ORIGINAL ARTICLE

Perioperative intravenous iron preserves iron stores and may hasten the recovery from post-operative anaemia after knee replacement surgery

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SUMMARY. In unilateral total knee replacement (TKR), perioperative blood loss, low transfusion thresholds and short hospital stay result in patients being discharged with low haemoglobin (Hb). We assessed the effects of perioperative administration of intravenous iron, with or without erythropoietin, plus a restrictive transfusion threshold (Hb < 80 g L⁻¹) both on transfusion rate and recovery from post-operative anaemia.

TRK patients received iron sucrose (2 x 200 mg per 48 h, iv) (Group IVI, n = 129). Patients with admission Hb < 130 g L⁻¹, also received erythropoietin (1 x 40 000 IU, sc) (Group EPO, n = 19). Perioperative clinical and laboratory data were obtained.

Mean Hb loss was 36 g L⁻¹, but only seven patients were transfused (5%). Pre-operatively, 66 (45%) patients did not have enough stored iron to compensate for Hb loss. At post-operative day 30, only 15% were anaemic, 70% of Hb loss and 92% of pre-operative Hb were recovered and ferritin increased by 73 μg L⁻¹ (P < 0.01), although erythropoietic response was higher in patients receiving erythropoietin (P < 0.05). No adverse effects of iron sucrose or erythropoietin were witnessed.

This protocol seems to reduce allogeneic blood transfusion rate and may hasten the recovery from post-operative anaemia in TKR patients, without depleting iron stores. Further studies are needed to ascertain which patients may benefit from extended intravenous iron and/or erythropoietin administration.

Key words: allogeneic transfusion, erythropoietin, iron sucrose, knee replacement, transfusion protocol.

Unilateral total knee replacement (TKR) can result in a substantial blood loss (Rosencher et al., 2003; Kumar et al., 2005), with the subsequent decrease in haemoglobin (Hb) concentration (30–50 g L⁻¹) (Rosencher et al., 2003). This leads to post-operative anaemia, despite that one-third of these patients receive allogeneic blood transfusion (ABT) (Thomas et al., 2001; García-Erce et al., 2002; Rosencher et al., 2003; Bong et al., 2004; Steinberg et al., 2004; Muñoz et al., 2005). In addition, the use of lower transfusion thresholds together with the shorter post-operative hospital stay results in patients being discharged with lower levels of Hb than previously accepted. However, several studies of the recovery from anaemia in the post-operative period of elective arthroplasty surgery showed the administration of oral iron to be inefficacious (Sutton et al., 2004; Wheetheral & Maling, 2004; Mundy et al., 2005; Wallis et al., 2005). Therefore, we undertook a prospective observational study to assess the effects of perioperative administration of intravenous iron, with or without recombinant human erythropoietin (rhEPO), on both the exposition to ABT and the recovery from post-operative anaemia.

PATIENTS AND METHODS

Patients

After approval by the Institutional Review Board, patients scheduled for elective TKR from October 2004 to June 2005 in a single institution were interviewed by the surgeon before surgery and gave informed consent to enter the study. Patients with
haematological diseases or coagulation disorders, with hepatic or renal diseases, under anticoagulant therapy or with known infection or malignancy at admission and those with pre-operative autologous blood donation, with post-operative blood salvage or without full blood counting performed one month after surgery were excluded.

Data collection
A set of demographical and clinical data were prospectively gathered for all patients, including gender, age, weight, height, American Society of Anesthesiologists (ASA) physical status scale, type of procedure, presence of anaemia (Hb < 130 g L\(^{-1}\) for men or Hb < 120 g L\(^{-1}\) for women) (World Health Organisation, 1968), perioperative Hb concentrations, transfusion rate (percentage of transfused patients), post-operative non-infectious and infectious complications (urinary tract, respiratory tract and wound infections) (Horan et al., 1992), adverse reaction to treatment, in-hospital mortality and length of hospital stay (LOS).

Surgical procedure
All patients were operated on by the same surgical team, under standardized anaesthesia, antibiotic and antithrombotic prophylaxis and post-operative analgesia. The same implant (Nex-Gen\textsuperscript{®}, Zimmer, Inc., Warsaw, IN) was used in all primary TKR, with all components being cemented. All procedures were performed using a pneumatic tourniquet, which was deflated after wound closure, and two closed suction drains, which were removed at the second postoperative day. All patients stayed at the post-anaesthesia recovery unit for at least 4–6 h before being transferred to the ward.

