

Erythropoietin in Patients Undergoing Elective Joint Arthroplasty and Preoperative Autologous Blood Donation

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Purpose. The aim of this study was to determine whether erythropoietin (EPO) supplementation permits an adequate autologous blood donation prior to elective hip or knee arthroplasty in patients with boundary hematocrit and hemoglobin (Hb) levels.

Materials and methods. Between January 2000 and December 2001, sixty-six patients were included in this study who required total hip or knee arthroplasty and who had also been enrolled in a preoperative transfusion program. Patients were classified into two groups, taking into account their hemoglobin levels: those with Hb < 13 g/dl (group 1, 37 patients) received EPO (10.000 IU, 3 times a week) throughout the transfusion program whereas those with Hb > 13 g/dl (group 2, 29 patients) were not given EPO before or during the self-transfusion program. Blood was extracted from patients in both groups once a week for one to three weeks; all patients received oral iron supplementation. In all patients, median hemoglobin and hematocrit values were determined before the first blood extraction (baseline values), during the preoperative period and at discharge; a record was made of the amount of blood extracted and transfused for each group. Twenty patients were excluded during the study since they did not fulfill the inclusion criteria (group 1: n = 12; group 2: n = 8). Lastly, the data corresponding to 46 patients was statistically analyzed (group 1: n = 25; group 2: n = 21).

Results. Although the median baseline hemoglobin and hematocrit values for group 2 were significantly higher than those for group 1 ($p < 0.001$), no differences were observed between both groups regarding their median levels during the preoperative and postoperative periods or at discharge.

Nor any differences were observed regarding the amount of blood extracted and transfused.

Conclusions. Differences observed in the baseline hemoglobin and hematocrit levels between the two groups were fully resolved thanks to the prophylactic administration of EPO during the preoperative self-transfusion program, which was concluded appropriately even for patients with boundary hemoglobin and hematocrit levels.

Key words: erythropoietin, autologous blood transfusion, blood donation, arthroplasty, knee/hip replacement.

La función de la eritropoyetina en pacientes sometidos a artroplastia articular electiva y a donación de sangre autóloga preoperatoria

Objetivo. El objetivo de este estudio ha sido evaluar si la suplementación con eritropoyetina (EPO) permite una apropiada donación de sangre autóloga previa a una artroplastia electiva de cadera o rodilla, incluso en pacientes con niveles límite de hematocrito (Hcto) y hemoglobina (Hb).

Material y método. Desde enero de 2000 hasta diciembre de 2001 fueron incluidos en este estudio 66 pacientes que requirieron artroplastia total de cadera o rodilla, a quienes se había inscrito previamente en un programa de autotransfusión preoperatoria. Los pacientes fueron clasificados en dos grupos teniendo en cuenta sus niveles de Hb: aquéllos con un nivel de Hb < 13 g/dl (grupo 1; 37 pacientes) recibieron EPO (10.000 UI, 3 veces por semana) durante el programa de autotransfusiones, mientras que a aquéllos con un nivel de Hb > 13 g/dl (grupo 2; 29 pacientes) no se les suministró EPO ni antes ni durante el programa de autotransfusión. A los pacientes de ambos grupos se les extrajo sangre una vez por semana durante un período de entre una y tres semanas, administrándoseles además hierro por vía oral. En todos los pacientes se evaluaron los valores de Hb y Hcto antes de la primera extracción de sangre (valores basales), en el período quirúrgico y al alta, registrándose además la cantidad de sangre recogida y transfundida para cada grupo.

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Durante el estudio se excluyeron 20 pacientes por no cumplir los criterios de inclusión (grupo 1, n = 12; grupo 2, n = 8). Finalmente, se analizaron estadísticamente los datos correspondientes a 46 pacientes (grupo 1, n = 25; grupo 2, n = 21).

Resultados. A pesar de que los valores basales de Hb y Hcto para el grupo 2 fueron significativamente más elevados que para el grupo 1 ($p < 0,001$), no se observaron diferencias entre ambos grupos en cuanto a sus niveles correspondientes durante el período preoperatorio, el postoperatorio y el momento del alta hospitalaria, ni tampoco en cuanto a la cantidad de sangre recogida y transfundida.

Conclusiones. La diferencia en los niveles basales de Hb y Hcto observada entre los dos grupos fue completamente corregida gracias a la administración profiláctica de EPO durante el programa de autotransfusión preoperatoria, el cual se desarrolló de forma adecuada incluso en aquellos pacientes con niveles límite de Hb y Hcto.

