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Is the Newest Fibrin Sealant an Effective Strategy to Reduce Blood Loss After Total Knee Arthroplasty? A Randomized Controlled Study

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ABSTRACT

An RCT was conducted to ascertain whether, compared to control management, topical application of a novel fibrin sealant (Evicel, J&J) in patients undergoing primary TKA reduces peri-operative blood loss. Sixty-two patients were randomized to receive topical application of Evicel (N = 31) or not (N = 31). The mean total blood loss was 1.9 L(±0.7) in the control group and 1.8 L(±0.5) in the treatment group ($P = 0.4$). The transfusion rate was 32.3% in the control group and 25.8% in the treatment group ($P = 0.5$). The transfusion rate decreased linearly with increasing preoperative Hb levels in the treatment group ($P = 0.005$). The results of this study suggest that topical application of this novel fibrin sealant doesn't reduce perioperative blood loss and the need for allogeneic blood transfusion.

Total knee arthroplasty (TKA) is an invasive surgical procedure that can expose patients to major perioperative bleeding, with recorded perioperative blood losses in primary TKA ranging from 800 to 1790 ml [1–3]. This blood loss results in a high rate of blood transfusions after TKA, with the incidence of such transfusions being from 10% to 58% in different series [4–7].

Allogeneic blood transfusion may result in the transmission of infectious diseases or cause various, severe immune-mediated adverse reactions [8–12]. Methods to prevent the need for allogeneic blood transfusion after TKA include hemodilution, perioperative blood salvage and reinfusion, hypotensive anesthesia, preoperative autologous blood donation and intravenous administration of tranexamic acid [3,6].

A more appropriate blood management strategy is based on enhanced hemostasis during surgery. In the last decade, the topical use of fibrin sealant has become a logical surgical stratagem for reducing blood loss in joint arthroplasty [13–15]. Fibrin sealants mimic the final step of the coagulation cascade reducing blood loss and transfusion requirements [16]. They are composed of two main components, fibrinogen and thrombin, which are mixed together during the application process. Fibrin sealant applied on the peri-prosthetic exposed tissues during the operation can promote the blood coagulation cascade reducing blood loss. There are different haemostatic agents available on the market and several authors have described making fibrin sealant for surgical use themselves [17,18].

A novel hemostatic agent derived from banked allogeneic human plasma (EVICEL, Johnson & Johnson Wound Management, Ethicon, Somerville, NJ, USA) has recently become available on the market for a variety of surgical specialties [19–21]. This is a new formulation of the previously available fibrin sealant (Quixil/Crosseal, Omrix Biopharmaceuticals, Somerville, NJ, USA) that contains only human components with no tranexamic acid that was found to potentially be associated with adverse outcomes or risk during surgerry [22,23]. To our knowledge there is little published evidence from prospective, randomized controlled trials on the effectiveness of this new product in TKA.

We, therefore, performed a randomized controlled trial in our institution to address the question of whether the topical application of this novel fibrin sealant in patients undergoing TKA reduces perioperative blood loss and the need for allogeneic blood transfusion by comparing these outcomes in the treated group and in a control group. The primary outcome measure was postoperative decrease in hemoglobin (Hb) level, with the hypothesis that this would be less in the fibrin sealant group than in the control group.

Materials and Methods

A randomized controlled study was designed to evaluate the effectiveness of a novel fibrin tissue adhesive in patients undergoing primary TKA. The study protocol was approved by the competent ethics review committee (authorization number 2603; February 18, 2011) and all patients gave written informed consent to participation in this clinical study.

This trial was registered with www.clinicaltrials.gov and the registry number is NCT01816282.

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Ninety-five patients with a diagnosis of osteoarthritis of the knee scheduled for primary TKA were evaluated between February 2011 and April 2012. Exclusion criteria were preoperative Hb level lower than 12 g/dl for male patients and lower than 11 g/dl for female patients, autoimmune or blood diseases, previous surgery to the knee with the exception of meniscectomy, anticoagulation therapy or any anti-platelet treatment that had not been suspended at least 4 days before the surgery.

Of 95 patients screened for eligibility, 62 were enrolled and randomized to receive the topical application of fibrin sealant (N = 31, treatment group) or not to receive any additional treatment (N = 31, control group) other than the TKA. Thirty-two patients did not meet the inclusion criteria and one patient declined to participate in the trial.

Neither pre-donation of autologous blood nor stimulation of erythropoiesis with erythropoietin-alpha or intravenous iron was allowed prior to the surgical intervention.

Prophylactic low molecular weight heparin therapy was started 12 h before the operation and postoperatively the patients were given 40 mg of enoxaparin per day (Clexane, Sanofi-Aventis SpA) subcutaneously for 35 days. Intravenous administration of tranexamic acid was not allowed in any patients.

All the procedures were performed by a single surgeon (P.R.). Patients were operated under spinal anesthesia with bupivacaine associated with a standard general anesthesia. The same surgical procedure was used in all 62 patients. A posterior-stabilized cemented prosthesis for primary TKA (P.F.C. Sigma, Depuy Johnson & Johnson, Warsaw, Indiana) was implanted via the medial parapatellar access with patellar resurfacing. A tourniquet was used and deflated after insertion of the prosthesis; the duration of tourniquet inflation was recorded.

