Prospective randomized study evaluating an absorbable cyanoacrylate for use in vascular reconstructions

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Background: **An easy-to-use vascular sealant with good safety and efficacy is needed to prevent anastomotic bleeding in vascular surgery. This study evaluated the safety and efficacy of cyanoacrylate surgical sealant in establishing hemostasis of expanded polytetrafluoroethylene to arterial vascular anastomoses in arteriovenous (AV) grafts and femoral bypass grafts.**

Methods: **This multicenter, randomized, controlled, open-label study was conducted in a hospital setting at 12 sites: 10 in the United States and 2 in Europe. A total of 151 patients undergoing femoral bypass procedures or AV shunt procedures for hemodialysis access using expanded polytetrafluoroethylene grafts were randomized 2:1 to receive cyanoacrylate surgical sealant or the control (oxidized cellulose) between April 26, 2004, and January 18, 2005. Randomization was stratified by clinical site and type of procedure. After the anastomosis, cyanoacrylate surgical sealant or the control was applied to all anastomosis sites for patients undergoing femoral bypass procedures and to only the arterial anastomosis sites for patients undergoing AV shunt procedures. The primary end point was the elapsed time from clamp release to hemostasis. Secondary end points were the proportion of patients achieving hemostasis at t = 0 (immediate), 1, 5, or 10 minutes after clamp release, use of additional adjunctive measures to achieve hemostasis, and occurrence of adverse events.**

Results: **Baseline demographics and clinical characteristics showed that the two treatment groups were similar at baseline. The mean time from clamp release to hemostasis was 119.3 seconds with cyanoacrylate surgical sealant vs 403.8 seconds with the control ($P < .001$). Immediate hemostasis was achieved in 54.5% of patients receiving cyanoacrylate surgical sealant and in 10% of those receiving the control. The proportion of patients requiring additional adjunctive measures was lower with cyanoacrylate surgical sealant, and the occurrence of adverse events was similar in both groups.**

Conclusions: **This study demonstrates that cyanoacrylate surgical sealant is effective at reducing the time to hemostasis and achieving immediate hemostasis in AV shunt and femoral bypass procedures and that it is safe for internal use. Cyanoacrylate surgical sealant is an easy-to-use vascular sealant with good safety and efficacy that significantly decreases anastomotic bleeding in vascular surgery. (J Vasc Surg 2006;44:1002-9.)**

Bleeding is regarded as a necessary, acceptable byproduct of vascular reconstruction. It is considered to be an unavoidable consequence of joining an expanded polytetrafluoroethylene (ePTFE) graft to an artery. Anastomotic bleeding, however, can be unpredictable, persistent, and occasionally limb and life threatening.[1] This is of particular importance for patients in compromised situations, such as those taking anticoagulants, those with friable vessels, or those with impaired clot formation. Consequently, a plethora of sealants and hemostatic agents have been developed to assist the surgeon in minimizing or controlling anastomotic bleeding, and use of these agents is becoming more widespread in surgical operations.[2-4] There are currently five families of these materials: fibrin sealant, cyanoacrylate, bovine collagen and thrombin, polyethylene glycol polymer, and albumin cross-linked with glutaraldehyde.[5-10] Despite the abundance and variety of these agents, an easy-to-use vascular sealant with good risk-benefit and cost-benefit ratios is still not widely available. Such an agent should be easily applied in a controlled fashion, highly predictable in creating hemostasis, and nontoxic and must not have an adverse affect on anastomotic patency. Additional attributes such as increased anastomotic strength and the potential to provide drug-delivery opportunities would also be beneficial.

Nonabsorbable cyanoacrylates for topical use are approved by the Food and Drug Administration for skin closure,[11,12] but none is currently approved for internal use. An absorbable cyanoacrylate surgical sealant (Ethicon OMNEX Surgical Sealant; Closure Medical Corporation, Raleigh, NC) has been developed that is composed of 2-octyl cyanoacrylate and butyl lactoyl cyanoacrylate. This sealant polymerizes to form a film that adheres to the tissue and/or synthetic material, creating a flexible physical seal

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that prevents leakage of blood.[13,14] The function of this sealant is mechanical and independent of the host coagulation cascade, which should stifle interpatient variability in clot formation. We have previously reported the results of our pilot study in which we investigated the use of cyanoacrylate surgical sealant in 10 patients undergoing arterial anastomosis of arteriovenous (AV) grafts.[13] The study was designed to gather initial safety and efficacy data to determine the appropriateness of conducting a larger, multicenter trial. The mean time from vascular clamp removal to hemostasis was 9.1 ± 28.8 seconds. Hemostasis was achieved in 90% (9/10) of patients by 1 minute and in 100% (10/10) of patients by 5 minutes, and no patient required further adjunctive hemostatic measures. On the basis of the results of the pilot study, a larger study was designed to determine the safety and efficacy of cyanoacrylate surgical sealant in establishing hemostasis of ePTFE to arterial vascular anastomoses in AV grafts and femoral bypass grafts. This article reports the results of this large, randomized, prospective, multicenter trial, which enrolled 151 patients.

