Perioperative intravenous iron, with or without erythropoietin, plus restrictive transfusion protocol reduce the need for allogeneic blood after knee replacement surgery

Jorge Cuenca, José A. García-Erce, Fernando Martínez, Luis Pérez-Serrano, Antonio Herrera, and Manuel Muñoz

BACKGROUND: Unilateral total knee replacement (TKR) results in a substantial blood loss and 30 to 50 percent of patients receive allogeneic blood transfusion (ABT). Therefore, the effectiveness of a restrictive transfusion trigger (hemoglobin [Hb] level < 8 g/dL) plus stimulation of erythropoiesis was evaluated, with or without blood salvage, for reducing ABT in TKR patients.

STUDY DESIGN AND METHODS: A series of 139 consecutive of primary TKR patients received perioperative iron sucrose (2 × 200 mg/48 hr, intravenously [IV]), plus preoperative erythropoietin (EPO; 1 × 40,000 UI, sc) if preoperative Hb level was less than 130 g per L (Group A). This protocol was applied to another series of 173 consecutive TKR patients who also received postoperative unwashed shed blood (USB) if preoperative Hb level was less than 130 g per L (Group B). Perioperative clinical and laboratory data were gathered.

RESULTS: No adverse effects of iron sucrose, EPO, or USB administration were witnessed, and only 13 patients received ABT overall (4%). No major differences in perioperative blood counts or iron metabolism variables were observed between groups, but stimulation of erythropoiesis seemed to be more pronounced in those patients receiving EPO (p < 0.05). There were no differences in postoperative complications between groups, but length of hospital stay for patients with a preoperative Hb level of less than 130 g per L was shorter in Group B (p < 0.05).

CONCLUSION: This blood saving protocol seems to be effective for reducing ABT in TKR patients. Which patients are more likely to benefit from either perioperative iron administration or selective addition of postoperative blood salvage to pharmacologic treatment, however, needs to be further evaluated.

ABBREVIATIONS: ABT = allogeneic blood transfusion; CRP = C-reactive protein; LHS = length of hospital stay; TSI = transferrin saturation index; USB = unwashed shed blood.

From the Departments of Orthopedic and Trauma Surgery and Hematology, University Hospital “Miguel Servet,” Zaragoza, Spain; and GIEMSA, School of Medicine, University of Málaga, Málaga, Spain.

Address reprint requests to: M. Muñoz, PhD, GIEMSA, Facultad de Medicina, Universidad de Málaga, Campus de Teatinos, s/n, 29071-Málaga, Spain; e-mail: mmunoz@uma.es.

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adopted, however, the real contribution of this strategies to ABT reduction decreases significantly. From these data it can be inferred that a transfusion protocol does in itself reduce by 25 to 30 percent the relative risk for ABT, and therefore it must be the first strategy to include in a blood saving program.

On the other hand, it is well known that preoperative hemoglobin (Hb) level is one of the strongest predictors for postoperative ABT after TKR and that stimulation of red blood cell (RBC) production may reduce the requirements for ABT in patients with mild anemia. For patients undergoing surgery for hip fracture repair, however, perioperative administration of iron sucrose, with or without recombinant human erythropoetin (rHuEPO), was also shown to be effective for reducing ABT rate.

In this work, we therefore evaluated the effectiveness of the implementation of a restrictive transfusion protocol (Hb < 80 g/L) plus perioperative stimulation of erythropoiesis, with or without postoperative blood salvage, at reducing the requirements for ABT in patients undergoing surgery for TKR.

PATIENTS AND METHODS

Patients

After approval by the institutional review board, patients scheduled for elective TKR from March 2003 to June 2005 in a single institution were interviewed by the surgeon before surgery to enter in a blood saving protocol. Patients with hematologic diseases, coagulation disorders, or hepatic or renal diseases; those under anticoagulant therapy or with known infection or malignancy at admission; and those with preoperative autologous blood donation were excluded.

