

# The Use of Fibrin Tissue Adhesive to Reduce Blood Loss and the Need for Blood Transfusion After Total Knee Arthroplasty

A PROSPECTIVE, RANDOMIZED, MULTICENTER STUDY\*

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## Abstract

**Background:** Total knee arthroplasty is associated with major postoperative blood loss of approximately 800 to 1200 milliliters, and blood transfusion is frequently required. With the increased concern about the risks of blood transfusion, various methods of blood conservation in orthopaedic surgery have been studied. The most appropriate solution, however, is to reduce the loss of blood during and after an operation. The present prospective, controlled, randomized study was designed to evaluate the hemostatic efficacy of the use of fibrin tissue adhesive in patients managed with total knee arthroplasty.

**Methods:** Fifty-eight patients who were scheduled to have a total knee arthroplasty were randomly divided into two groups: a control group, in which the standard means of hemostasis were applied, and a treatment group, in which the standard means to control local bleeding were applied and a fibrin tissue adhesive was sprayed on the internal aspects of the operative field before skin closure. All operations were performed in a bloodless field with use of a pneumatic tourniquet. All patients received low-molecular-weight heparin as thromboprophylaxis twelve hours before the operation and every twelve hours postoperatively. Blood loss during the operation was evaluated by measuring the volume in the suction apparatus and by estimating the amount of lost blood in the swabs at the end of the operation. The apparent postoperative lost

blood was determined by measuring the volume in the suction-drain bottles. All blood transfusions were recorded.

**Results:** The mean apparent postoperative blood loss (and standard deviation) in the fibrin-tissue-adhesive group was  $360 \pm 287.7$  milliliters compared with  $878 \pm 403.0$  milliliters in the control group, with a mean difference of 518 milliliters ( $p < 0.001$ ). The decrease in the level of hemoglobin was  $25 \pm 10$  grams per liter in the treatment group compared with  $37 \pm 12$  grams per liter in the control group ( $p < 0.001$ ). Sixteen patients (55 percent) in the control group required a blood transfusion and eight (28 percent) required two units of blood, whereas only five (17 percent) of the patients in the fibrin-tissue-adhesive group required a blood transfusion and only one (3 percent) required two units ( $p = 0.004$ ). The number of adverse events was comparable between the two groups. None of the adverse events were considered to be related to the use of fibrin tissue adhesive. One death, which was due to massive pulmonary embolism, was reported in the control group. No seroconversion was reported at three and six months after the operation.

**Conclusion:** The use of fibrin tissue adhesive in total knee arthroplasty seems to be an effective and safe means with which to reduce blood loss and blood-transfusion requirements. Furthermore, the importance of these findings was enhanced by a significant reduction in blood loss, in the postoperative decrease in the level of hemoglobin, and in blood-transfusion requirements despite preoperative thromboprophylaxis with low-molecular-weight heparin.

Total knee arthroplasty is associated with major postoperative blood loss, which is usually underestimated and often necessitates transfusion. Although the use of a tourniquet during the procedure may reduce the intraoperative blood loss, the postoperative blood loss, as determined by measuring the amount of suction drainage and as calculated on the basis of the decrease in the level of hemoglobin, can be considerable. Blood loss after total knee arthroplasty often amounts to 800 to 1200 milliliters, and blood transfusion is frequently required<sup>15,19,35,45,47,56</sup>.

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With the increased concern about the risks of blood transfusion, which include the transmission of viral diseases, such as the human immunodeficiency virus<sup>48</sup>, hepatitis<sup>26,33</sup>, and cytomegalovirus<sup>53,55,57</sup>, as well as transfusion reactions, there has been a constant search for new methods of blood conservation in orthopaedic surgery. Among the various methods are perioperative hemodilution<sup>43</sup>, intraoperative and postoperative salvage of blood and reinfusion<sup>15,20,23,24,34</sup>, the use of hypotensive anesthesia or epidural anesthesia, and the transfusion of predonated autologous blood<sup>7,9,12,13,18,37,38,58,62</sup>. However, a more rational approach would be to enhance hemostasis and sealing of vessels at the site of the operation in order to prevent or reduce blood loss.

