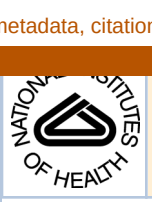



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# The Effect of Presurgery Recombinant Erythropoietin on Post-surgery Hematocrit following Orthognathic Surgery

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## Abstract

**Purpose—**Compare the post-surgery red cell mass as indicated by hematocrit value of orthognathic surgery patients given iron supplementation and a single presurgery dose of erythropoietin alpha(EPO) and patients who did not receive either EPO or iron supplementation (NEPO).

**Subjects and Methods—**Subjects who had a Lefort I osteotomy(LFI) or a combination of a LFI and bilateral sagittal split osteotomy(BSSO) between 2005 and 2008, and were at least 13 years of age, were included. Subjects were excluded if they had a history of maxillofacial trauma, a craniofacial syndrome, or a major systemic medical condition. Subjects had either the drug administered with iron supplements prior to surgery(EPO; Surgeon A protocol) or received neither (NEPO; Surgeon B protocol). Venous blood samples were taken, in accordance with clinic protocol, before surgery (before administration of EPO) and on post-surgery day 1. Multiple linear regression with backward selection was used to analyze the change in hematocrit value. Explanatory variables included group, pre-surgery hematocrit, age, gender, length of surgery, blood loss, and crystalloid (fluid replacement) volume.

**Results—**178 eligible patients were included: 86 patients (48%) had a combination LFI and BSSO and 92 patients (52%) an isolated LFI. 114 (64%) had erythropoietin alpha/ iron supplements administered presurgery, while 64 did not. The average change in hematocrit as an indicator of the change in red cell mass was statistically significantly different(P= 0.01) for the subjects who received preoperative administration of EPO with iron supplementation compared to



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those who did not receive EPO+Iron. The administration of EPO + iron was protective: the decrease in hematocrit after surgery was smaller for subjects in the EPO group even after controlling for age, gender, preoperative hematocrit, length of surgery, blood loss, and crystalloid (fluid replacement ) volume.

**Conclusions—**A single presurgery dose of erythropoietin with iron supplementation resulted in a smaller decrease, on average, in post-surgery red cell mass as indicated by hematocrit value in patients with complicated orthognathic surgery procedures.

## Introduction

Improvements in orthognathic surgical techniques over time, including a shorter operating time, use of hypotensive anesthesia, local anesthetics with vasoconstriction, blood salvaging methods, and careful management of blood coagulation, have reduced the blood loss that occurs during these procedures. A recent systematic review reported that the blood loss observed in patients during surgery, LeFort I or mandibular ramus osteotomies or both combined, was less than the usual limits set for blood transfusion.[1] However, even if a blood transfusion is not required according to more global guidelines for major surgery, perioperative consequences related to blood loss can result in decreased hemoglobin molecules available to oxygenate tissue. Consequences can potentially affect recovery even in usually healthy patients having orthognathic surgery. These consequences may include decreased endurance and a longer post-surgery healing period.[2–4]

Presurgery administration of erythropoietin alpha may be beneficial by increasing the red cell mass prior to surgery thereby preventing or reducing the reduction in red cell mass that occurs as a result of blood loss during the surgery.[5–7] Baseline hematological parameters for patients who received EPO before a total knee arthroplasty were not significantly different from those who had preoperative autologous blood donation, but the EPO group, on average, had significantly higher hemoglobin, hematocrit, and reticulocyte count by the day of surgery, and this difference remained for 1 to 2 days postoperatively.[5,7] These finding were also reported in a randomized trial of colorectal cancer patients having surgery.[6] Erythropoietin is a glycoproteinic hormone naturally produced by renal cortical interstitial cells. When production is stimulated by tissue hypoxia, erythropoietin interacts with erythrocytes in the bone marrow to increase red blood cell production. The action of erythropoietin alpha is identical to the naturally occurring erythropoietin and the presurgery administration bypasses the physiological mechanisms required for stimulation of production by the kidney.[8]