Palabras clave: *eritropoyetina, transfusión de sangre autóloga; donación de sangre, artroplastia, sustitución articular de rodilla/cadera.*

Erythropoietin (EPO) is a glycoproteic hormone produced mainly by renal cells that is capable of regulating the differentiation of erythroid progenitor cells to protoerythroblasts. To do this, EPO binds to the glycoproteic receptor of erythroid progenitor cells, located on the cells' surface¹⁻³.

Recombinant human EPO is identical, in its aminoacid sequence, to human EPO and has been frequently used to treat anemia in uremic patients. In the United States, EPO has also been authorized for AZT-induced anemia in HIV+ patients, for chemotherapy-induced anemia in non-myeloid neoplasms and to reduce the number of allogenic blood transfusions in elective surgery⁴.

In addition, in some European countries, EPO has been authorized to treat anemia in preterm infants and to stimulate preoperative blood donation, especially in the event of major elective orthopedic surgery^{4,5}. In fact, EPO can maintain hemoglobin and hematocrit levels in the pre-op period and in the course of blood autotransfusions, during and after joint arthroplasty^{6,7}.

To determine whether EPO supplementation permits an appropriate collection of autologous blood in the pre-op period, even in patients with borderline hemoglobin and hematocrit levels, and whether it succeeds in maintaining adequate hemoglobin and hematocrit levels postoperatively, we carried out a prospective non-randomized study in patients subjected to total hip or knee arthroplasty during a two-year period.

MATERIALS AND METHODS

Patients

Between January 2000 and December 2001, 85 consecutive patients were included in the study, who had been subjected to either total knee replacement (TKR) or total hip replacement (THR).

Preoperative autotransfusions were performed in 66 of the 85 patients. According to the Italian clinical guidelines, autologous transfusions are indicated in patients with preoperative hemoglobin levels higher than 11 g/dl and hematocrit levels > 33%. In addition, EPO can be administered perioperatively to patients with hemoglobin levels between 10 and 13 g/dl to accelerate red blood cell production and increase hemoglobin concentrations in patients subjected to elective orthopedic surgery with an autotransfusion program.

Following the abovementioned guidelines, we divided the population under study into two groups. In group 1 (37 patients), where the hemoglobin level ranged between 10 and 13 g/dl and hematocrit was lower than 39%, blood was collected preoperatively (1 to 3 times) after administration of 30.000 IUs of EPO for each collection bag extracted for autotransfusion (PABD): extractions were carried out once a week and EPO was administered subcutaneously at a dose of 10.000 IUs three times a week from the day each extraction was made.

In group 2 (29 patients), since hemoglobin and hematocrit levels exceeded the threshold value for EPO administration (hemoglobin > 13 g/dl, hematocrit > 39%), extraction of collection bags for autotransfusion (from 1 to 3 times) was accomplished without administration of EPO.

Both groups received oral iron supplementation (a daily dose of 525 mg ferrous sulphate up to the moment of surgery⁸). The procedure was performed 10 ± 2 days after the last autotransfusion.

The hemoglobin threshold under which a transfusion was deemed necessary was 8 g/dl although, when making the decision to transfuse, the patients' clinical needs and symptoms were also taken into account⁹.

Hemoglobin and hematocrit levels were recorded for all patients immediately prior to the first extraction (baseline), the day before surgery (pre-op), after surgery (post-op) and on discharge. Also, the total amount of blood collected and transfused per group was recorded.

At the end of the study, it was impossible to assess 20 patients (group 1, n = 12: 32.4%; group 2, n = 8: 27.6%) for the following reasons: non-compliance with the EPO administration protocol (group 1, n = 9), recovery of perioperative blood or infusion of plasma expanders (group 1, n = 2; group 2, n = 4), on-compliance with the autotransfusion protocol (group 2, n = 3) and failure to collect data (group 1, n = 1; group 2, n = 1). This means that only the data corresponding to 46 patients were analyzed. Of these 46 pa-