The use of plasma proteins at the site of the injury to reduce blood loss dates back to the beginning of the century, when Bergel<sup>4</sup> used dry plasma and Grey<sup>27</sup> used fibrin patches during operations. The modern concept of treatment with fibrin tissue adhesives, also known as fibrin glues or fibrin sealants, consists of the application of plasma fibrinogen mixed with thrombin to form a fibrin clot adhesive, and it was first reported, to our knowledge, by Cronkite et al.<sup>14</sup> during World War II. Commercial fibrin tissue adhesive became available in Europe in the late 1970s and has been used extensively since then for various indications, including hemostasis, sealing, and gluing, and as a vehicle for chemical and biological materials<sup>40</sup>. Because there is a lack of solid evidence concerning their safety and efficacy, most commercially available fibrin tissue adhesives still have not been approved by the Food and Drug Administration in the United States. Indeed, blood-bank products and bovine thrombin concentrates, which are much less safe than the commercial products, are used extensively

in the United States<sup>41</sup>. Fibrin tissue adhesive is composed of two main components: fibrinogen and thrombin. When mixed together, they mimic the last step of the coagulation cascade: thrombin activates fibrinogen to polymerize to an unstable clot, and factor XIII, which is present in the fibrinogen concentrate and is activated by thrombin (factor XIIIa), stabilizes the clot by catalyzing cross-linking between the fibrin molecules. Factor XIIIa also cross-links between natural plasmin inhibitors (which co-purify with fibrinogen) and the fibrinogen mesh to enhance clot resistance against fibrinolysis. Some products contain additional fibrinolytic inhibitors, such as bovine aprotinin or tranexamic acid<sup>41</sup>, although the contribution of such additives is controversial (Fig. 1).

Despite numerous publications on the use of fibrin tissue adhesive in all fields of surgery, evidence from controlled trials on the efficacy of fibrin tissue adhesive is lacking. Most reports have been descriptive and have been based on uncontrolled studies. Recent experimental and clinical trials have suggested that there is no benefit in the use of fibrin tissue adhesive for some of the indications<sup>32,44,49,54</sup> or that there may even be a harmful effect<sup>8,59</sup>.

We designed the present prospective, controlled, randomized study to evaluate the hemostatic efficacy of fibrin tissue adhesive in patients who were having a total knee arthroplasty and were managed preoperatively with low-molecular-weight heparin as prophylaxis against deep-vein thrombosis.

**Materials and Methods**

The present investigation was a multicenter, prospective, randomized, standard-treatment-controlled study.