The presurgery combination of Erythropoietin Alpha, given intravenously or subcutaneously, and oral iron supplementation has been used in orthopedic surgery since the 1990s. The use of erythropoietin alpha in major surgical procedures has been shown to decrease the frequency of transfusion, at surgery and in the immediate post-surgery period.[9–12] These outcomes were beneficial to patients even when the patients had an adequate red cell mass at surgery and did not require a transfusion by usual guidelines.[13] In a randomized trial of patients undergoing primary total joint arthroplasty, patients who received EPO had significantly higher vigor after surgery and required fewer transfusions than those patients who received a preoperative autologous donation.[9] Time to ambulation and time to discharge were significantly longer in patients who had transfusion while undergoing orthopaedic surgery compared to those who received EPO.[10]

The purpose of this retrospective study was to compare the change in red cell mass as indicated by the change in hematocrit values from pre- to post-surgery of orthognathic surgery patients who were given Trinsicon iron supplementation and a single presurgery

injection of erythropoietin alpha(EPO) and patients who did not receive either EPO or iron supplementation.

## Materials and Methods

The medical records of subjects previously enrolled in a study on the stability of orthognathic surgery procedures were reviewed for this retrospective assessment of the effects of EPO. The project was approved by the Biomedical Institutional Review Board. Subjects who had a Lefort I osteotomy (LFI) or a combination of a LFI and bilateral sagittal split osteotomy(BSSO) to correct a developmental dentofacial disharmony between 2005 and 2008, were at least 13 years of age, and healthy (ASA I or II) were eligible. Subjects were excluded if they had a history of maxillofacial trauma, a craniofacial syndrome, or a major systemic medical condition. Data from the medical records of 179 patients were included: 86 patients (48%) had a combination LFI and BSSO and 92 patients (52%) an isolated LFI. No patients received autologous blood pre or post-surgery. During the time frame of this study, only 1 patient received a homologous blood transfusion immediately post-surgery. This patient was excluded from the analysis.

Subjects either had the drug administered with iron supplements prior to surgery (EPO; Surgeon A protocol) or did not receive EPO or iron supplements (NEPO; Surgeon B protocol). Patients in the EPO group were prescribed a one month supply of Trinsicon (Iron, Vitamin C, Intrinsic factor, B12-UCB Inc, Rochester, NY) with instructions to take the supplement for two weeks prior to surgery and for two weeks after surgery. These same patients received a single subcutaneous injection of erythropoietin alpha (40,000U) approximately 1 week prior to surgery. The NEPO group was not given a subcutaneous injection of EPO or Trinsicon supplements.

All surgical procedures for the patients were performed in a similar manner. Each surgical team consisted of one faculty and one senior resident member. All of the surgeries were performed with hypotensive anesthesia, defined by a systolic blood pressure (SBP) of 90mm Hg. or less, maintained during the key points of the procedure in order to minimize blood loss. Specifically, hypotensive anesthesia was maintained at the time of maxillary down-fracture and continued through, at a minimum, the repositioning and fixation of the maxilla.

All presurgery blood samples were obtained at the presurgery workup appointment, but because of the timing of the clinical protocol for presurgery workups, the venous blood sample was obtained prior to the EPO injection. Blood loss at surgery was estimated by consensus between the anesthesiologist and the circulating operating room nurse using the contents of the suction bottle and the sponge count. The volume of fluid replacement (crystalloid) was obtained from the operative notes. The post-surgery venous sample was obtained on post-surgery day 1 prior to discharge. Hematocrit values (g/dL), the percentage of packed red blood cells in a sample of venous blood as a measure of red cell mass, were assessed at both visits and the difference between the pre- and post-surgery values (loss) was calculated.

Bivariate analyses were used to compare the characteristics and outcomes of the EPO and NEPO groups: chi-square analysis for nominal variables (type of procedure, gender, and ethnicity) and Wilcoxon rank sum test for age, length of surgery, blood loss, and fluid replacement. A linear regression model with backward selection was used to analyze the change in hematocrit. Potential explanatory variables were group (EPO vs NEPO), age at surgery, gender, preoperative hematocrit, length of surgery, blood loss, and crystalloid (fluid replacement) volume. Continuous explanatory measures were centered (value - mean ) prior

to analysis. Reference groups were EPO and male. All of the analyses were conducted using SAS (version 9.2).

## Results

Approximately two-thirds of the 178 subjects were female and, on average, 21 years of age (Table 1). Forty-eight percent of the subjects had both a BSSO and LF1. As expected, average length of surgery, estimated blood loss, and fluid replacement were higher for patients having LFI and BSSO as compared to LFI only (Table 1).