METHODS

Patients. Adult patients undergoing femoral-popliteal bypass or AV shunt procedures for hemodialysis access using ePTFE vascular grafts were enrolled between April 26, 2004, and January 18, 2005. Patients were excluded for (1) known hypersensitivity to formaldehyde or cyanoacrylate, (2) known pregnancy, (3) participation in another investigational study of a surgical/therapeutic device, drug, or biologic within the previous 6 months, (4) receiving anti–vitamin K anticoagulants within 4 days before surgery, (5) receiving low-molecular-weight heparin within 4 days before surgery, (6) utilization of gelatin- or collagen-coated graft material (eg, Vectra Vascular Access Graft; Thoratec Corporation, Pleasanton, Calif) for femoral bypass or AV shunt procedures, and (7) utilization of an autologous graft for femoral bypass or AV shunt procedures.

Patients were randomized within each investigative site by type of procedure in a 2:1 randomization by using blocks of three patients each. Two randomization lists were created for each site: one for femoral-popliteal bypass patients and one for AV shunts. After completion of the anastomosis, patients were randomized to one of two treatment groups, with randomization stratified by the type of peripheral vascular surgery (femoral bypass or AV shunt). Oxidized cellulose (Surgicel Absorbable Hemostat; Johnson & Johnson, New Brunswick, NJ), the current standard of care, was used in patients randomized to receive the control, and cyanoacrylate surgical sealant (Ethicon OMNEX Surgical Sealant; Closure Medical Corporation, Raleigh, NC) was used in patients randomized to receive the investigational device. Either cyanoacrylate surgical sealant or the control was placed in a box labeled with the patient number and procedure and sealed. The boxes were identical in size and shape, and the content of the box (cyanoacrylate surgical sealant or the control) was not indicated on the outside of the box. The boxes remained sealed until opened by the operating room staff. Physicians were to complete suturing the anastomosis before opening the box, thus eliminating any physician bias that may occur during the suturing process.

Treatment. At each site, standard practices were used in the surgical implantation of ePTFE vascular grafts. Surgeons were to use a 1:1 needle-thread ratio along the anastomotic suture line using 5-0 or 6-0 polypropylene sutures. Cyanoacrylate surgical sealant or the control was applied to all anastomotic sites for patients undergoing femoral bypass procedures and was applied to arterial anastomotic sites for patients undergoing AV shunt procedures. For cyanoacrylate surgical sealant, physicians waited 120 seconds before clamp release to allow the sealant to polymerize. The clamps were then removed, and circulation was restored through the graft. For the control, physicians were recommended to follow instructions for use. Treatment sites were observed, and the time from clamp release to hemostasis was measured with a calibrated stopwatch. Physicians were allowed to follow the standard of care for their facility in regard to which adjunctive measures, if any, were used. If additional measures were used to achieve hemostasis at an anastomotic site, the type of adjunct was recorded. Additional applications of cyanoacrylate surgical sealant (investigational device arm only) or control (control arm only), stitches, or pledgets; administration of protamine; or other standards of care for the center were permitted. Additional applications of cyanoacrylate surgical sealant were required to follow the per-protocol instructions for use, including reclamping, drying the area, applying the sealant, and waiting 120 seconds until clamp release. Protamine for reversal of heparin may have been used after clamp removal in cases of significant bleeding but should not have been used prophylactically. Once hemostasis had been achieved at all anastomotic sites for a patient, closure of the wound was initiated.