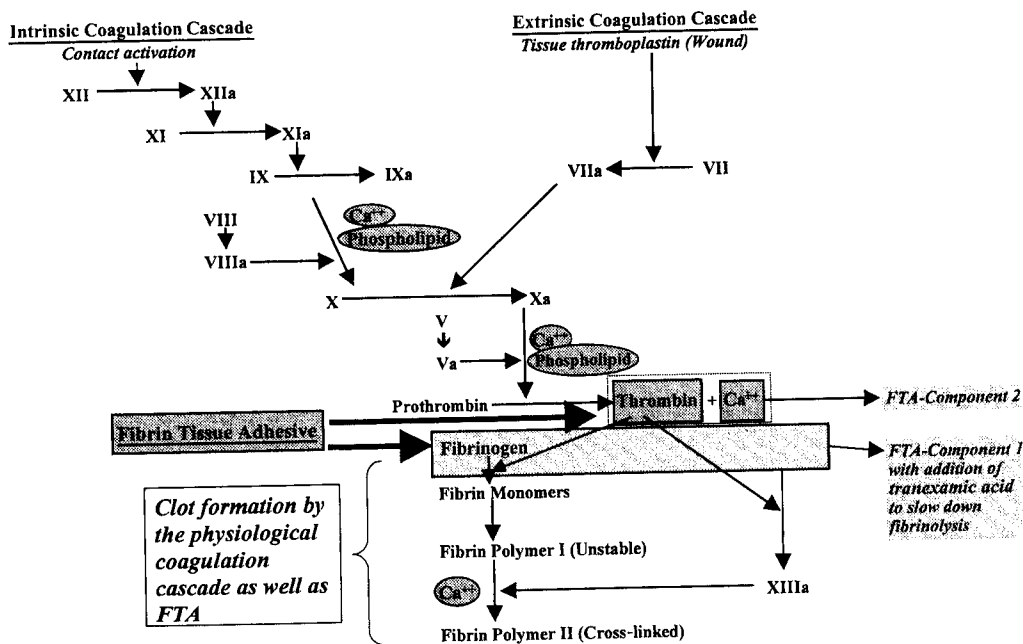


FIG. 1

Schematic drawing of the coagulation cascade and the composition of the components of the fibrin tissue adhesive (FTA).

TABLE I  
DATA ON THE PATIENTS

	Fibrin-Tissue- Adhesive Group (N = 29)	Control Group (N = 29)
Age* (yrs.)	68.9 ± 6.3 (60-82)	70.2 ± 8.2 (47-83)
Gender (F/M)	23/6	23/6
Mean height (cm)	160.4	162.7
Mean weight (kg)	76.7	76.9

\*The values are given as the mean and the standard deviation, with the range in parentheses.

It was approved by the ethics committee at each medical center and by the Ministry of Health. All patients gave informed consent.

Fifty-eight patients who had osteoarthritis of the knee and were scheduled to have a unilateral total knee arthroplasty with cement were enrolled in the study. There were forty-six women and twelve men. Twenty-nine patients were randomized to receive treatment with fibrin tissue adhesive (the treatment group), and twenty-nine were randomized to be managed with the standard method of hemostasis (the control group).

All implants were of the posterior cruciate-sparing type, and all were inserted with cement.

The randomization was determined according to patient number, which had been assigned with a computer-generated randomization list. The randomization was centralized, and the study monitor informed the surgeon of the patient's allocated treatment group during the operation, just before the application of the glue, if the patient was in the fibrin-tissue-adhesive group. This procedure was used to eliminate the possibility of bias, as the surgeon might have deviated from standard hemostatic techniques and practices as a result of awareness of the patient's study cohort. The fibrin tissue adhesive used in the present study was octacool F15 (Quixil; Omrix Biopharmaceuticals SA, Nes-Ziona, Israel). It consists of a cryoprecipitate-based fibrinogen at a concentration of fifty milligrams per milliliter and a high concentration of human thrombin (1000 international units per milliliter) dissolved in a solution of forty millimoles of calcium chloride per liter. An antifibrinolytic agent, tranexamic acid (ninety-five milligrams per milliliter), is added to the fibrinogen as a stabilizer. Both components undergo double viral-inactivation steps: treatment with solvent detergent followed by pasteurization (at 60 degrees Celsius for ten hours) for the fibrinogen and nanofiltration for the thrombin.

#### Operative Procedure

In order to control the variable factors, all of the surgeons discussed and agreed on the operative protocol and the sequence of the operative procedures before the study and they performed all of the operations in a uniform manner.

All of the operations were performed in a bloodless field with use of a pneumatic tourniquet. The tourniquet was deflated after the preparation of the femur and the tibia and before insertion of the prosthesis in order to obtain hemostasis by electrocautery of the major vessels. Then the tourniquet cuff was inflated again, before the prosthesis was inserted with cement. In all of the patients, the drill-hole in the femoral canal was plugged because plugging the guide-hole in the femoral canal during knee arthroplasty has been reported to reduce blood loss<sup>50</sup>.

After the prosthesis had been inserted with cement and before closure of the soft tissues, the knee joint and the entire operative field was thoroughly rinsed of any debris and was meticulously dried. The fibrin tissue adhesive (ten to twenty milliliters of combined product or one or two kits) was then applied by topical spraying with use of a double-syringe spray-device. The glue was sprayed over the tissues, into the joint itself, on the raw surfaces of the bones, on the muscles and tendons, and around and on the subcutaneous tissues while all of the so-called hidden pouches of the joint were exposed in order to cover as much surface area as possible with a film of glue. Drains were used in the joint and were connected to a high-vacuum-suction-drain bottle. The knee joint was then closed in layers. These stages of the procedure were identical for both groups, except for the application of the fibrin tissue adhesive.