Data collection

A set of demographic and clinical data was prospectively gathered for all patients, including sex, age, weight, height, ASA physical status scale, type of procedure, perioperative Hb concentrations, transfusion rate (percentage of transfused patients), and postoperative noninfectious and infectious complications (urinary tract, respiratory tract, and wound infections), according to the CDC criteria adverse reaction to treatment (metallic taste, headache, nausea, vomiting, hypotension, anaphylactic reactions), in-hospital mortality, and length of hospital stay (LHS).

Surgical procedure

All patients were operated on by the same surgical team, under standardized anesthesia, antibiotic and antithrombotic prophylaxis, and postoperative analgesia. The same implant (Nex-General, Zimmer Inc., Warsaw, IN) was used in all primary TKR, with all components being cemented. All procedures were performed with a pneumatic tourniquet, which was deflated after wound closure, and two to three closed-suction drains (two inside the joint and one subcutaneous [sc]), which were removed on the second postoperative day. All patients stayed at the postanesthesia recovery unit for at least 4 to 6 hours before being transferred to the ward.

Blood saving protocol

In Group A, a series of consecutive TKR patients received two doses of iron sucrose intravenously (IV; 200 mg, Venofer, Vifor, Saint Gallen, Switzerland), one 24 hours before surgery and one 24 hours after surgery. Patients with preoperative Hb levels of less than 130 g per L also received a single dose of rHuEPO (40,000 IU, sc; Eprex, Janssen-Cilag, Madrid, Spain; or Epopen, Laboratory Pensa, Barcelona, Spain) 24 hours before surgery. This protocol was applied to a second series of consecutive TKR patients who also received postoperative unwashed shed blood (USB) if their admission Hb level was less than 130 g per L (Group B). All patients received oxygen therapy (2 L/min) during the first 48 postoperative hours. No other blood saving method was used in any patient.

Postoperative blood salvage and return

At the end of surgery, the collection blood canister (Bello-Vac, AstraTech, Mölndal, Sweden) was connected to two joint drainage catheters through a Y-connector, and USB was collected without anticoagulant, at a negative pressure of less than 100 mmHg, and returned within the first 6 postoperative hours. A 40-µm screen filter, provided by the manufacturer, was intercalated in the patient’s line to eliminate microaggregates. The volume of recovered USB was converted into blood units according to the formula

\[ U = \frac{\text{USB volume (mL)} \times \text{USB hematocrit (%)}}{400} \times \text{preoperative hematocrit (%)} \]

Transfusion protocol

The anesthesiologist, who was unaware of the study, estimated blood losses and made decisions on transfusion, both at the operation theater and at the anesthesia recovery unit. In the ward, measurement of postoperative blood loss and decisions on postoperative transfusions were made by the attending surgeon. In these two groups of elderly patients, who may tolerate anemia poorly, transfusion was indicated when patient’s Hb level fell below 80 g per L or when patient presented symptoms of acute anemia (hypotension, tachycardia, tachypnea, dizziness, fatigue, etc.). This transfusion protocol was approved by the hospital blood transfusion committee, and it was uniformly applied by anesthesiologists and surgeons to all patients at the operation theater, the anes-
transfusion therapy, and the ward for the entire duration of hospitalization.16

Laboratory measurements

Full blood counts, including reticulocyte counts (%), were determined preoperatively and 1 and 7 days after surgery with an automated cell counter (Cell-Dyn 4000, Abbott Diagnostics, Wiesbaden, Germany), and serum transferrin receptor (Dade Behring Marburg GmbH, Marburg, Germany), as well as C-reactive protein (CRP, Immage II, Beckman-Coulter, Hialeah, FL), were measured preoperatively and postoperatively on Day 7. Iron deficiency was defined by a serum ferritin level of less than 30 ng per mL, and functional deficiency, by a ferritin level of less than 50 ng per mL and a CRP level of 5 mg per L.16

