

USE OF FIBRIN SEALANT TO REDUCE BLOODY DRAINAGE AND HEMOGLOBIN LOSS AFTER TOTAL KNEE ARTHROPLASTY

A BRIEF NOTE ON A RANDOMIZED PROSPECTIVE TRIAL

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Background: A phase-III trial that included fifty-three patients undergoing unilateral primary total knee arthroplasty with cement was conducted to investigate the hemostatic efficacy of fibrin sealant.

Methods: Following cementing of the joint, 10 mL of fibrin sealant was sprayed onto the wound before tourniquet deflation and wound closure. No placebo was used in the control group. All patients received drains.

Results: Within twelve hours after the surgery, the amount of bloody drainage was 184.5 ± 28.9 mL (mean and standard error) in the fibrin-sealant group (information available for twenty-three patients) and 408.3 ± 54.6 mL in the control group (information available for twenty-three patients) ($p = 0.002$, after adjustment for variance in the time that the drainage was measured). On the first postoperative day, the hemoglobin level had decreased by 20.1 ± 2.1 g/L in the fibrin-sealant group (information available for twenty-two patients) and by 27.3 ± 2.1 g/L in the control group (information available for twenty-four patients). After adjustment for baseline values, the decrease in the hemoglobin level was 28.9% less in the fibrin-sealant group than in the control group ($p = 0.005$, 95% confidence limits = 10.2, 43.7). There were no seroconversions in the fibrin-sealant group.

Conclusion: These results suggest that fibrin sealant can safely reduce bloody drainage following total knee arthroplasty while maintaining higher hemoglobin levels.

Substantially decreasing postoperative bloody drainage following total knee arthroplasty may reduce patient morbidity, the length of the stay in the hospital, and costs by eliminating the need for transfusions and, potentially, for drains. Furthermore, the use of effective intraoperative hemostatic agents may facilitate the earlier administration of anticoagulants as prophylaxis against deep-vein thrombosis, a measure recommended in a recent large-scale study¹. Since 1972, fibrin sealants have been increasingly used as hemostatic and sealing agents in a variety of surgical specialties^{2,4}, including, recently, total knee replacement³. Thus, it was hypothesized that fibrin sealant could improve hemostasis following knee arthroplasty.

Materials and Methods

A prospective, multicenter, randomized, controlled phase-III (expanded clinical) trial was performed, with the investigators blinded until the application of fibrin sealant just prior to wound closure. After giving their informed written

consent to a protocol previously approved by institutional review boards and the Food and Drug Administration, patients with osteoarthritis underwent primary unilateral total knee arthroplasty with cement, under tourniquet control, with hemostasis achieved with use of cauterization and diathermy. (Neither hemodilution nor hypotensive anesthesia was used.) Patients with a baseline hemoglobin level of ≤ 110 g/L and evidence of a bleeding or metabolic-based hemolytic disorder were excluded from the study. In the fibrin-sealant group, following cementing of the joint and before tourniquet deflation and wound closure, 10 mL of an investigational, virally inactivated fibrin sealant (Quixil; Omrix Biopharmaceuticals SA, Brussels, Belgium) was sprayed onto the raw surfaces of the exposed bone and soft tissue at a distance of approximately 15 cm with use of a dual-syringe spray device (International Patent Application Number PCT/Ep96/03975). No placebo was used in the control group. All patients had placement of drains according to standard practice, and all received a 30-mg dose of enoxaparin sodium (Lovenox) subcutaneously every

TABLE I Results of Viral Testing

Viral Marker	No. of Patients Tested at Baseline (Pos./Neg.)	No. of Patients Tested at 3 Mo. (Pos./Neg.)	No. of Patients Tested at 6 Mo. (Pos./Neg.)
IgG			
Anti-HIV Ab	36 (0/36)	42 (0/42)	41 (0/41)
Anti-HAV Ab	46 (7/39)	42 (4/38)	38 (4/34)
Anti-HCV Ab	43 (0/43)	42 (0/42)	41 (0/41)
Anti-HBc Ab	40 (4/36)	37 (3/34)	41 (2/39)
Anti-HbsAg	46 (0/46)	42 (0/42)	40 (0/40)
IgM			
Anti-HIV Ab	1 (0/1)	0	0
Anti-HAV Ab	1 (1/0)	0	0

twelve hours, starting twelve to twenty-four hours after the operation, for prophylaxis against deep-vein thrombosis.

Results

The treatment and control groups (consisting of twenty-five and twenty-eight patients, respectively) were statistically homogenous with respect to gender, age, weight, height, abnormalities with regard to medical history, and prior medications, with one exception: eight patients in the fibrin-sealant group were taking acetylsalicylic acid prior to surgery as opposed to four patients in the control group.

Within twelve hours postoperatively, the amount of drainage was 184.5 ± 28.9 mL (unadjusted mean and standard error) in the fibrin-sealant group (information available for twenty-three patients) and 408.3 ± 54.6 mL in the control group (information available for twenty-three patients). In the fibrin-sealant group, the mean hemoglobin level on the first postoperative day was 114.8 ± 2.7 g/L (information available for twenty-two patients), a decrease of 14.9% (20.1 ± 2.1 g/L) compared with the baseline (134.9 ± 2.6 g/L). In the control group, the mean hemoglobin level on the first postoperative day was 104.9 ± 2.6 g/L (information available for twenty-four patients), a decrease of 20.7% (27.3 ± 2.1 g/L) compared with the baseline (132.2 ± 2.5 g/L).

After adjustment for the time that the drainage was measured, the drainage within twelve hours postoperatively in the fibrin-sealant group was 55.6% less (95% confidence limits = 27.1 to 73.0) than that in the control group ($p = 0.002$). After adjustment for preoperative hemoglobin levels, the decrease in hemoglobin on the first postoperative day in the fibrin-sealant group was 28.9% less (95% confidence limits = 10.2 to 43.7) than that in the control group ($p = 0.005$).