The operations were performed by eight different surgeons in three medical centers. All of the surgeons performed operations with and without the fibrin tissue adhesive in patients included in the present study.

The AGC total knee prosthesis (Biomet, Warsaw, Indiana) was used in twenty-one patients (eleven in the control group and ten in the treatment group); the press-fit condylar total knee prosthesis (PFC; Johnson and Johnson Orthopaedics, Raynham, Massachusetts), in five patients (two in the control group and three in the treatment group); the Insall-Burstein II (Zimmer, Warsaw, Indiana), in twenty-eight patients (fourteen in each group); the Rotoglide total knee prosthesis (Corin Medical, Cirencester, Gloucestershire, United Kingdom), in two patients (one in each group); and the Howmedica total knee prosthesis (Howmedica, Rutherford, New Jersey), in two patients (one in each group). The two study groups were comparable with respect to all other parameters, such as age, gender, height, and weight (Table I).

Hemoglobin and hematocrit values were determined preoperatively and on the first, second, third, fifth, and seventh postoperative days. The preoperative platelet count, prothrombin time, and activated partial thromboplastin time were determined for all patients. The prothrombin time and the activated partial thromboplastin time also were evaluated immediately after the application of the glue. The loss of blood at the end of the operation was recorded by measuring the volume

in the suction apparatus and by estimating the amount of lost blood in the swabs. The apparent postoperative blood loss was recorded by measuring the volume in the suction-drain bottles. It is well known, however, that there is a substantial amount of inapparent postoperative blood loss, which is caused by extravasation of the blood into the tissues and therefore is not evacuated by the suction drainage<sup>35,39</sup>. Thus, total blood loss was also calculated with a formula, described by Gross<sup>28</sup>, which uses the maximum postoperative decrease in the hemoglobin value adjusted for the weight and height of the patient.

Determining the need for transfusion is a clinical challenge. In 1988, the National Institutes of Health Consensus Conference<sup>46</sup> on perioperative transfusion of red blood cells addressed this issue and established criteria and guidelines for the determination of the need for blood replacement. These guidelines are the basis for the regular practice concerning blood transfusion at our medical centers, and they were followed in our study as well. As the surgeon cannot be blinded to the application of fibrin tissue adhesive, the decision concerning postoperative blood-transfusion requirements could have been biased. In order to prevent this bias, the surgeons involved in this study (at all three centers) agreed that the decisions regarding blood-transfusion requirements would be made by a team of surgeons and not by the operating surgeon alone. The same team of surgeons made the decisions concerning blood-transfusion requirements for both the control group and the treatment group.

The team decision was based on the recommendations of the National Institutes of Health Consensus Conference<sup>46</sup> in 1988 and on good clinical judgment. Each transfusion was prescribed on the basis of the cardiovascular history, the present status, the decrease in hemoglobin level, the severity of blood loss, and the age of the patient.

Any wound complications, such as the formation of a hematoma, prolonged drainage from the wound or drain site, wound dehiscence, and any signs of infection or delayed healing, were recorded.

All of the patients received a subcutaneous injection of forty milligrams of a low-molecular-weight heparin (enoxaparin [Clexane]) as thromboprophylaxis twelve hours before the operation, and they continued to receive thirty milligrams of enoxaparin every twelve hours, beginning twelve hours postoperatively and continuing until discharge from hospital.

Doppler ultrasound studies (duplex ultrasonography) were performed to examine the lower limbs for deep-vein thrombosis between seventy-two hours postoperatively and the day of discharge from the hospital.

The patients were allowed to get out of bed on the second day after the operative procedure, and physiotherapy was started on the same day. The patients were encouraged to walk and exercise, as tolerated, under

the supervision of a physiotherapist.