Statistical analysis

Data were expressed as percentages or as the mean ± standard deviation (SD or incidence (%)). Pearson’s chi-square test or Fisher’s exact test was used for comparison of qualitative variables. Parametric two-way analyses of variance or nonparametric Kruskal-Wallis test were used for comparison of quantitative variables, after consideration of distributional characteristics. Multivariate logistic regression analysis was performed to obtain adjusted estimates of odds with 95% confidence intervals (CIs) of patients, procedure, and treatment factors associated with ABT. Variables were included in the multivariate model if they were significantly associated or if there was evidence of a substantial effect in the univariate analysis. All statistics were performed with computer software (SPSS 11.0, SPSS, Chicago, IL; licensed to the University of Málaga, Malaga, Spain), and a p value of less than 0.05 was considered significant.

RESULTS

Overall, 139 consecutive patients were included in Group A and 173 in Group B (Table 1). Before surgery, 24% of patients in Group A (33/139; 33 women) presented with a Hb level lower than 130 g per L and received iron sucrose plus rHuEPO, and 19% of patients in Group B (33/173; 2 men and 31 women) presented with a Hb level lower than 130 g per L and were assigned to iron sucrose plus rHuEPO and postoperative blood salvage. In both groups, patients with a preoperative Hb level of at least 130 g per L received intravenous iron sucrose only (Group A, n = 106; Group B, n = 140; Table 2).

There were no significant differences between groups regarding patient’s age, sex distribution, weight, height, type of procedure, preoperative Hb levels, or postoperative complications, but there were more patients with ASA physical score 3 in Group B, and LHS was more prolonged in Group A (Table 1). When patients with preoperative Hb levels of less than 130 g per L were compared to those with preoperative Hb levels of at least 130 g per L, however, there were also significant differences regarding sex distribution and perioperative Hb levels (Groups A and B, ABT (Group A), and LHS (Group A; Table 2). Overall, only 13 patients (4.2%) received ABT, without differences between groups, but those who received ABT showed lower preoperative Hb levels than those who did not (136 ± 8 g/L vs. 143 ± 10 g/L, respectively; p = 0.041). All transfusions were given within 48 hours after surgery. For patients with preoperative Hb levels of at least 130 g per L, there was a small but significant difference between groups (Table 2). For patients with preoperative Hb levels of less than 130 g per L, 15 of 33 patients in Group B, received a mean of 513 ± 161 mL of USB (equivalent to 1.0 ± 0.3 units/patient), but there were no differences in ABT rate when compared to those in Group A, but LHS

### TABLE 1. Demographic and clinical data of 312 patients undergoing major knee surgery, according to blood saving program

<table>
<thead>
<tr>
<th>Demographic or clinical data</th>
<th>Group A</th>
<th>Group B</th>
<th>p Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>139</td>
<td>173</td>
<td></td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>39/100</td>
<td>47/126</td>
<td>0.860</td>
</tr>
<tr>
<td>Age (years)</td>
<td>71 ± 7</td>
<td>71 ± 7</td>
<td>0.442</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>160 ± 7</td>
<td>160 ± 7</td>
<td>0.995</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>78 ± 12</td>
<td>77 ± 11</td>
<td>0.535</td>
</tr>
<tr>
<td>ASA classification</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>8 (5.8)</td>
<td>0 (0)</td>
<td>0.001</td>
</tr>
<tr>
<td>2</td>
<td>94 (67.6)</td>
<td>65 (37.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>3</td>
<td>37 (26.6)</td>
<td>108 (62.4)</td>
<td>0.001</td>
</tr>
<tr>
<td>Type of procedure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TKR primary</td>
<td>127 (91.4)</td>
<td>156 (90.2)</td>
<td>0.738</td>
</tr>
<tr>
<td>TKR others</td>
<td>12 (8.6)</td>
<td>17 (9.8)</td>
<td>0.720</td>
</tr>
<tr>
<td>Preoperative Hb (g/L)</td>
<td>138 ± 12</td>
<td>140 ± 12</td>
<td>0.086</td>
</tr>
<tr>
<td>Allogeneic transfusion</td>
<td>4 (2.9)</td>
<td>9 (5.2)</td>
<td>0.310</td>
</tr>
<tr>
<td>Complications</td>
<td>1 (0.7)</td>
<td>15 (12.4)</td>
<td>0.950</td>
</tr>
<tr>
<td>DVT/PE</td>
<td>2 (1.4)</td>
<td>0 (0.0)</td>
<td>0.198</td>
</tr>
<tr>
<td>Infections</td>
<td>3 (2.1)‡</td>
<td>4 (2.3)§</td>
<td>1.000</td>
</tr>
<tr>
<td>Others</td>
<td>6 (4.3)</td>
<td>10 (5.8)</td>
<td>0.750</td>
</tr>
<tr>
<td>Hospital stay (days)</td>
<td>10 ± 4</td>
<td>8 ± 2</td>
<td>0.001</td>
</tr>
</tbody>
</table>