114 patients (64%) had erythropoietin alpha/ iron supplements administered presurgery, while 64 patients did not (Table 1). The proportion of subjects in the EPO and the NEPO groups did not differ with respect to the distribution of gender or ethnicity (Table 1). Average presurgery hematocrit, age at surgery, length of surgery, estimated blood loss and fluid replacement volume were not significantly different between the EPO and NEPO patients (Table 1 and 2). However, the proportion of those who had LFI only was significantly different between the two groups, $P<0.01$ (Table 2). A higher percentage of subjects in the NEPO group had LFI only, 70%, as compared to the EPO group, 41%. For subjects having LFI only, the pre to post-surgery decrease in the mean hematocrit was 4.7g/dL for the EPO subjects and 5.4 for the NEPO subjects. Similarly, for subjects having LFI and BSSO the pre to post-surgery hematocrit differential was 8.2 g/dL for the EPO subjects and 10.2 for the NEPO subjects. As expected, the change in hematocrit was inversely related to length of surgery ($r=-.50$; $P<0.0001$), estimated blood loss ($r = -.48$; $P<0.0001$), and volume of crystalloid IV fluid received ($r=-.62$; $P<0.0001$) ie longer surgery times, greater blood loss, and greater volume of fluid received were associated with greater decrease in hematocrit from pre to post-surgery.

Age at surgery was not significantly related to the change in hematocrit after controlling for the other covariates ($P>0.05$). Each of the other explanatory variables were significantly related to the change in hematocrit even after adjustment for the other explanatory variables (Table 3). For example, the loss in hematocrit would be 0.56 g/dL greater for every 100 unit increase in blood loss above the average loss. The average change in hematocrit was statistically significantly different ($P = 0.01$) between the EPO and NEPO groups even after adjusting for pre-surgery hematocrit, sex, length of surgery, estimated blood loss, and fluid replacement volume (Table 3). The administration of EPO with iron supplementation was a protective factor. On average, subjects in the EPO group lost 1.37 g/dL less than those in the NEPO group after adjusting for the other covariates. Being male was also protective in that males tended, on average, to experience less of a decrease in hematocrit than females (Figure 1).

## Discussion

Presurgery administration of Erythropoietin Alpha with iron supplementation in patients having LFI or LFI and BSSO was associated with a statistically significant differential in the reduction in red cell mass pre to post-surgery as measured by hematocrit assessed from venous blood samples. These results demonstrate a statistically significant benefit in using EPO with iron supplementation. We hypothesize that this benefit reflects a maintenance or increase of hematocrit, used in this study as a surrogate for red cell mass, prior to orthognathic surgery as compared to no EPO or iron supplementation. The outcome was achieved with a singlepresurgery dose of EPO. The differential between the EPO and NEPO groups with respect to the loss in hematocrit from before to after surgery was greater for those patients who had LFI and BSSO than for those who had a LFI only: the decrease for patients with 2 jaw surgery in the NEPO group was 2 g/dL greater than in the EPO group

versus 0.7 greater decrease for the LFI only patients in the NEPO group. This suggests that patients that require a more involved and longer orthognathic surgical procedure may benefit more from the administration of EPO than those having a procedure limited to the maxilla. In most instances surgeons can estimate the complexity and the length of a planned surgery during the planning stages and include presurgery EPO when it might be beneficial, particularly to avoid homologous blood transfusion.

In orthopedic surgery, multiple presurgery dosing is common. For example, Feagan et al reported that patients responded best if red cell mass was increased to a higher level before or just after surgery. This was achieved giving 600 IU/kg (~40000U) erythropoietin every week, starting 4 weeks prior to surgery (Days -21, -14, -7, 0)or 300 IU/kg (~20000U) erythropoietin administered daily for 15 days (10 days presurgery and 5 days post-surgery).[11] Either of these two methods combined with daily iron supplementation of at least 200mg/day when receiving erythropoietin were successful in reducing the frequency of transfusion. It should be noted, however, that the blood loss expected with hip replacement surgery exceeds that expected with orthognathic surgery, even with two jaw osteotomies. Although EPO administration is common practice in major orthopedic surgery, this is the first report on the positive effect on hematocrit of EPO administration as a single presurgery dose in orthognathic surgery patients. The benefit, moreover, occurred in healthy, predominately young adults, who prior to surgery had hematocrit values in the normal range.