Stimulation of erythropoiesis
All TKR patients received two doses of iron sucrose iv (200 mg, Venofer\textsuperscript{®}, Vifor, Saint Gallen, Switzerland), one before surgery and one 48 h after surgery. In addition, patients presented with an Hb level of less than 130 g L\(^{-1}\) also received a single dose of rHuEPO (40 000 IU, sc; Eprex\textsuperscript{®}, Janssen-Cilag, Madrid, Spain, or Epopen\textsuperscript{®}, Lab. Pensa, Barcelona, Spain) before surgery. All patients received oxygen therapy (2 L min\(^{-1}\)) during the first 48 post-operative hours. No other blood-saving method was used in any patient.

Transfusion protocol
The anaesthesiologist, who was unaware of the study, estimated blood losses and made decisions on transfusion, both at the operation theatre and at the anaesthesia recovery unit. In the ward, measurement of post-operative blood loss and decisions on postoperative transfusions were made by the attending surgeon. In these two groups of elderly patients, who may tolerate anaemia poorly, transfusion was indicated when patient’s Hb level fell below 80 g L\(^{-1}\) or when the patient presented symptoms of acute anaemia (British Committee for Standards in Haematology, 2001). Assuming that one ABT unit will rise patients’ Hb by 10 g L\(^{-1}\), they received a number of blood units that were estimated to be enough to reach an Hb concentration 10 g L\(^{-1}\) above the transfusion trigger. For symptomatic transfusion, blood units were given one by one until the disappearance of symptoms of acute anaemia. This transfusion protocol was approved by the Hospital Blood Transfusion Committee, and it was uniformly applied by anaesthesiologists and the surgeon to all patients at the operation theatre, the anaesthesia recovery unit and the ward for the entire duration of hospitalization.

Laboratory measurements
The Hb, haematocrit (Hct), mean corpuscular haemoglobin (MCH), mean corpuscular volume (MCV), red cell distribution width (RDW) and reticulocyte counts (%) were determined pre-operatively and 1, 7 and 30 days after surgery (Cell-Dyn 4000, Abbot Diagnostics, Wiesbaden, Germany). The reticulocyte index (i.e. the reticulocyte percentage corrected for the reduction in red cell counts in anaemia to give a better approximation to the actual erythropoietic activity) was calculated according to the expression (Hillman & Finch, 1967):

\[
\text{Reticulocyte index} = \frac{\text{Reticulocyte }\% \times (\text{Patient’s Hct}/\text{Normal Hct})}{1 + 0.1 \times \text{RDW}}
\]

Iron metabolism parameters, including serum iron, transferrin, transferrin saturation index (TSI), ferritin (Cobas Mira Plus, Roche Diagnostics, Tokyo, Japan) and serum transferrin receptor (sTfR, Dade Behring Marburg GmbH, Marburg, Germany), as well as C-reactive protein (CRP, Immage II, Beckman-Coulter, Hialeah, FL), were measured pre-operatively and 1, 7 and 30 days after surgery.

Statistical analysis
Data were expressed as percentage (%) or as the mean ± SD (n). Pearson’s χ\(^2\) test or Fisher’s exact
test was used for comparison of qualitative variables. Parametric Student’s \( t \)-test or non-parametric Mann–Whitney \( U \)-test were used for comparison of quantitative variables, after consideration of distributional characteristics. For repeated measures, comparisons were carried out using a MANOVA test with a withinsubjects factor (up to four levels) and one between-factor (group). All statistics were performed with SPSS 11.0 (Licensed to the University of Málaga, Spain) and a \( P \) value < 0.05 was considered statistically significant.