† Between-group differences.
‡ Two urinary tract infections; one respiratory tract infection.
§ Four urinary tract infections.
TABLE 2. Demographic and clinical data of 312 patients undergoing major knee surgery, according to blood saving program (group) and preoperative Hb level*

<table>
<thead>
<tr>
<th>Demographic and clinical data</th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
</tr>
<tr>
<td>Number of patients</td>
<td>&lt;130†</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>33</td>
</tr>
<tr>
<td>Type of procedure</td>
<td>30 (91)</td>
</tr>
<tr>
<td>TKR primary</td>
<td>3 (9)</td>
</tr>
<tr>
<td>TKR others</td>
<td>2/31</td>
</tr>
<tr>
<td>Perioperative Hb (g/L)</td>
<td>125 ± 9</td>
</tr>
<tr>
<td>Preoperative</td>
<td>92 ±9</td>
</tr>
<tr>
<td>Postoperative Day 1</td>
<td>97 ±10</td>
</tr>
<tr>
<td>Transfusion</td>
<td>9 1 (1) II</td>
</tr>
<tr>
<td>Autologous</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hospital stay (days)</td>
<td>11 ±5</td>
</tr>
</tbody>
</table>

* Data are the mean ± SD or incidence (%).
† IV iron plus EPO.
‡ IV iron.
§ IV iron plus EPO plus postoperative blood salvage.
|| p < 0.05, Hb < 130 vs. Hb ≥ 130 g/L.
¶ p < 0.05, Group A vs. Group B.

TABLE 3. Perioperative iron metabolism and inflammation variables in a subset of 222 patients undergoing major knee surgery, according to preoperative Hb level

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
</tr>
<tr>
<td>Number of patients</td>
<td>&lt;130‡</td>
</tr>
<tr>
<td>Serum iron (µg/mL)</td>
<td>88 ±36</td>
</tr>
<tr>
<td>Preoperative</td>
<td>39 ±16</td>
</tr>
<tr>
<td>TSI (%)</td>
<td>27 ±13</td>
</tr>
<tr>
<td>Ferritin (ng/mL)</td>
<td>73 ±53</td>
</tr>
<tr>
<td>Preoperative</td>
<td>20 ±8</td>
</tr>
<tr>
<td>Postoperative Day 7</td>
<td>222 ±132</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>5 ±6</td>
</tr>
<tr>
<td>Preoperative Day 7</td>
<td>58 ±32</td>
</tr>
</tbody>
</table>

* Data are the mean ± SD of number of determinations.
† IV iron plus EPO.
§ IV iron plus EPO plus postoperative blood salvage.
‡ IV iron.
|| p < 0.05, Hb < 130 vs. Hb ≥ 130.
¶ p < 0.05, Group A vs. Group B.

was shorter in Group B than in Group A (Table 2). In addition, there was a trend to lower preoperative Hb levels in anemic patients who received ABT when compared to those who did not (118 ±10 g/L vs. 126 ±8 g/L, respectively; p = 0.065). For the entire series, the multivariate analysis showed that preoperative Hb level was the only variable that predicts transfusion: there is a twofold decrease in the transfusion risk per each 10 g per L increase in preoperative Hb (odds ratio, 1.94; 95% CI, 1.12-3.30; p = 0.016).

