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Length of Storage of Transfused Red Blood Cells and Risk of Prosthetic Joint Infection After Primary Knee Arthroplasty

Sandra P. Gómez-Lesmes, MD [a], Eduard Tornero, MD [b], Juan C. Martínez-Pastor, MD, PhD [b], Arturo Pereira, PhD [c], Miguel Marcos, PhD [a], Alex Soriano, PhD [d]

[a] Department of Internal Medicine, University Hospital of Salamanca-IBSAL, Salamanca, Spain
[b] Department of Orthopedic Surgery, Spain
[c] Service of Hemotherapy and Hemostasis, Spain
[d] Service of Infectious Diseases, IDIBAPS, University of Barcelona, Spain

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ABSTRACT

The aim of our study was to determine the potential influence of blood transfusion and the length of storage of packed red blood cells (RBC) on prosthetic joint infection after primary knee arthroplasty. From November 2007 to November 2009, all variables potentially associated with deep infection were registered in 1331 consecutive patients who underwent total knee arthroplasty. Infection was diagnosed in 32 (2.4%) patients. After adjusting for important variables, blood transfusion with RBCs stored >14 days was the strongest predictive factor for prosthetic joint infection within 90 days after primary knee arthroplasty (OR: 5.9, 95% CI: 2.6–13.2, $P < 0.001$). Blood saving techniques are desirable to reduce perioperative blood transfusion.

Blood transfusion has been associated with an increased risk of nosocomial infection in critically ill patients [1] and surgical-site infection after cardiac [2] and orthopedic surgery [3]. Recent data suggest that the length of storage of red blood cells is associated with structural and functional changes of red cells reducing their function altering both tissue oxygenation [4,5] and viability. As a result, plasma and tissue deposition of non-transferrin bound iron increases and this free iron promotes bacterial growth [6]. These mechanisms could explain the previously described association between infection and blood transfusion of old packed red blood cells (RBC). Particularly, an increased risk of infectious complications when storage duration was longer than 14 days has been demonstrated in trauma patients [7–9], and after cardiac surgery [10–12] or in those patients with septic shock [13].

Total knee arthroplasty is the most effective treatment for patients with severe joint disease. Prosthetic joint infection, however, is a potential complication reported in 0.4–2% of cases [3,14], which is associated with extended hospitalization, a long period of disability, suboptimal functional results and increased costs [15]. A number of risk factors for surgical-site infection (SSI) in total joint arthroplasty have been described including intrinsic patient characteristics (such as obesity, malignancy, hyperglycemia or rheumatoid arthritis), the use of specific aseptic measures (type of antiseptic, antimicrobial prophylaxis), surgical technique (duration of surgery, primary or revision arthroplasty) or post-operative factors (urinary tract infections) [3,16–22]. Blood transfusion has been identified as an independent predictor of peri-prosthetic joint infection in a recent retrospective study including more than 9000 primary hip or knee arthroplasties [3]. There is no information, however, about the potential influence of length of packed RBC storage on the risk of prosthetic joint infections. Since the rate of these infections is low and there are other predictors of infection, it is necessary to evaluate a well-documented and large cohort of homogeneous patients that allow us to perform an adequate adjustment for potential confounders.

The aim of our study was to determine the potential influence of blood transfusion and the length of storage on prosthetic joint infection within 90 days after primary knee arthroplasty in a cohort of patients that participated in a prospective, randomized and double-blind study of antibiotic prophylaxis that did not find differences between the 2 arms. Blood transfusion was prospectively collected from the anesthesia report and medical history and was matched with the database of our Blood Bank that also provides information about the length of storage of packed RBCs.

Patients and Methods

From November 2007 to November 2009, a prospective, single-center, randomized, double-blind, placebo control trial was performed in the

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Reprint requests: Alex Soriano, PhD, Service of Infectious Diseases, Hospital Clinic of Barcelona, C/Villarroel 170, 08036 Barcelona, Spain.

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Orthopedic Department of Hospital Clínic of Barcelona (EudraCT number: 2006-006699-40 and ISRCTN code: NCT00497341) that compared 2 different strategies of antimicrobial prophylaxis administration. Patients with allergy to penicillin were excluded from the study. All other consecutive patients who underwent a primary knee arthroplasty during the study period and signed the informed consent were included and prospectively followed-up for 90 days after surgery. The protocol was approved by the ethical committee of our hospital and the Spanish Drug Agency. The standard arm consisted of cefuroxime 1.5 g i.v. 10 minutes before tourniquet inflation, placebo 10 minutes before tourniquet release and cefuroxime 1.5 g i.v. 6 h after closing surgical wound. The experimental arm received cefuroxime 1.5 g i.v. 10 minutes before tourniquet inflation, cefuroxime 1.5 g i.v. 10 minutes before tourniquet release and cefuroxime 1.5 g i.v. 6 h after closing surgical wound. All the procedures were performed after the patient received spinal anesthesia in 4 operating rooms without laminar airflow. The leg was washed first with soap and then with 10% iodine povidone solution (Betadine, Meda Pharma Sau Laboratory). All the prostheses were cemented; 1 deep and 1 superficial drain tube that were left after closing the wound were removed within 24–48 h after the surgical procedure. No antimicrobial agent was added to the cement in any case. Indwelling urine catheters were used in all patients and were removed within the first 24 h after the surgical procedure. No statistically significant difference was observed between the 2 arms (unpublished data).