**RESULTS**

Overall, 148 of 194 consecutive patients met inclusion criteria. Forty-six patients were excluded because of post-operative blood salvage and reinfusion (\( n = 15 \)) or lack of blood counts at post-operative day 30 (PO30). Before surgery, seven patients were anaemic (4.7%; one man and six women; four inflammatory anaemia, one inflammatory anaemia plus iron deficiency and two anaemia of unknown cause). Among the nonanaemic patients, there were 10 with ferritin < 30 \( \mu \)g L\(^{-1} \), 16 with TSI < 20%, 7 with MCH < 28 pg, 0 with MCV < 80 fL, 14 with RDW > 15 and 34 with CRP > 5 mg L\(^{-1} \). Overall, 13% of the patients (19/148; 1 man and 18 women) presented an Hb level lower than 130 g L\(^{-1} \). Since this is the cut-off for intravenous iron + erythropoietin (EPO) administration to orthopaedic surgery patients in the European Union, they received iron sucrose plus rHuEPO (Group EPO). Patients with pre-operative Hb \( \geq 130 \) g L\(^{-1} \) received intravenous iron sucrose only (Group IVI, \( n = 129 \)) (Table 1).

There were not statistically significant differences between groups regarding patient’s weight or height, ASA physical score, type of procedure, ABT rate or LOS, but in the EPO group, patients were older and there were more women (Table 1). In addition, LOS was longer for patients with ABT than for those non-transfused (9.9 ± 2.1 vs. 7.4 ± 2.2, respectively; \( P = 0.004 \)). There were no differences between groups regarding perioperative levels of CRP, ferritin or TSI (data not shown), and no adverse effects of iron sucrose or erythropoietin administration were witnessed.

Perioperative Hb levels were always significantly lower in Group EPO than in Group IVI (Fig. 1A), despite a lower Hb lost (Table 2) and more pronounced stimulation of erythropoiesis, as reflected by the higher increase in reticulocyte index (Fig. 1B), sTfR concentrations (Fig. 1C) and RDW (13.2 ± 1.27 vs. 14.1 ± 2.1, for Groups IVI and EPO, respectively, at PO7; \( P < 0.01 \)). In this regard, for patients in Group EPO, 94% of perioperative Hb loss and 98% of pre-operative Hb levels were recovered at PO30, and 4 (21%) patients were anaemic, whereas for patients in Group IVI, these figures were 67% (\( P < 0.05 \)) and 91%, and 19 (15%), respectively (Table 2). No significant changes were observed in perioperative values of MCV or MCH between groups (data not shown).

Regarding iron reserves, post hoc analysis showed that 66 of the patients (45%; 56 in Group IVI, 10 in Group EPO) had pre-operative ferritin < 100 ng mL\(^{-1} \). However, the administration of intravenous iron resulted in an almost complete recovery from perioperative Hb lost at day 30, without a reduction of iron stores in any group (Table 2), although most of the patients with evidence of decreased iron availability (DIA; serum iron < 50 \( \mu \)g dL\(^{-1} \), TSI < 20%, ferritin < 50 ng mL\(^{-1} \) and CRP \( \geq 5 \) mg L\(^{-1} \)) (Table 3) presented pre-operative ferritin < 100 ng mL\(^{-1} \). In addition, there were no differences in Hb levels between patients with pre-operative ferritin levels lower or higher than 100 ng mL\(^{-1} \) or between patients with normal or high CRP at day 30 (Table 3).

**DISCUSSION**

As of January 2000, a conservative transfusion protocol (Hb threshold 90 g L\(^{-1} \)) was introduced in our institution, resulting in a reduction of TKR patients being transfused (54% vs. 30%) (García-Erce et al., 2002). To further reduce these figures, we implemented
blood-saving protocol for TKR based on our experience in hip surgery (Cuenca et al., 2004; García-Erce et al., 2005; Muñoz et al., 2005a), in which the use of a restrictive transfusion protocol and the stimulation of erythropoiesis with intravenous iron sucrose were the cornerstones. In addition, patients with pre-operative Hb < 130 g L\(^{-1}\) received one pre-operative dose of rHuEPO (40 000 IU, sc).

This protocol has proved to be useful since the proportion of transfused patients (5%) was greatly reduced with respect to previous series where one-third of these patients received ABT (Thomas et al., 2001; García-Erce et al., 2002; Rosencher et al., 2003; Bong et al., 2004; Steinberg et al., 2004; Muñoz et al., 2005b), this proportion being higher for patients with pre-operative Hb lower than 130 g L\(^{-1}\) (García-Erce et al., 2002; Bong et al., 2004; Karkouti et al., 2005; Muñoz et al., 2005b; Weber et al., 2005). In addition, for patients with pre-operative Hb lower than 130 g L\(^{-1}\), our blood-saving protocol seems to be as effective as another more complex and expensive protocol, using rHuEPO alone (Golberg et al., 1996; Stowell et al., 1999; Karkouti et al., 2005; Rosencher et al., 2005; Weber et al., 2005) or in combination with other blood-sparing methods (Couvret et al., 2004; Kourtzis et al., 2004; Minoda et al., 2004), with a transfusion rate ranging from 4.5% to 16.4%.