Perioperative inflammation (CRP) and iron metabolism variables were available for only 222 patients (71%). Preoperatively, 7 percent of patients (21/312) had mean corpuscular Hb values of less than 28 pg; 10 percent (23/228), iron deficiency (serum ferritin < 30 ng/mL); 8 percent (18/228), functional iron deficiency (serum ferritin < 50 ng/mL and CRP > 5 mg/L), and 65 percent (149/263) serum ferritin levels of less than 100 ng per mL. No differences were observed between groups and subgroups, either preoperatively or on Postoperative Day 7, except for preoperative serum iron and TSI within Group A (Table 3). A stimulatory effect of the treatment on the erythropoiesis was observed on Postoperative Day 7, as reflected by the reduction of TSI in patients receiving IV iron (34 ±17% vs. 22 ±14%, for Preoperative and Postoperative Day 7, respectively; p <0.001) or IV iron plus rHuEPO (24 ±11% vs. 18 ±7%, respectively; p <0.01), as well as by the increase in reticulocyte index (Fig. 1) and Hb levels (Fig. 2) in both groups. This effect seemed to be more pronounced in those patients receiving rHuEPO, however, as reflected by the higher increase in reticulocyte index and serum transferrin receptor concentrations (p <0.05; Fig. 1). No adverse effects of iron sucrose, EPO, or USB administration were witnessed.

DISCUSSION

As of January 2000, a conservative transfusion protocol (Hb threshold of 90 g/L) was introduced in our institution resulting in a reduction of the number of TKR patients receiving transfusions (54% vs. 30%). To further reduce these figures, as of March 2003, we implemented a blood saving protocol for TKR, similar to that used for hip fracture repair, in which in a restrictive transfusion protocol (Hb < 80 g/L and/or signs and symptoms of anemia) and the stimulation of erythropoiesis with IV iron sucrose were the cornerstones. In addition, one preoperative dose of rHuEPO (40,000 IU, sc; Group A) or rHuEPO plus postoperative blood salvage (Group B) was given to patients with preoperative Hb levels of less than 130 g per L.
L (the cutoff for rHuEPO administration to patients undergoing elective orthopedic surgery in Europe) because these patients have a higher risk of receiving transfusions.\textsuperscript{3,7,8} The fundamental appreciation that transfusion threshold is one of the most significant determinants of transfusion seems to have been lost in the clinical setting, and as a result we are probably overusing blood transfusing after elective joint replacement.\textsuperscript{17} In this respect, a randomized trial in critically ill patients found that a restrictive transfusion threshold (Hb < 70 g/L) was as safe as a liberal transfusion threshold (Hb < 100 g/L).\textsuperscript{18} The transfusion threshold used in this study (Hb < 80 g/L), however, seems more appropriate for surgical patients with no risk factors for ischemia, because they have a much lower degree of monitoring, whereas a threshold of 90 to 100 g per L can be justified for patients who are considered at risk.\textsuperscript{14,15} In addition, attention needs to be paid to signs and symptoms of anemia, because they are variable depending on the patient’s age, body temperature, medications, rate of volume loss, and comorbidities.

In agreement with previous observations,\textsuperscript{7,8} multivariate analysis showed preoperative Hb to be the only...
independent risk factor for ABT in TKR. The blood saving protocol used in this study, however, has proved to be useful because the proportion patients receiving transfusions (2.9% for Group A, 5.2% for Group B) was greatly reduced with respect to that of previously published series2-4,7,8,17,18 despite 21 percent (66/312) of the patients presented a preoperative Hb level of lower than 130 g per L. In addition, because iron sucrose is considered to be a safe IV iron formulation,20 it is not surprising that no adverse effects of iron sucrose administration were witnessed either in this study or in the previous ones.3,10 In addition, for patients with a preoperative Hb level of less than 130 g per L, our blood saving protocol seems to be as effective as either another more complex and expensive protocols, with rHuEPO alone12,21 or in combination with other blood conservation methods,22-24 or a flow chart on a safe IV iron formulation,20 it is not surprising that no presented a preoperative Hb level of lower than 130 g per L, our blood saving protocol seems to be as effective as either another more complex and expensive protocols, with rHuEPO alone12,21 or in combination with other blood conservation methods,22-24 or a flow chart on the use of blood transfusion, with a lower transfusion trigger (Hb < 70 g/L).25

