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Preoperative haematinics and transfusion protocol reduce the need for transfusion after total knee replacement☆

Jorge Cuenca [a], José A. García-Erce [b], Fernando Martínez [a], Rafael Cardona [a], Luís Pérez-Serrano [a], Manuel Muñoz [c,*]

[a] *Department of Orthopaedic and Trauma Surgery, University Hospital ''Miguel Servet'', Avenida Isabel la Católica, 1-4, 50008-Zaragoza, Spain*
[b] *Department of Haematology, University Hospital ''Miguel Servet'', Isabel la Católica, 1-4, 50008-Zaragoza, Spain*
[c] *GIEMSA, School of Medicine, University of Málaga, Boulevard Louis Pasteur s/n, 29071-Málaga, Spain*

KEYWORDS
Knee replacement;
Allogeneic transfusion;
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Abstract *Background:* Unilateral total knee replacement (TKR) can result in a substantial blood loss and 30–50% of these patients receive allogeneic blood transfusion (ABT), this transfusion rate may be even higher among anaemic patients.
Patients and methods: We assessed the requirements for ABT in 156 consecutive patients undergoing surgery for primary TKR, who received iron ferrous sulphate (256 mg/day; 80 mg of Fe^{2+}), vitamin C (1000 mg/day) and folic acid (5 mg/day) during the 30–45 days preceding surgery, and who were transfused if Hb <80 g/L and/or clinical signs/symptoms of acute anaemia/hypoxemia (Group 2). A previous series of 156 TKR patients serves as a control group (Group 1).
Results: Compared to those in Group 1, patients in Group 2 presented a lower transfusion rate (5.8% vs. 32%, for Group 2 and Group 1, respectively; $p < 0.01$), and a lower transfusion index (1.78 ± 0.44 vs. 2.22 ± 0.65 units per transfused patient, respectively; $p < 0.05$). After patient's stratification according to a preoperative Hb above or below 130 g/L, the differences in transfusion rate remained significant, although 19% of patients from Group 2 still needed ABT if their preoperative Hb <130 g/L.

☆ *Ethical statement*: This study has been approved by the Institutional Review Board of the University Hospital ''Miguel Servet'', Zaragoza, Spain, and all patients gave informed consent to enter the study.
Conflict of interest statement: We declare that no benefits or founds were received in support of the study.

* Corresponding author. Tel.: +34 952 131540; fax: +34 952 131534.
E-mail address: mmunoz@uma.es (M. Muñoz).

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Conclusion: This protocol seems to be effective for avoiding ABT in non-anaemic TKR patients, whereas for anaemic patients another blood saving strategy, such us preoperative erythropoietin administration or postoperative blood salvage, should be added to further increase its effectiveness.

Introduction

Unilateral total knee replacement (TKR) can result in a substantial blood loss[1,2] and 20–50% of these patients receive allogeneic blood transfusion (ABT).[2–4] However, allogeneic blood is a scarce and increasingly expensive resource and ABT is not a risk free therapy for orthopaedic patients.[2,3] All these have prompted the development of different methods to reduce or avoid ABT in these patients, including implementation of restrictive transfusion protocols,[5] use of postoperative autotransfusion[1,6,7] and administration of pharmacological agents.[8]

On the one hand, a recent meta-analysis of randomised clinical trials concluded that preoperative autologous blood donation (PABD) (RR 0.16; 95%CI 0.07–0.36) and perioperative cell salvage (RR 0.35; 95%CI 0.21–0.52) decrease the frequency of exposures to ABT when compared with a control in orthopaedic surgery.[9] However, the real contribution of autologous blood to ABT reduction decreases if a transfusion protocol is adopted.[9] From these data it can be inferred that a transfusion protocol does in itself reduce by 25–30% 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 Hb level is one of the strongest predictors for postoperative ABT after TKR,[4,10,11] and that stimulation of erythrocyte production may reduce the requirements for ABT in patients with mild anaemia.[8]

In this work, we therefore evaluated the effectiveness of the implementation of a restrictive transfusion protocol together with the preoperative administration of haematinics to reduce the requirements for ABT in patients undergoing surgery for TKR, with special interest on those patients with mild anaemia (Hb <130 g/L).