Autologous blood transfusion has been used effectively to avoid homologous blood use in orthognathic surgery patients at our center for two decades. Subjects were transfused with their own blood only when they were sufficiently awake in the recovery room to identify their signature on the blood storage bag. This procedure minimized the danger of receiving the wrong blood; no orthognathic surgery patients received the wrong autologous blood while this procedure was employed. The use of EPO and iron supplementation was initiated when autologous blood donation with elective surgery was discouraged at our academic center because of the complexity of the administration and the expense use ratio of the required protocols in parallel with protocols for homologous blood. Pola et al have enumerated the possible unwanted clinical side-effects of autologous blood donation and transfusion in addition to the administrative complexity. [14]

Our study has limitations even for patients having orthognathic surgery. The subjects were young and healthy. The same degree of benefit may not accrue to older patients or those with a chronic systemic disease. Only clinical outcomes were measured. It is possible that quality of life outcomes such as the return to a usual lifestyle or sports and recreation may be the most important benefit of maintaining a red cell mass close to presurgery values, particularly for active young adults. The study was not randomized; all the data were gathered retrospectively. Although the surgery protocols and the conduct of the surgery itself are similar at UNC no matter who the attending faculty surgeon is, the subjects were not randomized to surgery team or to administration of EPO. The data on blood loss were estimated in the operating room reasonably accurately, but no data were collected on blood loss in the hours following surgery. In addition, hematocrit offers a reasonable estimate of a patient's red cell mass but values in the post-surgery period are affected by the status of a patient's hydration. The regimen for fluid administration in the operating and recovery room was similar for all UNC patients, but the results were not controlled for the volume and type of IV fluids or colloid administered. Data also were not controlled for body mass index, a variable that could also affect both clinical and quality of life outcomes. However, the data we report has the potential to be beneficial to patients having complex jaw surgery. This study should be followed by a prospective, randomized trial of EPO with iron supplementation in patients who are having LFI/BSSO surgery. Further studies might suggest a benefit to patients from EPO administration with other maxillofacial surgery

procedures. Both clinical and quality of life outcomesin the post-surgery period should be assessed.

How might clinicians interpret and apply our findings at this time? Our data indicate the efficacy of a single dose administration of EPO with iron supplementation. If a complicated and lengthy orthognathic surgery is anticipated, this schedule of EPO administration should be considered as an alternative to homologous or autologous blood administration or no replacement of red cell mass.

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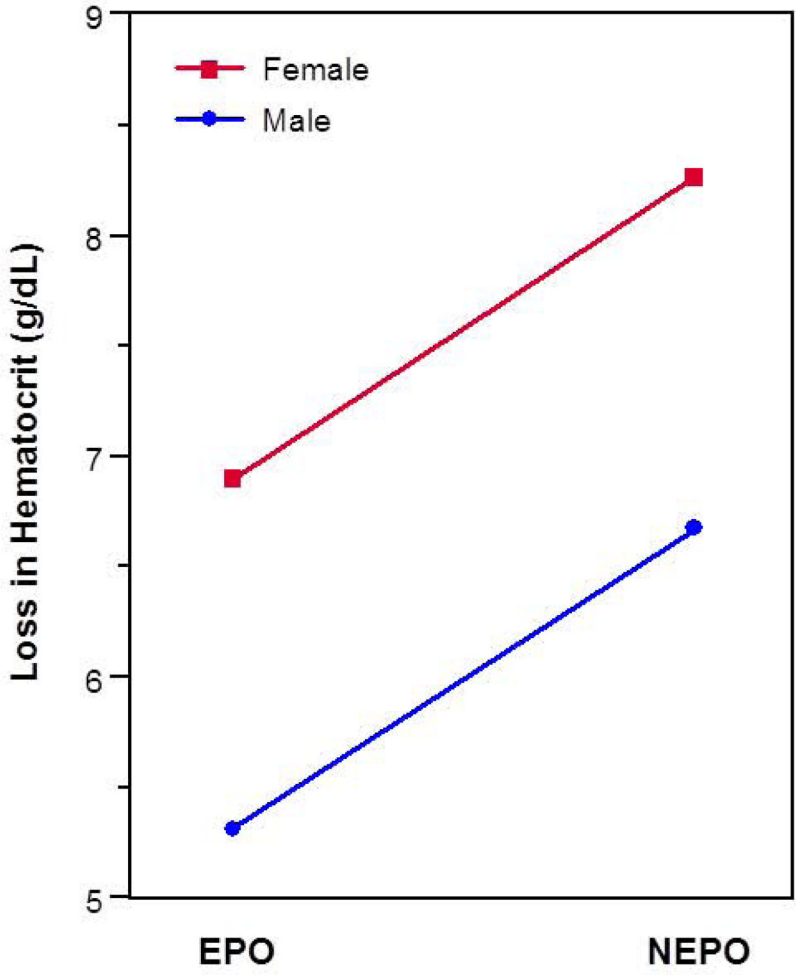