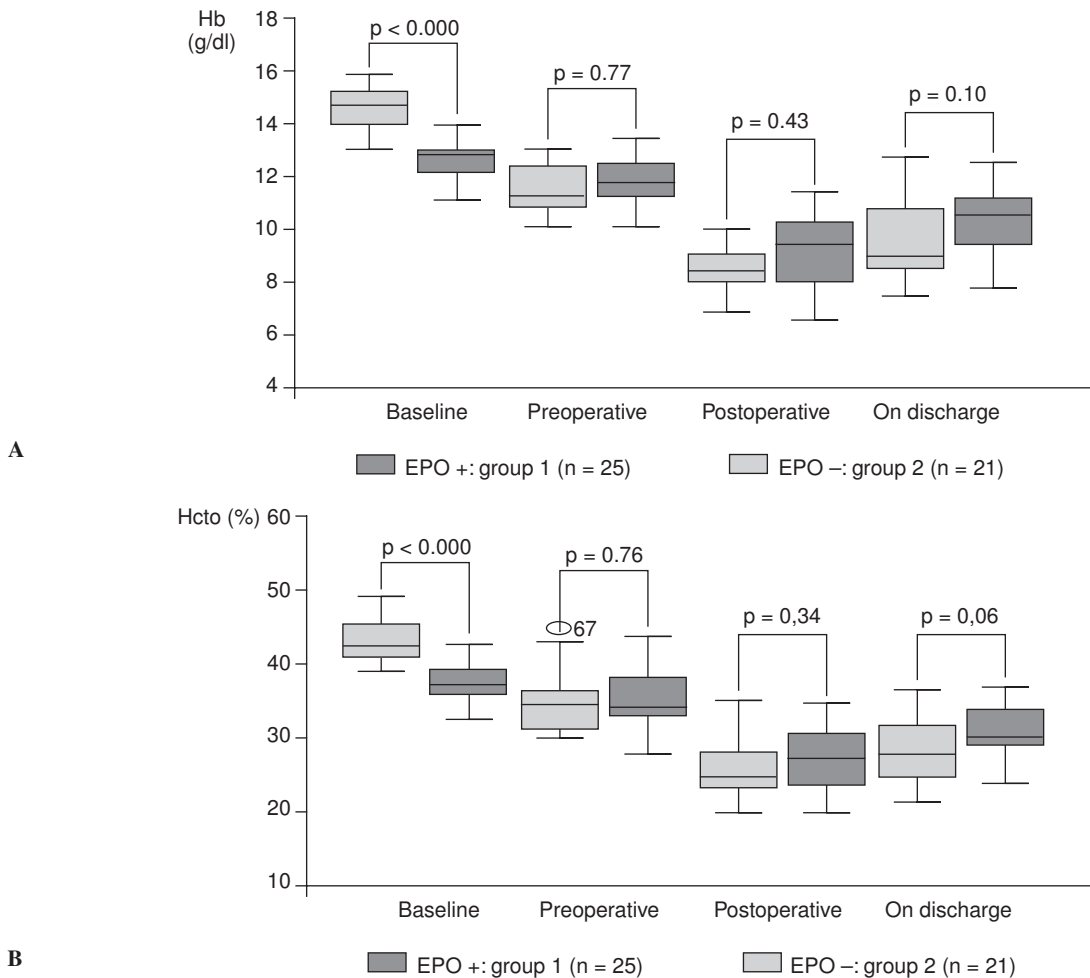


Figure 1. Curves represent baseline, pre-op, post-op and on-discharge levels for (A) hemoglobin and (B) hematocrit. The upper and lower edges of the boxes indicate the 25% and 75% percentiles; the horizontal lines inside the boxes indicate mean values. The lines below and above each box indicate the standard deviation. P values corresponding to the intra- and intergroup statistical analysis were calculated using Mann Whitney's U test for dependent and independent parametric variables. EPO: erythropoietin; Hb: hemoglobin; Hcto: hematocrit.

tients that were assessed, 13 underwent a TKR and 33 a THR.

The statistical analysis was made using the SPSS 10.0 for Windows software (SPSS Inc., Chicago, IL, USA). Data are presented as either mean deviation ± standard deviation or median ± interquartile amplitude. Parametric (Student's t test) and non parametric (the Wilcoxon test for paired data and Mann-Whitney's U test for unpaired data) tests were used in order to compare the different values obtained. Values of $p < 0.05$ were considered statistically significant. The study was approved by our hospital's Ethical Committee

RESULTS

Of the 25 patients in group 1, 18 (72%) were subjected to THR and 7 (28%) to TKR; of the 21 patients in

group 2, 15 (71.4%) underwent THR and 6 (28.6%) to TKR. No differences were observed when comparing the mean age of the two populations under study, i.e. 68.2 ± 7.7 years and 67.3 ± 8.2 years in groups 1 and 2 respectively ($p = 0.53$).