Patients and methods

Patients

After approval by the Institutional Review Board, during a 12 month period, all patients scheduled for elective primary TKR in a single institution were interviewed by the surgeon at least 1 month before surgery to enter in a blood saving protocol. Patients with haematological diseases or coagulation disorders, those under anticoagulant therapy or with known infection or malignancy at admission and those with revision surgery or preoperative autologous blood donation were excluded. Finally, 156 TKR patients entered the study (Group 2). A previous series of another 156 TKR patients who met these inclusion criteria and underwent surgery before the implementation of the blood saving protocol, served as the control group (Group 1).

Data collection

A set of demographical and clinical data was gathered for all patients, including gender, age, preoperative Hb concentration at the time of surgeon's interview, 24 h postoperative Hb concentration, transfusion rate (percentage of transfused patients), transfused units, transfusion index (blood units per transfused patient), and length of hospital stay.

Surgical procedure

All patients were operated on by the same surgical team, under standardised anaesthesia, antibiotic and antithrombotic prophylaxis, and postoperative analgesia. The same implant (Nex-Gen®, Zimmer, USA) was used in all knees, with all components being cemented. All procedures were performed using a pneumatic tourniquet that was deflated after wound closure, and three closed suction drains (two inside the joint and one subcutaneous), which were removed at the second postoperative day. All patients stayed at the post-anaesthesia recovery unit for at least 2 h before being transferred to the ward.

Blood saving protocol

In Group 2, patients received iron ferrous sulphate (256 mg/day; 80 mg of Fe^{2+}), vitamin C (1000 mg/day) and folic acid (5 mg/day) during the 30–45 days preceding surgery, and referred adverse effects of the treatment were recorded. Normovolaemic patients were transfused if their Hb felt below 80 g/L and presented clinical signs/

symptoms of anaemia/hypoxemia, (e.g., hypotension, tachycardia, tachypnea, dizziness, fatigue, etc.) or at a higher Hb if they presented clinical signs and were at risk (e.g., coronary or valve heart disease or obstructive pulmonary disease). In the control group, patients did not received preoperative haematinics and transfusion decisions relied only in a Hb level below 90 g/L. All patients received oxygen therapy (2 L/min) during the first 48 postoperative hours. No other blood saving method was used in any patient.

Statistical analysis

Data were expressed as percentage (%) or as the mean ± SD (*n*). Pearson's chi-squared test or Fisher's exact test was used for comparison of qualitative variables, and Student's *t* test, Mann–Whitney *U* test or Wilcoxon's rank test for comparison of quantitative variables. 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

There were not statistically significant differences between groups regarding patient's age, gender distribution, anaesthetic risk (ASA I-III), Hb at preoperative assessment, or length of hospital stay (Table 1). At preoperative assessment, 17% of patients in Group 1 (26/156; 24 women and 2 men), and 20% of patients in Group 2 (31/156; 25 women and 6 men) presented a Hb level lower than 130 g/L (p = NS).

When compared to Group 1, this blood saving protocol resulted in a lower percentage of transfused patients (5.8% vs. 32%, for Group 2 and Group 1, respectively; chi-squared = 35.1, $p < 0.01$) and no serious adverse effects of haematinic administration was reported by the patients. In Group 1, 15 patients received transfusion on the second postoperative day or later, whereas in Group 2 all transfusions were given with the first 24 postoperative hours. The differences in transfusion rate remained significant after patient's stratification according to preoperative Hb: 19.3 vs. 61.5% for Hb <130 g/L (chi-squared = 10.6, $p < 0.01$), and 2.4 vs. 26.1% for Hb ≥130 g/L (chi-squared = 28.9, $p < 0.001$), for Group 2 and Group 1, respectively (Fig. 1). Similarly, a lower transfusion index was recorded for Group 2 when compared to Group 1 (Table 1). After patient's stratification according to preoperative Hb, these differences remained significant only for patients with Hb ≥130 g/L ($p < 0.05$) (Fig. 1). Finally, as shown in Table 1, 24 h postoperative Hb levels were significantly higher in Group 2 with respect to Group 1 ($t = -2.06$, $p < 0.05$), and this difference was even higher after subtracting the effect of transfusions given within the first 24 postoperative hours (100 ± 14 vs. 107 ± 16 g/L, for Group 1 and 2, respectively; $t = -4.73$, $p < 0.01$).