Follow-up. Patients receiving AV shunts had their distal radial pulse assessed upon release from the operating room, release from the recovery room, discharge from the hospital, or 48 hours after treatment (whichever was first) and during posttreatment follow-up assessments at 4 weeks (±7 days) and 12 weeks (±7 days). The pulse may have been assessed by palpation, stethoscope, or Doppler ultrasonography. Patients receiving femoral bypass procedures underwent vascular assessment upon release from the operating room and release from the recovery room. Patients had their ankle-brachial index measured upon discharge from the hospital or 48 hours after treatment and during their follow-up visits at 4 and 12 weeks (±7 days). All patients had their closed treatment sites visually inspected upon release from the operating room, release from the recovery room, discharge from the hospital, or 48 hours after treatment and during post-treatment follow-up visits at 4 and 12 weeks (±7 days).

Primary end point. The primary end point was the elapsed time between the release of the surgical clamps and complete sealing of the suture line, which was recorded in

seconds. For femoral bypass patients who had more than one anastomotic site treated, the site with the longest time to hemostasis was used for the primary analysis. Any time to hemostasis that was >10 minutes was treated as 10 minutes in the primary analysis.

Secondary efficacy end points. One of the secondary end points was the proportion of patients achieving hemostasis at t = 0 (immediate), 1, 5, or 10 minutes after clamp release. For femoral bypass patients who had more than one anastomotic site treated, the site with the longest time to hemostasis was used for these analyses. Another end point was the frequency of using additional adjunctive measures to achieve hemostasis. For femoral bypass patients who had more than one anastomotic site treated, each patient was classified as having had a specific additional adjunctive measure or not.

Safety end points. Safety end points included adverse events and device-related adverse events during the index hospitalization, from hospital discharge through the 12-week follow-up period, and from the index hospitalization through the 12-week follow-up period. Adverse events that were classified by the clinical investigator as (1) serious and severe, (2) definitely, probably, or possibly device-related, or (3) serious or that were not listed in the protocol as potential adverse events were adjudicated by a data safety monitor.

Statistical methods. The sample size was based on a standard deviation of time to hemostasis of 3.8 minutes.[15] A total of 150 patients in a 2:1 randomization provided 80% power to reject the noninferiority null hypothesis if the true mean time to hemostasis was 0.6 minutes faster with cyanoacrylate surgical sealant than with the control and 80% power to reject the superiority null hypothesis if the true mean time was 1.9 minutes faster. Baseline comparisons were made between treatment groups by *t* tests for continuous variables and χ^2 tests for categorical variables. All analyses were based on the intent-to-treat data set, which included all patients in the treatment group to which the patients were randomized, irrespective of the treatment they actually received. The primary analysis was an analysis of variance, which included the effects of treatment group, procedure (femoral bypass procedures or AV shunt procedures), and study center. Secondary analyses (hemostasis within various intervals and the use of additional adjunctive measures to achieve hemostasis) were performed by the Cochran-Mantel-Haenszel procedure, stratified by procedure and study center. Subgroup analyses were performed on the primary and secondary efficacy variables by type of procedure.

Approval. This study was conducted in compliance with the US Code of Federal Regulations and ethical principles from the Declaration of Helsinki. Institutional review boards (United States) or ethics committees (Europe) at each institution approved the study before study initiation. Informed consent was obtained from all patients.

Table I. Patient demographics at baseline

Variable	*Cyanoacrylate surgical sealant (n = 101)*	*Control (n = 50)*	P *value*
Age, y (mean ± SD)	60.8 ± 14.3	61.4 ± 13.9	.83
Sex			
Male, n (%)	66 (65.3)	28 (56.0)	.26
Female, n (%)	35 (34.7)	22 (44.0)	
Procedure			
Femoral bypass, n (%)	46 (45.5)	23 (46.0)	.96*
Fem-pop, above the knee	22/38 (57.9)	13/17 (76.5)	.43
Fem-pop, below the knee	7/38 (18.4)	2/17 (11.8)	
Fem-fem	4/38 (10.5)	0/17 (0)	
Aorto-fem	5/38 (13.2)	2/17 (11.8)	
AV access, n (%)	55 (54.5)	27 (54.0)	
Upper arm	20 (36.4)	9 (33.3)	.93
Lower arm	31 (56.4)	16 (59.3)	
Brachial	1 (1.8)	1 (3.7)	
Groin	1 (1.8)	0 (0)	
Upper leg	1 (1.8)	1 (3.7)	

AV, Arteriovenous.
*Femoral bypass vs AV access.
Fem-Pop, femoral to popliteal.