The treatment may stimulate the erythropoiesis in two ways. On the one hand, the increased erythropoietic effect (4.5-5.5 times that of basal) of IV iron that lasts for 7 to 10 days, after which the iron is sequestered by the reticuloendothelial system.26 In addition, if the patient's iron stores were depleted going into the procedure, the blood loss could not be corrected by endogenous RBC production. Hence, patients with preoperative ferritin levels of less than 100 ng per mL (65%) did not have enough stored iron to reconstitute their perioperative Hb loss (35 g/L) and keep a normal iron store (ferritin 30 ng/mL).27 and therefore were more likely to benefit from perioperative iron sucrose. On the other hand, the pharmacokinetic profile of rHuEPO after the sc administration of 40,000 IU, reaching peak concentrations over 1000 IU per L within 1 day, closely parallels that of acute inflammation after TKR.28,29

Hence, the effectiveness of our blood saving protocol is most probably due to the use of a restrictive transfusion threshold to avoid early ABT (<48 hr), and the stimulatory effect of supraphysiologic doses of IV iron with or without rHuEPO on erythropoiesis, which seems to overcome the depression of EPO production and action, as well as the functional iron deficiency status, that follows to major surgery,30-32 thus avoiding late ABT (>72 hr).7

Unfortunately, this study lacks a control group, thus precluding a comparative assessment of the effect of the administered drugs on erythropoiesis. It may be inferred, however, from some indirect evidence: first, from the significant increase in Hb levels between Postoperative Day 2 and 7 (Fig. 2); second, from the difference in rate of Hb recovered postoperatively in patients underwent spinal fusion who were treated for 6 days with oral iron fumarate or IV iron sucrose (2.5 ± 1.2 g/L/day vs. 3.6 ± 0.8 g/L/day, respectively; p = 0.03);33 third, the fact that IV iron sucrose has been shown to increase Hb levels in patients with inflammatory anemia scheduled for orthopedic surgery,34 and fourth, from comparison of the net postoperative reduction in Hb levels observed in this study with that of a previous one, after subtracting the effect of blood transfusion (−36 ± 14 g/L vs. −41 ± 13 g/L, respectively; p = 0.047).19

On the other hand, the net postoperative reduction in Hb levels in this study was higher for patients receiving iron sucrose than for those receiving iron sucrose plus rHuEPO (−37 ± 13 vs. −51 ± 14 g/L, respectively; p = 0.005), suggesting that the stimulation of erythropoiesis was more pronounced in patients receiving iron sucrose plus rHuEPO than in those receiving iron sucrose alone. In contrast, there was no difference in postoperative Hb decrease between patients receiving rHuEPO in both groups (−30 ± 15 g/L vs. −33 ± 14 g/L, for Groups A and B, respectively; p = 0.379), suggesting that USB return did not result in any additional benefit to the patients, although a reduction in LHS was observed. This reduction in LHS is difficult to evaluate, however, because without rigid criteria for discharge, it may be that standards change slightly during the time period.

In conclusion, although preoperative improvement of Hb levels before the scheduled surgical procedure should be desirable,35 we believe that this blood saving protocol, consisting of a restrictive transfusion trigger plus perioperative administration of IV iron sucrose with or without rHuEPO, is effective for reducing ABT in TKR patients. More research is needed, however, to ascertain which patients are more likely to benefit from either perioperative iron administration or selective addition of postoperative blood salvage to pharmacologic treatment to avoid ABT exposure.

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REFERENCES