Table 1 Demographic and clinical data of two series of patients undergoing surgery for total knee replacement with (Group 2) or without (Group 1, control) preoperative oral haematinic supplements (ferrous sulphate, 240 mg/day; vitamin C, 1000 mg/day; and folic acid, 5 mg/day, for 30–45 days prior to surgery) and restrictive transfusion protocol

	Group 1[a]	Group 2[b]
Patients (*n*)	156	156
Age (years)	70 ± 5	71 ± 6
Gender (M/F)	48/108	53/103
Preoperative Hb (g/L)	139 ± 13	141 ± 13
24 h postoperative Hb (g/L)	105 ± 12	108 ± 14*
Transfused patients (*n*, %)	50 (32)	9 (5.8)**
Transfused units (*n*, %)		
0	110 (68)	147 (94.2)
1	3 (2)	2 (1.3)
2	36 (23)	7 (4.5)*
3	11 (7)	0 (0)
Transfusion index (units/ transfused patient)	2.22 ± 0.65	1.78 ± 0.44***
Length of hospital stay (days)	12 ± 4	11 ± 5

Data are expressed as mean ± SD, incidence or %. *$t = -2.06$, $p < 0.05$, Group 1 vs. Group 2; **chi-squared = 35.1, $p < 0.01$, Group 1 vs. Group 2; ***$W = 191.5$, $p < 0.05$, Group 1 vs. Group 2.
[a] Transfusion protocol: Hb <90 g/L.
[b] Transfusion protocol: Hb <80 g/L and/or signs/symptoms of acute anaemia/hypoxemia.

Discussion

Allogeneic blood transfusions are often necessary during and after total hip and total knee arthroplasty because of perioperative blood loss-induced anaemia. However, the rate of postoperative infection is significantly higher in receiving ABT than in those receiving autologous blood or in those non-transfused, most probably due to a transfusion-related immuno-depression.[2,3] In addition, there are ABT-related risks, such as transfusion

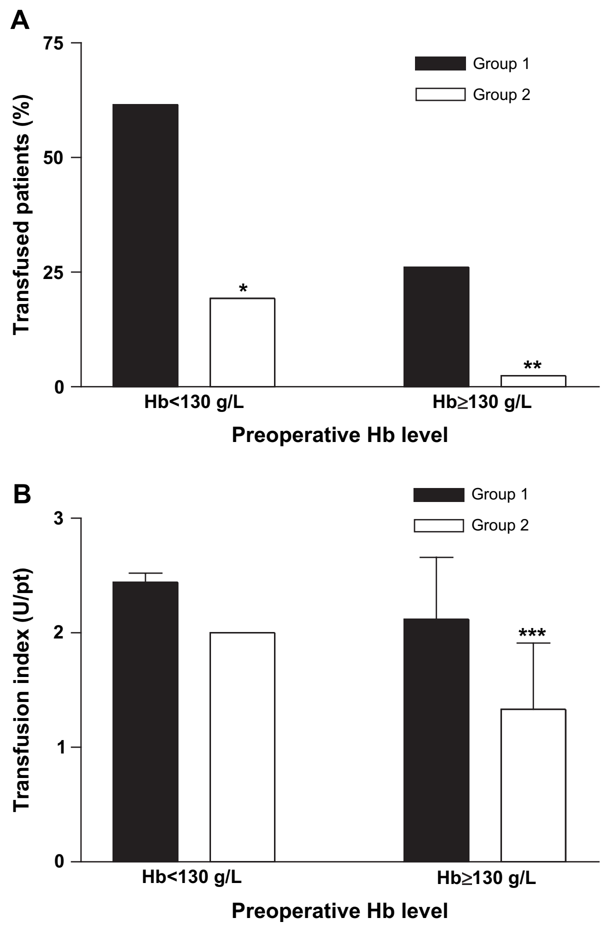

Figure 1 Allogeneic transfusion in patients undergoing primary total knee arthroplasty, according to the preoperative haemoglobin level. (A) Percentage of transfused patients (*chi-squared = 10.6, $p < 0.01$, **chi-squared = 28.9, $p < 0.01$, group 1 vs. group 2). (B) Transfusion index (units per transfused patient) (***$W = 24$, $p < 0.05$, group 1 vs. group 2).

reactions through storage-induced mechanisms, errors in blood administration and viral or bacterial contamination, which have led to the development of different strategies to reduce or avoid the need for ABT.