As indicated in figures 1A y 1B, hemoglobin and hematocrit median baseline values for group 2 were significantly higher than those for group 1 (mean hemoglobin was 14.7 g/dl vis à vis 12.85 g/dl, $p < 0.001$; mean hematocrit was 42.6% vis à vis 37.65%, $p < 0.001$). When comparing group 1 with group 2, no significant differences were observed as regards the mean hemoglobin and hematocrit values recorded preoperatively, postoperatively and on discharge (table 1, figs. 1A and 1B). However, the result of comparing the hematocrit level on discharge in both groups was $p = 0.06$.

Intra-group statistical analysis revealed a considerable

Table 1. Characteristics of the population under study: mean (baseline, pre-op, post-op and on-discharge) hemoglobin and hematocrit values of the blood collected and results of the intra- and intergroup statistical analysis (p values group 1/ group 2)

	EPO + (group 1)	EPO - (group 2)	P values (group 1/group 2)
Patients n = 46	25	21	
(Mean) age	68.2 ± 7.7 years	67.3 ± 8.2 years	p=0.53
Hb (g/dl) (median values)			
Baseline	12.85 (11.1-14.0)	14.7 (13.0-15.9)	p < 0.001
Preoperative	11.75 (9.0-14.7)	11.3 (10.1-15.9)	p = 0.77
Postoperative	9.5 (6.6-13.7)	8.5 (6.9-12.8)	p = 0.43
On discharge	10.6 (7.8-12.6)	9.0 (7.5-12.8)	p = 0.01
Hcto (%) (median values)			
Baseline	37.65 (32.7-42.8)	42.6 (38.8-49.2)	p < 0.000
Preoperative	33.95 (27.9-43.5)	34.4 (30.0-44.7)	p = 0.76
Postoperative	27.9 (20.0-40.6)	24.8 (20.0-35.3)	p = 0.34
On discharge	30.5 (23.9-37.0)	28.0 (21.5-36.3)	p = 0.06

EPO: erythropoietin; EPO +: group 1; EPO -: group 2; Hb: hemoglobin; Hcto: hematocrit.

Table 2. Preoperative Autologous Blood Donation (PABD) in group 1 (EPO +) and group 2 (EPO -); results of the inter-group statistical analysis (p values)

PABD	EPO + (group 1)	EPO - (group 2)	P values
Patients	25	21	
Extraction carried out			
Total	66 (100%)	50 (100%)	
Mean	2.38 ± 0.15	2.54 ± 0.1	p = 0.48
Transfusion carried out			
Total	53 (80.3%)	42 (84%)	
Mean	2 ± 0.13	2.1 ± 0.14	p = 0.75
Non transfused			
Total	13 (19.7%)	8 (16%)	

EPO: erythropoietin; PABD: Preoperative Autologous Blood Donation.

drop in hemoglobin and hematocrit levels both from baseline to pre-op values (p < 0.001) and from pre to post-op values (p < 0,001), as well as a significant increase (p < 0,001) in hemoglobin and hematocrit levels at discharge when compared with the postoperative levels recorded for both groups (table 1).

For patients in group 2 a mean of 2.54 ± 0,1 PABD was collected; and a mean of 2.1 ± 0.14 PABD was reinfused further to surgery. In group 1, these values were 2.38 ± 0.15 PABD collected prior to surgery and 2.0 ± 0.13 PABD reinfused postoperatively. No statistically significant differences were found when comparing both groups in terms of the number of PABDs collected and transfused (P = 0.48 y P = 0.75 respectively). In group 1, 66 PABD units were collected preoperatively, whereas in group 2 this figure was of 50 units. Of the PABDs collected, 42 units (84%) were transfused in group 2 and 53 units (80.3%) in group 1 (table 2).

DISCUSSION

Major elective orthopedic surgery is often associated with the need to perform allogenic blood transfusions. Bierbaum et al¹⁰ gathered data about the blood management of 9,482 patients undergoing either THR or TKR and concluded that 46% of patients receive an (allogenic or autologous) blood transfusion and that 34% of patients requiring a transfusion receive allogenic blood. In OSTHEO, a recent European study, over 50% of the population transfused received allogenic blood¹¹.

New surgical techniques and the wider use of autotransfusions have reduced the risk of being exposed to allogenic blood transfusions, although patients with low hemoglobin and hematocrit levels at the time of surgery cannot be fully protected against the risk of being exposed to such transfusions. In the OSTHEO study, 32% of patients transfused were included in an autologous blood donation program, as compared with 60% mentioned by Bierbaum et al, although a small albeit representative population in these groups received an allogenic transfusion^{10,11}.