The safety of the fibrin tissue adhesive was assessed by monitoring adverse events, vital signs, and laboratory findings. Serological tests for the human immunodeficiency virus, cytomegalovirus, and the hepatitis-B, C, and A viruses were performed preoperatively and were repeated at three and six months postoperatively to ensure that no seroconversion had occurred.

The primary end point of this study with regard to the efficacy of the fibrin tissue adhesive was a reduction in blood loss, as determined by measurement of postoperative bleeding, of at least 30 percent after use of the fibrin tissue adhesive compared with that in the control group. This criterion was chosen with statistical considerations. Secondary efficacy parameters were the magnitude of the reduction in the hemoglobin and hematocrit levels as well as in blood-transfusion requirements and the development of hematoma.

The functional recovery of the patient and the range of motion were recorded at the follow-up examinations.

#### *Statistical Methods*

Demographic data and other baseline parameters were analyzed statistically to check the comparability of the two study groups. Statistical analyses were also performed on the safety and efficacy parameters. Safety was assessed by comparing the two groups with respect to the frequency of adverse events and the outcome complications (wound infections, hematoma, and deep-vein thrombosis) after the operation. Efficacy was evaluated by determining the significance of the differences between the results for the two groups after the treatment period. Graphical methods were used for descriptive presentation and for assessment of normality. The two-sample t test as well as the nonparametric Mann-Whitney U test were used to compare the two groups. The paired t test and the Wilcoxon signed-rank test were used for the assessment of changes within the groups. Analysis of covariance was applied for comparison of the groups when it was necessary to adjust the post-treatment levels to the pretreatment levels of the same parameters. For the qualitative parameters, tests for contingency tables, such as Pearson chi-square statistics and Fisher's exact test, were applied. A two-tailed p value of 0.05 or less was considered to be significant for all analyses performed.

#### **Results**

The treatment and control groups were comparable in terms of the characteristics of the patients (Table I).

The intraoperative blood loss was similar for the two groups.

The mean apparent postoperative blood loss (and standard deviation) was  $360 \pm 287.7$  milliliters in the fibrin-tissue-adhesive group compared with  $878 \pm 403.0$  milliliters in the control group. The difference of 518 milliliters was significant ( $p < 0.001$ ) (Fig. 2).

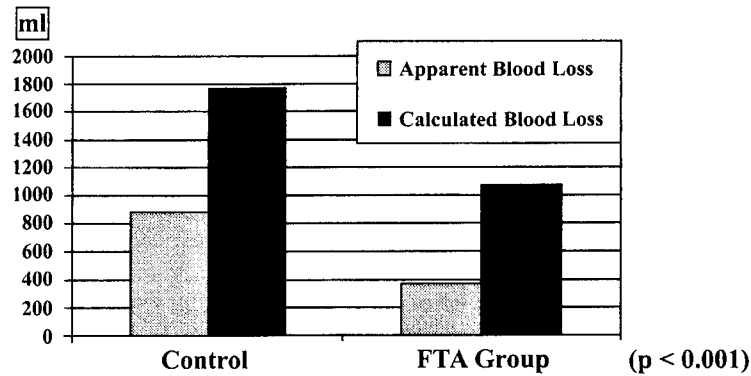


FIG. 2

Graph showing the apparent and calculated<sup>28</sup> blood loss in the control and fibrin-tissue-adhesive (FTA) groups.

The mean decrease (and standard deviation) in hemoglobin concentration after the operation was  $25 \pm 10$  grams per liter in the fibrin-tissue-adhesive group compared with  $37 \pm 12$  grams per liter in the control group, suggesting a larger blood loss than was demonstrated by the volume of drained blood. The difference in the hemoglobin values between the two groups was found to be significant ( $p < 0.001$ ) (Fig. 3).

The calculated blood loss<sup>28</sup> was greater than the observed loss in both groups, but it was found to be significantly lower in the fibrin-tissue-adhesive group ( $1063.0 \pm 481.95$  milliliters) than in the control group ( $1768.0 \pm 614.60$  milliliters) ( $p < 0.001$ ) (Fig. 2).

