Intraarticular Fibrinogen Does Not Reduce Blood Loss in TKA: A Randomized Clinical Trial

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Abstract

Background Bleeding remains an ongoing concern after total knee arthroplasty (TKA). Intraarticular application of human fibrinogen with a topical thrombin has been described to stop diffuse bleeding in knee arthroplasty.

Questions/purposes It was hypothesized that the use of human fibrinogen as a topical agent would result in a reduction of bleeding and transfusions required after TKA; secondary end points included comparison of early clinical results including pain scores and range of motion (ROM) at 6 weeks and complications after surgery.

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Methods Two hundred patients undergoing TKA were randomized into a double-blind clinical trial to receive either intraarticular fibrinogen 2 minutes before tourniquet release or no such treatment. Postoperative hemoglobin and hematocrit levels, drain output, and transfusion requirements were recorded and blood loss was calculated. Clinical outcomes and adverse events were tracked prospectively. Descriptive analysis was performed using a two-sample t-test.

Results There were no differences in calculated blood loss between the fibrinogen and the control groups; the mean postoperative drain output was 780 ± 378 mL in the fibrinogen group compared with 673 ± 301 mL in the control group ($p = 0.029$), but the hemoglobin drop at Day 2 was 3.47 ± 1.53 g/L in the fibrinogen group and 3.84 ± 1.24 g/L in the control group ($p = 0.051$). There were no differences in transfusions, early ROM, visual analog pain scores, or complications between the groups.

Conclusions The use of fibrinogen in TKA did not lead to a significant reduction of blood loss or transfusions in primary TKA for osteoarthritis. Given the lack of benefits and the costs this procedure adds to TKA, its routine use cannot be justified during primary TKA for osteoarthritis.

Level of Evidence Level I, therapeutic study. See Guidelines for Authors for a complete description of levels of evidence.

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Introduction

Blood loss after TKA can lead to significant morbidity. Hemarthrosis may lead to increased pain that can interfere with physiotherapy and delay rehabilitation. They may also result in prolonged drainage from the wound [3]. Bleeding can lead to higher transfusion requirements elevating risks of infection, allergic reactions, and healthcare costs [17].

The estimated mean blood loss after TKA has been reported to be as high as 1500 mL [10]. Some of it may be apparent as postoperative drainage but up to 50% of blood loss may be hidden [15]. After TKA the indications and thus the incidence of transfusions differ largely between studies and institutions, but one study reported a postoperative hemoglobin drop of 40% leading to transfusions in 30% of the men and 48% of the women [6].

The surgeon has a number of tools to minimize blood loss with conventional means such as hypotensive anesthesia, the use of a tourniquet, and meticulous hemostasis. However, most of the blood loss in TKA occurs in the immediate postoperative period [7, 9, 14]. Some authors state that this blood loss mainly originates from bone cuts uncovered by cement and implants [9, 11, 13].

The concept of topical application of agents to control bleeding is not new. The use of plasma proteins at the site of the injury was described in the beginning of the last century in the German literature [2], and some early experience with fibrin sealants was reported during World War II [5]. Efforts have been made to use hemostatic agents such as thrombin-based sealants intraoperatively to minimize blood loss and decrease transfusion rates with little success [8]. Systemic tranexamic acid may be a more effective approach [7] but may also be associated with some risks, although recent systematic reviews have failed to demonstrate any difference in adverse events associated with the use of tranexamic acid [1, 19]. Topical application of tranexamic acid has been shown to reduce postoperative blood loss [18].

Human fibrinogen with a topical thrombin has been described to stop diffuse bleeding in TKA in small studies [9, 16] and could be a promising approach to reduce bleeding and consequently lead to lower transfusion rates. Human fibrinogen and thrombin are mixed with calcium and sprayed into the surgical side to mimic the final phase of the coagulant cascade [9].