Differences between the fibrin-sealant group and the control group with regard to transfusion requirements and adverse events following surgery did not reach significance with the numbers available; however, trends in favor of the use

of fibrin sealant were noted. Nine patients (36%) in the fibrin-sealant group received transfusions (fourteen units of blood or blood products) compared with fourteen patients (50%) in the control group (twenty-seven units of blood or blood products) ($p = 0.19$). A hematoma developed in one patient (4%) in the fibrin-sealant group and in four patients in the control group (14%). No patients had seroconversion for any of the markers tested (Table I).

Discussion

In this study, the fibrin-sealant group had less bloody drainage in the initial twelve hours and a smaller decrease in the hemoglobin level on the day after the surgery than did the control group. It has been argued that the use of such hemostatic agents during joint replacement may be unnecessary because of the ease with which lost blood can be replaced with autologous predonated blood⁶. While autologous predonated blood is not associated with the risk of viral disease transmission, the rates of administrative error and bacterial overgrowth (the two factors most frequently associated with immediate posttransfusion deaths) are comparable with those associated with the use of homologous blood⁷. Moreover, authors of recent studies have argued that using autologous instead of homologous blood results in little health benefit at considerable additional cost⁸. On the other hand, even with current safety guidelines and the implementation of nucleic acid testing, there remains a risk of homologous transfusion-transmitted human immunodeficiency virus, hepatitis-B virus, and hepatitis-C virus^{9,10}. Thus, there continue to be strong health and economic benefits to minimizing postoperative transfusion rates of any type.

Another potential advantage of improved hemostatic techniques is that they may help to reduce the prevalence of the serious and sometimes fatal thromboembolic events associated with this procedure¹¹ by allowing prophylaxis against deep-vein thrombosis to be started earlier. It has been argued that earlier, more intensive prophylaxis against deep-vein thrombosis is needed¹. Unfortunately, the use of anticoagu-

lants for routine prophylaxis can be associated with increased blood loss¹². A randomized, controlled, clinical trial was recently conducted in Israel with use of a protocol similar to the one used in the present study, except that patients received anticoagulation therapy preoperatively as well as postoperatively³. In that study, fibrin sealant was shown to significantly reduce blood loss ($p < 0.001$), hemoglobin levels ($p < 0.001$), and transfusion requirements ($p = 0.004$) following total knee arthroplasty.

Thus, fibrin sealant reduces bloody drainage following total knee arthroplasty and minimizes decreases in postoperative hemoglobin levels. Fibrin sealant may facilitate more aggressive anticoagulation to reduce the prevalence of postoperative deep-vein thrombosis, pulmonary embolus, and death following knee arthroplasty. This study confirms the viral safety and low rate of complications associated with fibrin sealant. ■

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References

1. White RH, Romano PS, Zhou H, Rodrigo J, Bargar W. Incidence and time course of thromboembolic outcomes following total hip or knee arthroplasty. *Arch Intern Med.* 1998;158:1525-31.
2. Radosevich M, Goubran HA, Burnouf T. Fibrin sealant: scientific rationale, production methods, properties, and current clinical use. *Vox Sang.* 1997;72:133-43.
3. Rousou J, Levitsky S, Gonzalez-Lavin L, Cosgrove D, Magilligan D, Weldon C, Hiebert C, Hess P, Joyce L, Bergsland J, Gazzaniga A. Randomized clinical trial of fibrin sealant in patients undergoing re-sternotomy or reoperation after cardiac operations. A multicenter study. *J Thorac Cardiovasc Surg.* 1989;97:194-203.
4. Spotnitz WD. Fibrin sealant in the United States: clinical use at the University of Virginia. *Thromb Haemost.* 1995;74:482-5.
5. Levy O, Martinowitz U, Oran A, Tauber C, Horoszowski H. 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. *J Bone Joint Surg Am.* 1999;81:1580-8.
6. Mannucci PM. Hemostatic drugs. *N Engl J Med.* 1998;339:245-53.
7. Birkmeyer JD, Goodnough LT, AuBuchon JP, Noordzij PG, Littenberg B. The cost-effectiveness of preoperative autologous blood donation for total hip and knee replacement. *Transfusion.* 1993;33:544-51.
8. Etchason J, Petz L, Keeler E, Calhoun L, Kleinman S, Snider C, Fink A, Brook R. The cost effectiveness of preoperative autologous blood donations. *N Engl J Med.* 1995;332:719-24.
9. Schreiber GB, Busch MP, Kleinman SH, Korelitz JJ. The risk of transfusion-transmitted viral infections. The Retrovirus Epidemiology Donor Study. *N Engl J Med.* 1996;334:1685-90.
10. Murthy KK, Henrard DR, Eichberg JW, Cobb KE, Busch MP, Allain JP, Alter HJ. Redefining the HIV-infectious window period in the chimpanzee model: evidence to suggest that viral nucleic acid testing can prevent blood-borne transmission. *Transfusion.* 1999;39:688-93.
11. Ansari S, Warwick D, Ackroyd CE, Newman JH. Incidence of fatal pulmonary embolism after 1,390 knee arthroplasties without routine prophylactic anticoagulation, except in high-risk cases. *J Arthroplasty.* 1997;12:599-602.
12. Hull R, Raskob G, Pineo G, Rosenbloom D, Evans W, Mallory T, Anquist K, Smith F, Hughes G, Green D, Elliott G, Panju A, Brant R. A comparison of subcutaneous low-molecular-weight heparin with warfarin sodium for prophylaxis against deep-vein thrombosis after hip or knee implantation. *N Engl J Med.* 1993;329:1370-6.