The blood-transfusion requirements in the fibrin-tissue-adhesive group also were found to be significantly lower than those in the control group. Only five patients (17 percent) in the fibrin-tissue-adhesive group required a blood transfusion and only one (3 percent)

required two units of blood, whereas sixteen patients (55 percent) in the control group required a blood transfusion and eight (28 percent) required two units ( $p = 0.004$ ) (Fig. 4).

#### Adverse Events

The frequency of adverse events was comparable between the two groups: twenty-six patients (90 percent) in the fibrin-tissue-adhesive group and twenty-seven (93 percent) in the control group had an adverse event. There were fifty-two adverse events in the fibrin-tissue-adhesive group, and thirty-nine (75 percent) of these events were considered mild. There were forty-nine adverse events in the control group, and thirty-three (67 percent) of these events were considered mild. Fever was the most common adverse event associated with the operation, with no difference in frequency between the two groups (twenty-three patients [79 per-

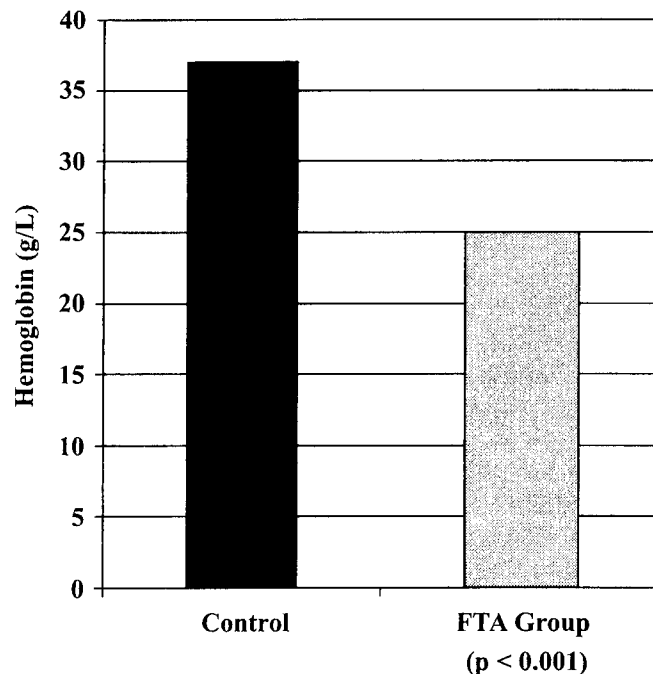


FIG. 3

Graph showing the postoperative decrease in the hemoglobin levels in the control and fibrin-tissue-adhesive (FTA) groups.

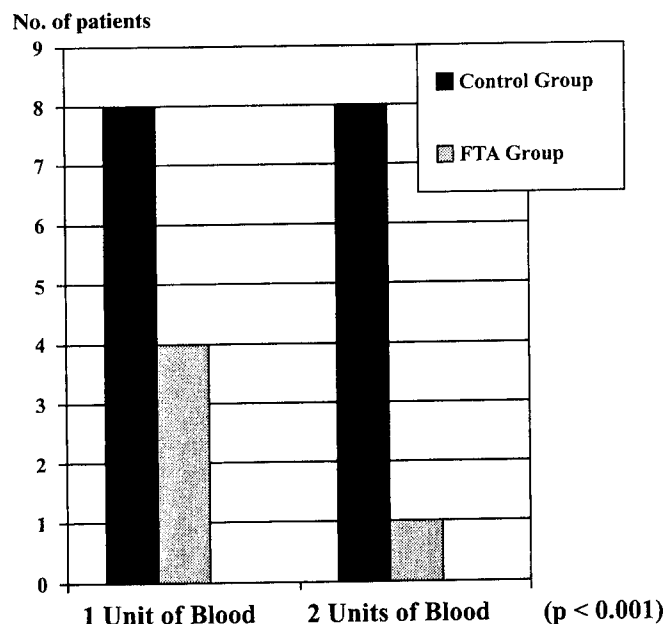


FIG. 4

Graph showing the blood-transfusion requirements in the control and fibrin-tissue-adhesive (FTA) groups.

cent] in the treatment group and twenty-four [83 percent] in the control group). Superficial wound infection was suspected in two patients (7 percent) in the fibrin-tissue-adhesive group and in one patient (3 percent) in the control group. All of these infections were controlled with antibiotic treatment.