It was hypothesized that the use of human fibrinogen as a topical agent would result in a reduction of bleeding and transfusions required after TKA; secondary end points included comparison of early clinical results including pain scores and ROM at 6 weeks and complications after surgery.

Patients and Methods

In this study, 200 patients of two surgeons (MPF, SBH) undergoing unilateral TKA for osteoarthritis were prospectively included in a double-blind randomized clinical trial to either receive intraarticular fibrinogen (Evicel; Ethicon, Johnson & Johnson, Somerville, NJ, USA) or no such treatment. Patients older than 18 years who were able and willing to give informed consent were eligible for the study. We excluded patients who had a previous arthrotomy, known bleeding disorders, diagnosis other than osteoarthritis, and use of clopidogrel-containing products before surgery. All eligible patients between September 2010 and June 2012 were invited to participate.

The study received institutional review board approval and follows the principles as articulated in the Declaration of Helsinki. Patients provided informed consent for TKA and for participation in the study. They all donated exactly one unit of autologous blood 4 weeks preoperatively. Patients were uniformly asked to stop taking NSAIDs before surgery.

TKA was performed with a tourniquet through a medial parapatellar approach under hypotensive spinal anesthesia and a femoral nerve block. The tourniquet was inflated before incision and released before wound closure. Discrete bleeding vessels were cauterized. All patients received a posterior-stabilized TKA (either Nexgen, Zimmer, Warsaw, IN, USA, or Legion, Smith & Nephew, Memphis, TN, USA).

A randomization list had been generated with computer support. Randomization was determined before surgery through a sealed opaque envelope system ("Yes": Evicel, "No": control group [8]). Envelopes were opened after the cementing of components. In the control group the tourniquet was released and hemostasis obtained with electrocautery followed by wound closure. In the fibrinogen group, the spray was applied as described subsequently. Randomization envelopes were accounted for at the end of the study. Patients and assessors were blinded to the randomization.

Evicel was used as suggested in the manufacturer's instructions. In the treatment group, after implantation of components, Evicel was applied with a spray applicator to all uncovered bone surfaces, tibial pinholes, and soft tissues. All aspects of the knee were addressed taking it through a full ROM to reach the posterior soft tissues in hyperflexion and the extensor mechanism and lateral and medial gutters in full extension. In each case, a 10-mL vial of the product was used (approximately USD 465 per case). The Evicel was allowed to dry for 2 minutes before tourniquet release. Additional hemostasis of the soft tissues was performed thereafter if necessary using electrocautery before proceeding with insertion of drains and wound closure. No irrigation was used after application of Evicel.

Two 3.175-mm deep drains (ConstaVac; Stryker, Kalamazoo, MI, USA) were inserted and left on low-flow suction (25 mmHg) for 24 hours. The capsule and subcutaneous tissue were closed meticulously in layers and the skin was closed with either staples or monocryl with Dermabond (Ethicon, Johnson & Johnson). A compressive bandage was applied and left in place until the second postoperative day.

Coumadin was used for deep venous thrombosis prophylaxis for 6 weeks postoperatively giving the first dose the night after surgery aiming for a therapeutic international normalized ratio (INR) from 2 to 2.5. All patients had a preoperative INR of < 1.4. A controlled passive motion device (6 hours a day until discharge), physical therapy, and mobilization were started the first postoperative day.

A common trigger point for transfusions was determined as a hemoglobin level < 8 g/dL unless medical reasons necessitated a transfusion above that level. This threshold was used for autologous and homologous transfusions.