The effectiveness of our blood-saving protocol is most probably due to the erythropoietic effect of intravenous iron, overcoming the DIA status induced by systemic inflammatory response that follows to major surgery (Biesma et al., 1995; Van Iperen et al., 1998). This DIA status is not corrected by oral iron (Sutton et al., 2004; Wheetheral & Maling, 2004; Mundy et al., 2005) since intestinal iron absorption is decreased in the presence of inflammation-induced high hepcidin levels (Fleming & Bacon, 2005). On the other hand, when parentally administered, the iron–carbohydrate complexes are metabolized, the iron is released and then binds to transferrin in the plasma and the redundant carbohydrate moiety is then cleared via the liver (MacDougall, 2000). Intravenous iron emerged as a therapeutic option for the treatment of DIA in these patients since the increased erythropoietic effect (4.5–5.5 times that of basal) of intravenous iron lasts for 7–10 days, after which the iron is sequestered by the reticuloendothelial system (Goodnough et al., 2000). The addition of EPO in patients with pre-operative Hb < 130 g L\(^{-1}\) (the cut-off for EPO administration in orthopaedic surgery) might further enhance the effects of iron on erythropoiesis, as endogenous erythropoietin secretion is reduced after surgery (Biesma et al., 1995; Van Iperen et al., 1998), and hepcidin may also inhibit erythroid colony formation at low erythropoietin concentrations (Dallalio et al., 2005).

In addition, the net post-operative reduction in Hb levels in this study was higher for patients receiving iron sucrose than for those receiving iron sucrose plus sucrose.
rHuEPO (38 vs. 27 g L\(^{-1}\), respectively; \(P < 0.01\)) (Table 2), despite they had similar weight, height and post-operative blood loss (Table 1). These data, together with the significantly higher increases in RDW, reticulocyte index and sTfR concentrations (Fig. 1), strongly suggest that the stimulation of erythropoiesis during the first seven post-operative days was more pronounced in patients receiving iron sucrose plus rHuEPO than in those receiving iron sucrose alone, whereas no differences were observed in Hb recovery from PO7–30 (Table 2). Overall, patients receiving rHuEPO showed a higher recovery of pre-operative Hb levels at PO30, although there was no difference in the prevalence of anaemia between groups (19/129 vs. 4/19; \(P = 0.48\)) (Table 2).

On the other hand, assuming that 1 µL\(^{-1}\) of ferritin is roughly equivalent to 8 mg of stored iron and that 165 mg of iron is needed to reconstitute 10 g L\(^{-1}\) of Hb in a 70-kg adult (Worwood, 1979), 66 (45%) patients did not have enough stored iron (pre-operative ferritin < 100 µg L\(^{-1}\)) to reconstitute their perioperative Hb loss (37 ± 15 g L\(^{-1}\)) and keep a normal iron store (ferritin ≥ 30 µg L\(^{-1}\)) (Table 2), especially if intestinal iron absorption is diminished. Consequently, they would be more likely to benefit from perioperative iron sucrose. However, the administration of intravenous iron resulted in 70% recovery of perioperative Hb loss and 92% recovery of pre-operative Hb levels at day 30 (Table 2), without difference between patients with pre-operative ferritin levels lower or higher than 100 µg L\(^{-1}\) or with or without persistence of inflammation at PO30 (Table 2). In contrast, most of the patients with evidence of DIA (Beutler et al., 2003) at PO30 presented pre-operative ferritin < 100 µg L\(^{-1}\) (Table 3). This post hoc analysis seems to indicate that patients with pre-operative ferritin < 100 µg L\(^{-1}\) might also benefit from a larger dose of iron sucrose (e.g. 3 × 200 mg).

