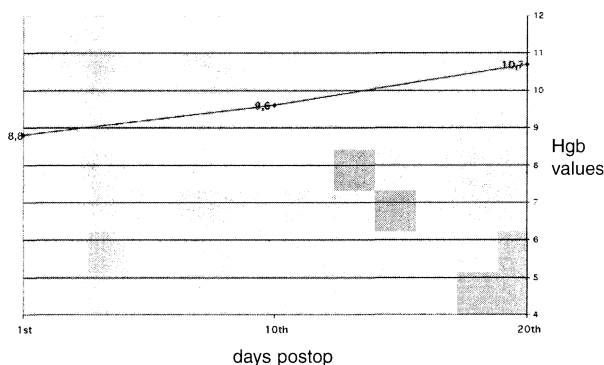


Figure 1. — Mean hemoglobin values (dots) from baseline on postoperative day 1, on the 10th postoperative day and the 20th postoperative day. The rise in hemoglobin values in the study group has a linear-like pattern.

Of note is also the fact that this rise seemed to continue throughout the following weeks, although this perception could not be confirmed due to loss of follow-up in many [12] patients, which is the reason why these data are not exhibited.

Discharge from the clinic was delayed in nine patients. Six patients left the hospital one day later and three others had two days of additional hospitalization. The reasons that account for these delays were mainly correlated with anemia (6 patients), febrile episodes (2 patients), and complications from the surgical wound (1 patient).

Conclusions

Anemia can vastly affect surgical outcome by increasing morbidity. Therefore it is very likely that a combination of r-HuEPO and iron enables patients to achieve a steeper rise in hemoglobin during the early postoperative period, thus enabling patients to soon regain full recuperative power.

Since the hemoglobin and hematocrit values correlate with the patients quality of life parameters and given that most of the patients had benign pathology, the treatment of anemia might moderate undesirable symptoms like fatigue and weakness enhancing recuperative power and vigor during early postoperative recovery.

Loss of energy, reduced vitality and fatigue are consequences of anemia related to gynecologic bleeding for many patients [3-5]. Fatigue is the most common symptom (91%) after hysterectomy, even more prevalent than pain [4].

Bieber [6] in his article stresses certain aspects on the biology of erythropoiesis with clinical importance.

In gynecologic surgery the administration of r-HuEPO in cases where autologous blood transfusion can be avoided is challenging, since it can guarantee an uneventful postoperative period with rapid resuscitation without posing the patient to the well-established risks of transfusions.

Several efforts were made for the correction of anemia in gynecologic patients from the time that r-HuEPO became clinically available [7-10]. In all cases the investigators reached similar conclusions; most studies indicated a medium-to high efficacy of r-HuEPO administration.

We are not unaware of the fact that our study might suffer from some discrepancies:

First, since our study was not a two-sided, blinded, prospective investigation, an expected postoperative rise in hematocrit and hemoglobin values that represents the natural course of events in an anemic patient was not taken into account. We should note here that Larson *et al.* [1] in their study of preoperative r-HuEPO administration in patients with benign pathology (uterine myoma) questioned the addition of r-HuEPO to the conventional iron supplementation therapy, citing that these two approaches might be of equal efficacy.

Second, intravenous fluid administration on postoperative day 1 might have resulted in a misinterpretation of the initial hct figure below the actual values due to hemodilution, while on day 10 and 20 this administration had well-before discontinued.

Third, our patients were not consistent concerning their total iron gauges; both serum ferritin and transferrin saturation varied largely within our study group therefore they might not have responded in a similar manner to r-HuEPO administration. Moreover, this is the reason we omitted interpretation of ferritin, transferring, haptoglobin, iron, and total iron-binding capacity alterations during the study period. Iron depletion states reflect the often-urgent character of gynecologic surgery; therefore prolonged recruitment periods would be necessary if pre-

requisites concerning iron saturation parameters were preset.

Our investigation was also out of the rationale of the so-far administration of r-HuEPO, which is usually given as prophaxis. However, r-HuEPO has also been used in the past in obstetric patients in a non-prophylactic setting [11].

The points made in this paper do not imply in any way that the postoperative administration of r-HuEPO is superior to the early preoperative one, taking into account that the major end point which was no other than the avoidance of blood transfusions, often repeated, was not achieved in six patients (18.2%) in total in our analysis.

Despite the fact that a larger population of patients is required to obtain more valid conclusions, it is evident that health-related quality of life should also be considered in a cost-benefit analysis, as Larson *et al.* [1] also point out.

However our study suggests that r-HuEPO by facilitating postoperative recovery also has a place in the treatment of the postoperative anemic patient who undergoes major gynecologic surgery.

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