Primary outcomes were defined as follows. Drains were pulled exactly 24 hours after the end of surgery and the drain output was recorded. Transfusions were documented. Hemoglobin and hematocrit levels as well as coagulation profiles were determined the day of surgery before and after TKA and on postoperative days 1, 2, and 3 through blood draws. Blood loss was calculated as described by Charrois et al. [4]: total blood loss (mL of erythrocytes: 100% hematocrit) = compensated blood loss + noncompensated blood loss; compensated blood loss (mL) = number red blood cell units $\times$ mL red blood cells per red blood cell unit (180 mL for autologous and 200 mL for homologous units); noncompensated blood loss (mL): = total blood volume $\times$ (preoperative hematocrit – postoperative hematocrit; total blood volume (mL): in men = $604 + 0.0003668 \times [\text{height (cm)}]^3 + 32.2 \times \text{weight (kg)}$; in women = $183 + 0.000356 \times [\text{height (cm)}]^3 + 33 \times \text{weight (kg)}$).

Secondary outcomes included ROM and pain scores preoperatively and at 6 weeks followup. Pain scores were recorded at rest, at night, with activity, and with therapy. At the 6-week visit, ROM, pain scores, and complications were recorded.

For calculation of sample size, the following inputs were used as described in an earlier study [8]: 80% power, a critical p value of 0.05, and a mean difference and SD of 150 ± 350 mL of drain output. A sample size of 98 subjects per group was calculated to give a post hoc power of 85% to detect differences in drainage. A two-sample t-test was applied for continuous variables. A chi-square test was used for discrete variables. A p value of < 0.05 was considered significant.

Table 1. Comparison of baseline demographic, radiographic, and operative characteristics between groups

Variable	Control		Evicel		p value
	Mean	SD	Mean	SD	
Age (years)	66.33	8.38	67.85	10.18	0.250
Body mass index (kg/m ²)	31.91	6.9	30.82	6.94	0.268
Weight (lbs)	200.12	46.15	191.16	45.81	0.173
Height (inches)	66.42	4.27	66.05	4.66	0.556
Tourniquet time (minutes)	53.67	8.94	55.84	8.92	0.101

Of 200 enrolled patients, two had to be excluded. One drain was pulled too early and in another case, Evicel was not usable leaving 98 patients in the Evicel group and 100 in the control group.

There were no differences between groups at baseline in terms of age, body mass index, or preoperative deformity (Table 1).

Results

Blood Loss and Transfusions

There were no differences in calculated blood loss between the groups on DLy 2 (Evicel: 1441 ± 1209 mL, control: 1409 ± 1286 mL, $p = 0.44$). There was a higher average drain output at 24 hours in the Evicel group (Fig. 1; 780 versus 673 mL, $p = 0.029$) as recorded 24 hours after surgery. There were no significant differences in hemoglobin values preoperatively or at Day 0 or 1 after TKA. A small but significant difference was noted on Day 3 in favor of the Evicel group (9.6 versus 9.3, $p = 0.045$; Fig. 2).

There were no differences in autologous or homologous transfusion rates between groups (0.38 versus 0.46 units per patient, $p = 0.314$; and 0.24 versus 0.3 units per patient, $p = 0.595$, respectively) (Table 2). There were no differences in transfusion rates above the threshold of hemoglobin of 8 g/dL given for medical reasons. There were no significant differences in drain output, total blood loss, or transfusion rates between surgeons whose patients were enrolled in this trial.

Pain, Range of Motion, and Complications

No significant differences were noted in visual analog scale pain scores at 6 weeks followup (3.9 in control group, 4.3 in Evicel group; Table 2). Neither were there any differences in knee ROM at 6 weeks followup (114.1° in the control group and 112.4° in the Evicel group; Table 2).

Fig. 1 Comparison of drain outputs between study and control groups, demonstrating a significantly higher mean value in patients treated with fibrinogen sealant ($p = 0.029$).

Fig. 2 There were no significant differences in hemoglobin (HGB) values preoperatively or at Day 0 or 1 after TKA. Minor differences were noted Day 2 reaching statistical significance in favor of the Evicel group at Day 3 (9.6 versus 9.3, $p = 0.045$). POD = postoperative day.