Moreover, this Hb reconstitution was attained with only a 5% ABT rate and without a reduction of iron stores in any group (Table 2), whereas Wallis et al. (2005) using oral iron or no treatment found a similar Hb reconstitution (80%) at PO56, but 40% of their patients received ABT (mean: 2-25 units, range: 1–4)

Table 2. Change in Hb at day 7 and day 30 compared with change in ferritin at day 30, according to treatment and to CRP level (mg L\(^{-1}\)) at day 30

<table>
<thead>
<tr>
<th>Group</th>
<th>Hb (g L(^{-1}))</th>
<th>Anaemia</th>
<th>Ferritin (µg L(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DS</td>
<td>PO7</td>
<td>ΔHbp</td>
</tr>
<tr>
<td>IVI</td>
<td>145</td>
<td>107</td>
<td>–38</td>
</tr>
<tr>
<td>EPO</td>
<td>123*</td>
<td>96*</td>
<td>–27*</td>
</tr>
<tr>
<td>Ferritin DS &lt;100</td>
<td>141</td>
<td>104</td>
<td>–37</td>
</tr>
<tr>
<td>Ferritin DS ≥100</td>
<td>145</td>
<td>108</td>
<td>–37</td>
</tr>
<tr>
<td>CRP PO30 ≤5</td>
<td>143</td>
<td>106</td>
<td>–37</td>
</tr>
<tr>
<td>CRP PO30 &gt;5</td>
<td>141</td>
<td>106</td>
<td>–35</td>
</tr>
<tr>
<td>All patients</td>
<td>142</td>
<td>106</td>
<td>–36</td>
</tr>
</tbody>
</table>

IVI, intravenous iron only (\(n = 129\)); EPO, intravenous iron + erythropoietin (\(n = 19\)); DS, day of surgery; PO7, post-operative day 7; PO30, post-operative day 30; ΔHbp, Hb loss between DS and PO7; ΔHbr, Hb reconstituted between PO7 and PO30; ΔFerritin, ferritin fall between DS and PO30.

*\(P < 0.01\), IVI vs. EPO; **\(P < 0.01\), ferritin DS < 100 vs. ferritin DS ≥100; ***\(P < 0.01\), CRP PO30 ≤5 vs. CRP PO30 >5.

Table 3. Anaemia and iron status before surgery (DS) and at post-operative day 30 (PO30), according to pre-operative ferritin levels <100 µg L\(^{-1}\) (\(n = 66\)) or ≥100 µg L\(^{-1}\) (\(n = 82\))

<table>
<thead>
<tr>
<th>Ferritin &lt; 100 µg L(^{-1})</th>
<th>Ferritin ≥ 100 µg L(^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaemia</td>
<td>DS</td>
</tr>
<tr>
<td>TSI &lt; 20%</td>
<td>3</td>
</tr>
<tr>
<td>Ferritin &lt; 30 µg L(^{-1}) and CRP ≤ 5 mg L(^{-1})</td>
<td>13</td>
</tr>
<tr>
<td>Ferritin &lt; 50 µg L(^{-1}) and CRP &gt; 5 mg L(^{-1})</td>
<td>8</td>
</tr>
<tr>
<td>sTfR &gt; 3-5 mg L(^{-1})</td>
<td>10</td>
</tr>
</tbody>
</table>

*Data are \(n (\%)\).
and there was a significant reduction of ferritin levels in non-transfused patients.

Finally, despite these apparent beneficial effects, there are some concerns regarding the incidence of serious adverse effects of intravenous iron preparations. In this respect, iron sucrose seems to be a safe intravenous iron formulation (Silverstein & Rodgers, 2004), and consequently it is not surprising that no adverse effects of iron sucrose administration were witnessed in this study. In contrast, up to 20% of patients receiving post-operative oral iron supplementation reported some adverse effects (Sutton et al., 2004; Wheatheral & Maling, 2004; Mundy et al., 2005).

In conclusion, the results of this observational study suggest that this blood-saving protocol, consisting of a restrictive transfusion trigger plus perioperative administration of intravenous iron sucrose (400 mg) ± rHuEPO (4 000 IU), seems to be effective in significantly reducing ABT rate while hastening the recovery from post-operative anaemia after TKR surgery, without inducing iron depletion. However, to further reduce the prevalence of post-operative anaemia, patients with pre-operative ferritin <100 ng mL⁻¹ might receive a larger dose of iron sucrose. Obviously, more studies to confirm this hypothesis are warranted.

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