In subjects with normal iron reserves who are extracted blood for an autotransfusion (PABD), and who receive iron supplementation, the mean time needed to reestablish the mass of red blood cells in 15 to 20 days from extraction⁸. Therefore, it is rather unlikely to collect a sufficient amount of PABD for major elective surgery using only iron supplementation. EPO administration increases the preoperative red blood cell mass as well as the hemoglobin concentration and hematocrit levels¹², thereby making autologous transfusions possible in anemic patients, especially if they are due to undergo major elective orthopedic surgery^{5,13,14}. This means that pre-op use of EPO increases the number of patients capable of donating the number of blood units suggested by the *Maximum Surgical Blood Order Schedule* (MSBOS)

and the *Schedule of Optimal Preoperative Collection of Autologous Blood* (SOPCAB), thus achieving an adequate postoperative reestablishment of their blood mass and compensating for perioperative blood loss¹³.

Autologous autotransfusions are useful before elective surgical procedures, such as joint replacement surgery, characterized by high levels of blood loss. The advantages of this method include the need of less bank blood, the stimulation of erythropoiesis and the elimination of the risk of infectious disease transmission^{6,15}. Stowell et al¹⁶ observed that, in patients with a hemoglobin level lower than 13 g/dl, isolated EPO offered better results than autologous autotransfusion as regards perioperative blood status and global (and more specifically allogenic) transfusion needs, although this latter advantage did not show statistical significance. Mercuriali et al showed that anemic patients (baseline hematocrit level < 40%) treated with EPO and PABD received less allogenic blood than those treated only with PABD⁸.

In our series, in spite of the difference observed between the two groups as regards hemoglobin and hematocrit mean baseline values, similar preoperative hemoglobin and hematocrit levels were detected in both groups ($p = 0.77$ y $p = 0.76$ respectively), which shows that EPO supplementation effectively reduced differences between both groups during the PABD program. What's more, although the differences between both groups in terms of post-op red blood cell levels were not significant, these levels were slightly higher in group 1 than in group 2. The difference peaked, yet without reaching statistical significance, when hemoglobin ($p = 0.1$) and hematocrit ($p = 0.06$) levels were compared at the time of discharge. It should be said that out of the 6 patients excluded on account of the use of pre-op blood recovery, 4 were in group 2, whereas only 2 came from the EPO group.

Patients in group 1 managed to preoperatively donate an average 2.38 ± 0.15 units, of which an average 2.0 ± 0.13 was transfused postoperatively, which entails a reinfusion rate of 80.3%. Likewise, a high reinfusion rate (84%) was noticed in patients not receiving EPO (group 2), showing a correct management of the collection-reinfusion cycle of the PABD program.

To the best of our knowledge, this is the first study that compares a group with high hemoglobin and hematocrit levels with a moderately anemic one. Repeated flebotomy of non EPO-supplemented PABD could trigger a suboptimal erythropoietic response and hinder the recovery of hemoglobin levels: our data show that EPO improves the preoperative blood status in the group of borderline patients, in spite of their participation in the PABD program. Although the EPO + PABD regime has not shown a good cost/effectiveness ratio¹⁷, it undoubtedly reduces anemic patients' need for allogenic blood, which is still a scarce commodity.

As regards quality of life and speedy recovery of vigor further to orthopedic surgery, it has recently been shown that it is important to achieve high hematocrit levels after THR and TKR, since this will permit quick physical rehabilitation which, in turn, will lead to a prompt discharge^{7,18}. In our study, we obtained high postoperative hemoglobin and hematocrit levels in a population (group 1) whose baseline levels would have jeopardized an appropriate post-op recovery as well as, in some cases, the chance of collecting enough PABD units preoperatively.

To conclude, the results of this study emphasize the importance of EPO administration to patients due to be subjected to an autologous autotransfusion program who have low or borderline hemoglobin and hematocrit levels. In our experience, EPO helps obtain pre- and postoperative hemoglobin and hematocrit levels similar to those of patients not subjected to treatment with EPO (on account of having high baseline hemoglobin and hematocrit levels), which shows that in certain patients scheduled for elective joint replacement the EPO + PABD protocol could prove extremely effective at controlling preoperative anemia, making it possible to perform appropriate autologous autotransfusions even in patients with borderline baseline hemoglobin and hematocrit levels.

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Conflict of interests

The authors have declared that they have no competing interests.