There were two wound healing problems in the Evicel group, which resolved with conservative measures. By the 6-week followup, there had been reported cases of gastrointestinal-related problems (control: three nausea and vomiting, one diarrhea; Evicel: five patients with nausea and vomiting), cardiac (control: four patients with tachycardia; Evicel: one left bundle branch block, one atrial fibrillation, three patients with tachycardia) or blood pressure issues (control: four with hypotension; Evicel: six with hypotension, two with hypertension), urinary tract infections (one control, one Evicel), fever (three control, four Evicel), and several cases of confusion (one control, four Evicel). There was no association between Evicel use and

the occurrence of these adverse events. There were no cases of cellulitis, deep venous thromboses, revisions, or stiffness requiring manipulation in this series.

Discussion

Blood loss after TKA can result in the need for transfusions, which add cost and risk to the procedure, and postoperative anemia is associated with medical complications [3, 17]. The initial hypothesis that topical fibrinogen would result in a reduction of drain output, hemoglobin drop, and lead to a reduction of transfusions required when used in TKA was not confirmed in this randomized, double-blind trial.

This study had several limitations. First, all patients donated one autologous unit of blood preoperatively, which may have made transfusion after TKA more likely; however, this should not have affected the treatment group differently from the control group. Second, all patients received suction drains for 24 hours after surgery. It is unlikely, however not impossible, that this drainage may have affected the impact of topically applied fibrinogen. It should also be noted that blood transfusions are required more frequently in TKA patients that received drains [12]. Third, measuring blood loss in a controlled clinical trial environment is a complex science, which is prone to multifactorial bias such as the hydration status of the patient undergoing hypotensive anesthesia that we tried to cope with performing a randomized trial.

There was no difference in calculated blood loss or transfusions between the groups. There are two earlier studies on the use of fibrinogen for bleeding control in TKA. Levy et al. [9] presented a prospective, controlled, randomized study including 58 patients undergoing TKA using a human fibrin tissue adhesive from a different manufacturer (Quixil; Omrix Biopharmaceuticals SA, Nes-Ziona, Israel). The protocol of their multicenter approach was comparable to this study. The differences were that they used cruciate-retaining knees and low-molecular-weight heparin was used for thromboprophylaxis. They identified significant advantages for the treatment group in terms of postoperative drain output, hemoglobin drop, and transfusion rates. Wang et al. [16] reported on similar results with the same product in a cohort of 53 patients undergoing TKA. The results of these two studies stand in contrast with our data. One reason for the difference could be the routine use of hypotensive anesthesia, which may result in increased bleeding when blood pressure returns to normal in the recovery room. Another reason is that Quixil also contains tranexamic acid, which has been demonstrated to be effective on its own in reducing blood loss [18].

Table 2. Secondary outcomes in both groups

Secondary outcome	Control Mean	Evicel Mean	p value
Postoperative range of motion (degrees)	114.06	112.38	0.316
Change in visual analog scale score (6 weeks) with activity (points)	3.92	4.30	0.383
Number of autologous transfused units	0.38	0.46	0.314
Number of homologous transfused units	0.24	0.30	0.595
Drain output at 24 hours (mL)	673.13	780.2	0.029

The use of topical fibrinogen in TKA did not result in any differences in pain, ROM, or complications. There are some possible disadvantages that may be associated with the use of topical fibrinogen. The intraoperative use of cell savers is not recommended when using topical fibrinogen. It is unclear whether topical fibrinogen can provoke anaphylaxis or trigger allergies. There is at least a theoretical risk of transmission of viral infections from thrombin or matrix because fibrinogen and thrombin are products of human origin. This was the primary reason that patients decided not to enroll in the study. We did not observe any such complications in this study.

Our results suggest that the use of topical human fibrinogen does not lead to a relevant reduction in blood loss or transfusions in primary TKA for osteoarthritis. Given the lack of benefit and the costs this procedure adds to TKA, its routine use in patients with osteoarthritis cannot be justified.

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