All patients received the same treatment following the standard operating technique with the only difference between the control and treatment group being the additional application of fibrin sealant just before wound closure, and after standard hemostasis had been carried out. After positioning the prosthesis, the surgical field was cleaned with physiological saline solution to remove debris from the soft tissue. Primary hemostasis of visible blood vessels was achieved with electrocautery after the release of the tourniquet. The surgeon was blinded to the patients' treatment allocation until the application of the fibrin sealant reducing the possibility of bias.

A block randomization procedure was used to generate the randomization list by dedicated software (StatsDirect Ltd, Cheshire, UK). An independent operator not involved in the surgical treatment prepared sealed, opaque numbered envelopes containing the treatment assignment. The envelopes were opened just before wound closure.

In patients in the treatment group, 5 ml of EVICEL, composed of human derived fibrinogen (from 250 to 450 mg) and thrombin (4000–6000 IU) in two separate vials, was sprayed over the periprosthetic tissues using the corresponding fibrin sealant double syringe spray device at a distance of at least 10–15 cm. The fibrin sealant was sprayed over the exposed soft tissue paying particular attention to the posterior region of the joint and to the subcutaneous areas.

After the application of the fibrin sealant the wound was sutured and two aspiration drains were placed within the joint and in the subcutaneous field. No placebo was used in the control group.

After the surgery a vascular bandage was applied and the leg was maintained in extension.

The drains were removed in the morning of the first postoperative day and the apparent postoperative blood loss was recorded. In no case was the blood in the drains re-infused into patients.

In the post-operative period an absolute indication for transfusion was Hb level <8 g/dl. In other cases, for Hb values lower than 9 g/dl, the decision regarding blood transfusion was based on the clinical condition of the patient, considering cardiovascular history, ASA score and clinical tolerance of the anemia [24].

Bleeding-related outcome measures included total blood loss, changes in Hb levels, drained blood loss and the number of patients requiring allogeneic blood transfusions. Hb levels were measured before surgery and at 12 h and 1, 2, 3 and 7 days after surgery.

The perioperative blood loss was calculated based on changes in Hb level [25]. Assuming that the blood volume V_0 on the seventh day after surgery was the same as that before surgery the loss of Hb was estimated according to the following formula:

$$\text{Hb}-\textit{loss}(\text{g}) = \text{Vo}(1) \times \left(\text{Hb}_{\text{pre-op}}(\text{g/1}) - \text{Hb}_{\text{7day post-op}}(\text{g/1})\right) + \text{Hb}-\textit{transfused}\ (\text{g})$$

where:

- Hb-*loss* (g) was the amount of hemoglobin lost
- $\text{Hb}_{\text{pre-op}}$ (g/l) was the hemoglobin level before surgery
- $\text{Hb}_{\text{7day post-op}}$ (g/l) was the hemoglobin level on postoperative day 7
- Hb-*transfused* (g) was the total amount of allogeneic hemoglobin transfused; a unit of banked blood was considered to contain 52 g of hemoglobin.
- V_0 (l) was the patient's total blood volume and was calculated using Nadler's formula: [26]

$$V_{0\text{male}}(1) = 0.3669 \times \text{height}(\text{m})^3 + 0.03219 \times \text{weight}(\text{Kg}) + 0.6041$$

$$V_{0\text{female}}(1) = 0.3561 \times \text{height}(\text{m})^3 + 0.0338 \times \text{weight}(\text{Kg}) + 0.1833$$

The total blood loss was calculated as follows:

$$\text{Blood loss (l)} = \text{Hb-}\textit{loss}\ (\text{g})/\text{Hb}_{\text{pre-op}}\ (\text{g/l})$$

Statistical Analysis

To determine the necessary sample size, a power analysis was conducted considering the effects of fibrin sealant on the postoperative decrease in Hb level. The power analysis showed that to detect a difference of 1 g/dl in the postoperative decrease in Hb level between the two groups with a standard deviation of 1.3 g/dl, at least 30 patients would be needed for each group. These numbers were based on a power ($1 - \beta$) of 0.80 and a significance level of 5% (two-sided).

Continuous variables were expressed as the mean (± standard deviation). Categorical variables were presented as percentages of cases.

We tested differences between the treatment and control group for continuous variables with an unpaired Student t or Mann–Whitney test, according to the characteristics of the data distribution.

The chi-square test was used to assess differences in the proportions of patients needing transfusions in the two groups, with the chi-square test for trend applied to investigate whether there was a linear trend for increasing values of preoperative Hb.

Variables were entered into a forward stepwise logistic regression model to identify factors independently associated with the risk of blood transfusion.

Statistical analyses were carried out using SPSS Version 17 (SPSS Inc., Chicago, IL, USA). For all analyses, a P value < 0.05 was considered statistically significant.

Results

The treatment and control groups were comparable in terms of the patients' baseline characteristics (Table 1). The duration of tourniquet inflation was 55 min (±9.5) and 54 min (±9.7) in the treatment and control group, respectively ($P = 0.8$). The duration of surgery in the