Two patients in the fibrin-tissue-adhesive group had clinical signs of deep-vein thrombosis, with negative findings on Doppler ultrasound scans, and one patient in the control group died of massive pulmonary embolism three weeks after the operation.

None of the adverse events were considered to be related to the study treatment. With the numbers available, no significant difference was detected between the groups with respect to the postoperative range of motion or the progress of the rehabilitation.

No seroconversion for viruses was reported at three and six months after the operation.

### Discussion

The amount of blood loss after a total knee arthroplasty is usually underestimated<sup>35</sup>, as was shown in the present study by the differences between the apparent and the calculated<sup>28</sup> blood loss.

The volumes of blood loss and the need for transfusion in the control group in our series were similar to the data reported in previous studies on blood loss associated with total knee arthroplasty<sup>2,3,5,16,30,35,39,45,60</sup>.

A significant reduction was detected in both the apparent and the calculated total blood loss resulting from total knee arthroplasty in the group treated with fibrin tissue adhesive compared with those values in the control group ( $p < 0.001$ ). The treatment group had a far smaller postoperative decrease in the hemoglobin level

than the control group, and the difference was significant ( $p < 0.001$ ). These effects may play a beneficial role in the achievement of early and better postoperative rehabilitation<sup>10</sup>.

The results of our study suggest that the use of fibrin tissue adhesive in total knee arthroplasty reduces the postoperative extravasation of blood into the tissues as well as the apparent blood loss, thereby preventing the formation of hematoma. Theoretically, this may reduce the rate of infection and promote healing. Our results are supported by the findings of Marmor et al.<sup>39</sup>, who demonstrated that fibrinogen concentrates reduce the inapparent blood loss; however, in our study, the apparent blood loss was found to be significantly reduced as well ( $p < 0.001$ ).

The use of fibrin tissue adhesive was found to significantly reduce the total number of units of blood transfused postoperatively to one-fourth of that in the control group (six compared with twenty-four units of blood;  $p < 0.001$ ). It also significantly reduced the number of patients requiring blood transfusion (five compared with sixteen;  $p = 0.004$ ). In addition, only one patient in the treatment group received two units of blood compared with eight patients in the control group.

Total knee arthroplasty is associated with a high risk of postoperative thromboembolism<sup>11,22,29,36</sup>. Most deep-vein thromboses are thought to be formed during the operative procedure; therefore, preoperative thromboprophylaxis with low-molecular-weight heparin is superior to postoperative thromboprophylaxis alone<sup>22,29,42</sup>. It is a well accepted practice in most countries outside the United States to use thromboprophylaxis preoperatively.

Hull et al.<sup>31</sup> showed that preoperative administration of low-molecular-weight heparin before a total hip re-

placement reduces the rate of deep-vein thrombosis by approximately 50 percent compared with postoperative thromboprophylaxis only. In their study, 8.8 percent (forty-four) of 499 patients who had been managed preoperatively with low-molecular-weight heparin were found to have deep-vein thrombosis on bilateral venography performed postoperatively, whereas 15.6 percent (102) of 652 patients who had received only postoperative thromboprophylaxis with low-molecular-weight heparin had deep-vein thrombosis postoperatively ( $p < 0.001$ ). Similar results have been reported for total knee replacements<sup>29</sup>.

Total knee arthroplasty is associated with major postoperative bleeding. Furthermore, there have been concerns that preoperative thromboprophylaxis with low-molecular-weight heparin may substantially increase postoperative bleeding and bleeding complications as well as increase the need for postoperative blood transfusions<sup>22,25</sup>.