**Figure 1.**
Estimated Loss in Hematocrit by Gender and EPO Group at the Average Values for Preoperative Hematocrit, Length of Surgery, Blood Loss and Fluid Replacement

**Table 1**

Comparison of Patient Characteristics between EPO and NEPO groups and between LeFort 1 only and LeFort 1/BSSO groups.

| | **EPO** | **NEPO** | **P value** | **LeFort 1** | **Lefort 1 / BSSO** | **P value** |
|---|---|---|---|---|---|---|
| | **N (%)** | **N (%)** | | **N (%)** | **N (%)** | |
| Gender | | | 0.15 | | | 0.57 |
| Male | 48 (42) | 20 (31) | | 37(40) | 31 (36) | |
| Female | 66 (58) | 44 (69) | | 55 (60) | 55 (64) | |
| Race | | | 0.13 | | | 0.04 |
| Caucasian | 96 (84) | 48 (75) | | 69 (75) | 75 (87) | |
| Non-Caucasian | 18 (16) | 16 (25) | | 23 (25) | 11 (13) | |
| | Median (IQR) | Median (IR) | | Median (IQR) | Median (IQR) | |
| Age at Surgery | 18 (17–23) | 18 (17–23) | 0.84 | 18 (17–23) | 19 (17.22) | 0.57 |
| Preop Hematocrit | 41.4 (38–44) | 40.8 (38.5–42.8) | 0.18 | 41.2 (38.7–43.3) | 41.1 (38.0–44.0) | 0.91 |

**Table 2**

Comparison of surgical factors between EPO and NEPO groups and between LeFort 1 only and LeFort 1/BSSO groups.

| | **EPO** | **NEPO** | **P value** | **LeFort 1** | **Lefort 1 / BSSO** | **P value** |
|---|---|---|---|---|---|---|
| | **N (%)** | **N (%)** | | **N (%)** | **N (%)** | |
| Procedure | | | 0.0002 | | | |
| Lefort I & BSSO | 67 (59) | 19 (30) | | | | |
| Lefort 1 only | 47 (45) | 45 (70) | | | | |
| | Median (IQR) | Median (IR) | | Median (IQR) | Median (IQR) | |
| Length of Surgery | 3.0 (2.5–4.0) | 2.5 (2.0–4.0) | 0.08 | 2.5 (2–3) | 4.0 (3–5) | <.0001 |
| Fluid Replacement | 2800 (2100–3600) | 2600 (2000–3200) | 0.11 | 2150 (1825–3000) | 3200 (2700–4000) | <.0001 |
| Blood Loss | 300 (200–350) | 250 (200–350) | 0.07 | 200 (200–300) | 350 (250–400) | <.0001 |

## Table 3

Effect of Explanatory Factors on the loss in hematocrit (g/dL) from before surgery to iafter surgery.

| Variable | Estimate | SE | F Value | P value |
|---|---|---|---|---|
| Intercept | 8.27 | 0.44 | 352.6 | <.0001 |
| Preoperative Hematocrit | 0.40 | 0.08 | 22.09 | <.0001 |
| Gender (Male) | −1.37 | 0.49 | 7.84 | 0.006 |
| Group (EPO) | −1.59 | 0.61 | 6.86 | 0.01 |
| Length of Surgery | 0.83 | 0.24 | 12.28 | 0.001 |
| Blood Loss | 0.005 | 0.002 | 9.47 | 0.003 |
| Crystalloid | 0.0008 | 0.0003 | 8.59 | 0.004 |