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 transfusion after elective joint replacement.[5] In this respect, a randomised 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).[12] However, a higher transfusion threshold seems more appropriate for surgical patients with no risk factors for ischaemia, as they have a much lower degree of monitoring. In addition, attention needs to be paid to signs and symptoms of anaemia, as they are variable depending on the patient's age, body temperature, medications, rate of volume loss and co-morbidities.

As of January 2000, a conservative transfusion protocol (Hb threshold 90 g/L) was introduced in our institution. Patients in the control group (Group 1) were managed with this conservative transfusion protocol resulting in 32% of patients being transfused and in a transfusion index of 2.22 units per transfused patient. To reduce these figures, we implemented a blood saving protocol for TKR in which in a more restrictive transfusion protocol (Hb <80 g/L) was the cornerstone. Additionally, all patients received oral haematinics for 30—45 days prior to surgery to improve erythropoiesis, as low iron stores and folate deficiency are not uncommon among elderly patients.[13,14] This protocol has proved to be useful since the transfusion rate (5.8%) and the transfusion index (1.78 units per transfused patient) in patients from Group 2 were reduced with respect to both the previous series in our institution (Group 1) and other published series.[2—6] Moreover, for patients with preoperative Hb <130 g/L, our protocol seems to be as effective as other more complex and expensive protocols, involving the use of rHuEPO alone or in combination with other blood conservation methods, or a flow chart on the use of blood transfusion, with a lower transfusion trigger (Hb <70 g/L).[15—18]

This greater effectiveness is probably due to the stimulatory effect of haematinics on erythropoiesis,[19] although part of the observed effect could reflect changes in the general attitude towards allogeneic transfusion. In this regard, a randomised trial on iron pre-load for major joint replacement showed that at least 18% of patients attending for hip or knee replacement were anaemic and benefited significantly from preoperative iron supplements over 4 weeks.[13] In addition, iron supplementation in patients without obvious anaemia protects against a fall in Hb during the immediate post-operative period, suggesting a widespread underlying depletion of iron stores in this group despite a normal Hb.[13] However, when administered after surgery, oral iron was not effective in rising Hb levels[20,21] since post-operative erythropoiesis is limited by the inflammatory effects of surgery on iron metabolism.[22,23] On the other hand, a population-based study ($n = 1562$) of older persons revealed that up to 20% of them were at high risk of folate deficiency and, consequently, they should be considered for treatment.[14]

The stimulatory effect of preoperative haematinics may also be inferred from comparison of data obtained both groups. As shown in Table 1, there were no differences between series in preoperative Hb at the time of surgeon's interview, but at 24 h postoperative Hb was significantly higher in Group 2. However, the transfusion index was higher in Group 1 than in Group 2 (Table 1), and it can be assumed that transfusion of one packet red cell unit increases patient's Hb by 10 g/L and that perioperative blood loss was similar in both series. Thus, by subtracting the effect of transfusion given within the first 24 postoperative hours, the preoperative treatment would account for a reduction in postoperative Hb drop of about 7 g/L (100 ± 14 vs. 107 ± 16 g/L, for Groups 1 and 2, respectively; $p < 0.01$).This effect seems to be important as 15 patients from Group 1 received transfusion on the second postoperative day or later, whereas all patients in Group 1 where transfused within the first 24 h postoperative hours. In addition, the differences in transfusion rate would have been remained if the same transfusion threshold (Hb <90 g/L) would have been used in both groups (32 vs. 12%, for Groups 1 and 2, respectively; $p < 0.01$). Hence, in contrast to postoperative oral iron,[20,21] preoperative haematinic supplements including oral iron may enhance erythropoiesis[13] and, within a coordinated blood saving strategy, it may help to reduce postoperative transfusion requirements.[19]

In conclusion, this blood saving protocol seems to be effective for reducing ABT in TKR patients, although the limitations derived from study design preclude establishing whether this is due to the use of oral haematinics or a more reluctant transfusion protocol. Despite this, we believe that the use of a restrictive transfusion threshold might contribute to an early ABT reduction (<48 h), whereas the stimulatory effect of perioperative administration of haematics on erythropoiesis might contribute to avoiding late ABT (>72 h). In addition, the use of intravenous iron might also be considered for those patients who do not tolerate oral iron and when time to surgery is too short for oral therapy.[24,25] Finally, since 19% of the anaemic TKR patients still needs ABT, it becomes evident that some additional blood saving method, such us postoperative blood salvage[1,6] or preoperative administration of recombinant human erythropoietin,[26] should be associated to reduce further the need for ABT.

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