The intraoperative blood loss associated with total knee arthroplasty does not impose a substantial problem, as most of these procedures are performed in a bloodless field obtained with use of a pneumatic tourniquet. The bulk of the blood loss occurs after the operation<sup>2,5,30,45</sup>. There are several explanations for postoperative bleeding associated with total knee arthroplasty. After any operation, the fibrinolytic system is transiently activated<sup>32</sup>, and this phenomenon is greater after osteotomy<sup>6</sup>. The use of a tourniquet also may contribute to the considerable postoperative bleeding because reactive hyperemia may develop secondary to prolonged ischemia in the limb, with an increase in the fibrinolytic activity after release of the arterial tourniquet<sup>21</sup>. In several studies, continuous bleeding from venous sinuses of the cut cancellous bone<sup>45,61</sup> was implicated as the major source of blood loss. Some authors have shown that bleeding may be potentiated by suction drainage<sup>51</sup>.

Surgeons have a conflict between the need to provide optimum thromboprophylaxis (preoperatively) and the need to address the high risk of bleeding. In the United States, the current recommended practice for the administration of low-molecular-weight heparin to prevent deep-vein thrombosis is to start thromboprophylaxis twelve hours postoperatively, with no preoperative thromboprophylaxis. The present study showed that the use of fibrin tissue adhesive may allow the use of full-dose preoperative thromboprophylaxis with low-molecular-weight heparin, thereby reducing the risk of deep-vein thrombosis without increasing the risk of postoperative bleeding in patients who are

having a total knee arthroplasty. The fact that the fibrin-tissue-adhesive group in our study had a significant reduction in blood loss and blood-transfusion requirements after total knee arthroplasty compared with that in the control group ( $p < 0.001$ ) despite preoperative thromboprophylaxis with forty milligrams of low-molecular-weight heparin enhances the importance of these findings.

The use of the fibrin tissue adhesive was found to significantly reduce the apparent blood loss, the decrease in the level of hemoglobin, the total calculated blood loss, and the blood-transfusion requirements ( $p < 0.001$  for all) (Figs. 1, 2, and 3).

The prevention of blood loss, including the prevention of concomitant compartmental shifts in body fluid, is definitely superior to the replacement of blood loss<sup>10</sup>. It is much safer for a patient to receive a multidonor viral-inactivated blood product (fibrin tissue adhesive) than to receive homologous blood that cannot be viral-inactivated<sup>44</sup>. The effectiveness of the fibrin tissue adhesive in reducing blood loss may be explained by its ability to seal and plug the bone-marrow sinusoids and consequently to prevent oozing of blood. Furthermore, as extravasation of the fibrinolytic agents from the cut edges of tissues (bone and soft tissues) is prevented, fibrin tissue adhesive may suppress the enhanced fibrinolytic state.

The very high concentration of thrombin in the particular preparation of fibrin tissue adhesive used in the present study creates a fibrin tissue adhesive that clots very fast. In this preparation, the fibrin clot is already created at the aerosol state and therefore immediate hemostasis is induced when it arrives on the tissues. This feature prevents extravasation of fibrinolytic agents and polymorphonuclear cells from the edges of the cut bone and tissue and hence may reduce the inflammatory reaction at the operative site. A high concentration of thrombin creates a fine fibrin network with small pores, which act as a mechanical barrier for polymorphonuclear cells and reduce inflammation and adhesions<sup>1,17</sup>. The addition of tranexamic acid to the fibrin tissue adhesive as a fibrinolytic inhibitor may play an additive role in the stability of the glue<sup>2,30,41</sup>.

In conclusion, we found that the use of fibrin tissue adhesive is an efficient means with which to reduce blood loss and blood-transfusion requirements in patients having a total knee arthroplasty who are managed preoperatively with low-molecular-weight heparin.

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## References

1. Amrani, D. L.; DiOrto, J. P.; Delmotte, Y.; Krack, G. F.; and White, R.: In vitro characterization and structural basis for in vivo efficacy of fibrin sealant in preventing formation of surgical adhesions [abstract]. *Thromb. and Haemost.*, OC-790 Supplement, June 1997.
2. Benoni, G., and Fredin, H.: Fibrinolytic inhibition with tranexamic acid reduces blood loss and blood transfusion after knee arthroplasty. A prospective, randomised, double-blind study of 86 patients. *J. Bone and Joint Surg.*, 78-B(3): 434-440, 1996.