The variables recorded were age, sex, comorbidity, body mass index (BMI), acenocoumarol or steroid therapy, basal and post-surgical hemoglobin levels, American Society of Anesthesiologists (ASA) score, National Nosocomial Infection Surveillance (NNIS) score, use of tranexamic acid, surgical case order (within each day), the duration of surgery and ischemia, days of draining tubes in place, number and storage time (days) of packed red blood cells (RBC) transfused within the preoperative period (days 0–5), presence of deep wound infection according to Centers for Disease Control and Prevention criteria [23] within 90 days after the surgical procedure, and the microorganisms isolated from these infections. Before surgery, patients were evaluated at the anesthesiology clinic and submitted to a hemoglobin improvement protocol if the preoperative hemoglobin level was below 130 g/L. The protocol consisted of oral or intravenous iron and one or two doses of 40000 UI of erythropoietin until they achieved this level pre-operatively. Tranexamic acid (Amchafibrin, Laboratory Fides-Rottapharm, Almassera, Valencia, Spain) was infused at a dose of 10 mg/kg immediately before inflating the tourniquet and immediately after releasing it except in patients with a history of, or evolving, arterial or venous thromboembolic disease or known congenital thrombophilia. Transfused blood consisted in pre-storage leucoreduced packed RBCs stored in SAG Manitol for a maximum of 42 days. During the surgical procedure and the first 6 h after the procedure, a RBC transfusion was given when the hemoglobin level was <9 g/dL. After this period, the threshold for RBC transfusion was <8 g/dL; for patients with a history of cardiac ischemic disease, the transfusion threshold was 9 g/dL. The number of packed RBCs administered was obtained from the anesthesia report, medical history and matched with the database of our blood bank that also provides information about the length of storage of transfused RBC units.

Since the differentiation between superficial and prosthetic joint infection is particularly difficult after knee arthroplasty, we have an aggressive diagnostic protocol that consists of open debridement obtaining deep periprosthetic samples in all patients in whom infection is suspected. The protocol for culturing samples from periprosthetic tissue consisted of: aspirated synovial fluid and inoculated into aerobic and anaerobic blood culture flasks (Bactec 9240 system; BD Diagnostic Systems) and incubated for 5 days. Positive cultures were identified by conventional microbiological methods. Solid samples from periprosthetic tissue with visual signs of infection (inflammation, granulation, necrosis or purulence) were taken and placed in sterile containers. Swab cultures were obtained by passing a sterile swab over the intracapsular area, bone, or fluid and immediately placed in transport medium (AMIES transport medium). The periprosthetic tissue and swabs were cultured in thioglycolate broth, blood agar under aerobic conditions, and Schaedler agar under anaerobic conditions and were incubated for up to 5 days. Positive cultures were re-grown in the appropriate medium. All microorganisms isolated were identified by standard biochemical procedures. An antibiogram for all isolates was performed by the microdilution method [24]. In all patients who underwent open debridement the liner was changed. Broad-spectrum antibiotics were started after obtaining samples for culture (vancomycin plus ceftazidime) and after obtaining microbiology results, the antibiotics were adapted according to the antibiogram. The median duration of antibiotic treatment was 3 months.

Statistical Analysis

Continuous variables were expressed as mean and standard deviation (SD) or median and interquartile range (IQR), according to variable distribution. Continuous variables were age (years), body mass index (BMI, kg/m^2), duration of intervention (minutes), duration of tourniquet (minutes), postoperative fluid drainage (mL), use of draining tubes (days), hemoglobin levels before surgery and after surgery (g/L), number of packed RBC transfused, C-reactive protein levels before surgery (CRP, mg/dL), number of packed RBCs transfused and time from arthroplasty to diagnosis of deep wound infection (days). Categorical variables were sex, comorbidity (defined as the presence of diabetes mellitus, liver cirrhosis, chronic renal failure, rheumatoid arthritis, or chronic obstructive pulmonary disease), type of microorganism isolated, preoperative physical status classification assessed by the American Society of Anesthesiologist (ASA) score, NNIS risk index score (1 point if the patient has an operation that is classified as either contaminated or dirty, 1 point if the patient has an ASA score of 3, 4, or 5 and 1 point if the duration of the operation exceeds the 75th percentile), need for transfusion and length of storage of packed RBCs ($\leq$14 days versus >14 days) and surgical case order within each day. Since the pathophysiologic mechanism linking the length of RBC storage and clinical outcomes is still imperfect, the categorization is usually based on the authors' criterion [25].

The association of recorded variables with deep infection was analyzed as follows: continuous variables with normal distribution were compared by using the Student's T test and variables that did not meet normal distribution were analyzed by simple logistic regression. The comparison of qualitative variables was done by using the χ^2 test or the Fisher's exact test, when necessary.

A multivariable logistic regression analysis was performed to identify the independent variables associated with deep wound infections within 90 days after surgery. Variables with a P value <0.20 in the univariate analysis were included in the logistic regression model. Transfusion of packed RBCs was included as a three-category variable (no transfusion, packed RBC stored $\leq$14 and >14 days). The tolerance and the variance inflation factor (VIF) were used to check for multicollinearity. The presence of interaction and the role of confounding factors were evaluated. The assessment of the model fit was done with the Hosmer–Lemeshow test. Statistical significance was defined as a two-tailed P value <0.05. The analysis was done with the SPSS program (version 19.0; SPSS, Inc., Chicago, IL).

Results

During the study period, 1331 consecutive patients undergoing primary knee arthroplasty were included. Overall mean age (SD) of patients was 71.9 (7.97) years and 71.3% of patients were female. Median (SD) BMI was 31.13 (4.82) kg/m^2 and 200 patients (15%) had an ASA score $\geq$3. Deep wound infection was diagnosed in 32 (2.4%) patients within 90 days after surgery. Median (IQR) time from surgery to diagnosis of infection was 25 (20–28) days. All patients received appropriate antibiotic prophylaxis according to the protocol detailed