RESULTS

Investigational sites and patient accounting. A total of 151 patients were randomized (2:1) to receive cyanoacrylate surgical sealant or the control at 12 sites (10 in the United States and 2 in Europe). In Europe, all 25 patients were randomized for femoral bypass procedures (17 to cyanoacrylate surgical sealant and 8 to the control). In the United States, 82 patients were randomized for AV shunt procedures (55 to cyanoacrylate surgical sealant and 27 to the control), and 44 were randomized for femoral bypass procedures (29 to cyanoacrylate surgical sealant and 15 to the control).

All 151 patients completed the operation, and 149 were discharged from the hospital alive. A total of 141 patients completed the 4-week follow-up, and 126 (81 in the cyanoacrylate surgical sealant group and 45 in the control group) completed the 12-week follow-up, thus completing the study. For the 25 patients who did not complete the study, the reasons were as follows: 5 died, 2 were lost to follow-up, 9 were withdrawn by the investigator, 4 were withdrawn because of patient choice or inability to complete the study, 4 had the graft removed, and 1 had a leg amputated above the knee. Of the 9 patients withdrawn by the investigator, 7 were in the cyanoacrylate surgical sealant group and were withdrawn due to graft removal (n = 2), graft occlusion/clotting (n = 4), and ligated graft (n = 1), and 2 were in the control group and were withdrawn as a result of graft occlusion/clotting (n = 1) and explanted graft (n = 1).

Baseline demographics. Patient baseline demographics and clinical characteristics (medical history and baseline use of anticoagulant and antiplatelet medications) are summarized in Tables I and II, respectively. The statistical

Table II. Patient clinical characteristics at baseline, including medical history/risk factors and anticoagulant/antiplatelet medications taken regularly before enrollment

Characteristic	*Cyanoacrylate surgical sealant (n = 101)*	*Control (n = 50)*	P *value*
Medical history/risk factors			
Currently on dialysis	47 (46.5)	22 (44.0)	.77
Months on dialysis, mean (range)	23.5 (0-168)	16.9 (1-84)	
Hypertension	88 (87.1)	42 (84.0)	.60
History of chronic liver disease	6 (5.9)	2 (4.0)	1.0
History of renal insufficiency	56 (55.4)	27 (54.0)	.87
History of renal failure	53 (52.5)	28 (56.0)	.68
PVD	54 (53.5)	27 (54.0)	.95
Anticoagulant/antiplatelet medications			
Aspirin	43 (42.6)	32 (64.0)	.013
Clopidogrel	14 (13.9)	10 (20.0)	.33
Anti–vitamin K anticoagulants*	10 (9.9)	12 (24.0)	.021
Heparin	7 (6.9)	1 (2.0)	.27
Cilostazol	1 (1.0)	1 (2.0)	1.0
Dipyridamole	0 (0)	1 (2.0)	.33

PVD, Peripheral vascular disease.
*Patients were required to have been off anti–vitamin K anticoagulants for at least 4 days before the index procedure.
Data are n (%) unless otherwise noted.

Table III. Difference in mean time from clamp release to hemostasis between groups

	AV shunt		*Femoral bypass**		*All patients**	
Variable	*Cyanoacrylate surgical sealant (n = 55)*	*Control (n = 27)*	*Cyanoacrylate surgical sealant (n = 46)*	*Control (n = 23)*	*Cyanoacrylate surgical sealant (n = 101)*	*Control (n = 50)*
Time to hemostasis (s)						
Mean†	77.8	346.6	159.4	461.9	119.3	403.8
Difference (95% CI)	−268.7 (−338.2 to −199.3)		−302.4 (−402.6 to −202.3)		−284.4 (−342.9 to −226.0)	
P value						
Noninferiority‡	—		—		<.001	
Superiority	<.001		<.001		<.001	

AV, Arteriovenous; *CI,* confidence interval.
*The anastomotic site with the longest time was used for femoral bypass patients with multiple sites treated. All times >10 minutes were replaced by 10 minutes.
†Adjusted for study center and type of procedure.
‡Test of the hypothesis that the cyanoacrylate surgical sealant mean is no more than 1 minute longer than that of the control.

comparisons reported in the tables reveal that the two groups were similar at baseline. Preprocedural use of aspirin and warfarin ($P < .05$) and the proportion of patients with diabetes ($P = .057$) were higher in the control group. When these variables were added to the primary statistical model, the difference in mean time to hemostasis between cyanoacrylate surgical sealant and the control increased from 284 to 301 seconds, thus indicating that they had no effect on the primary analysis.

Primary end point. The primary outcome measure, time from clamp release to hemostasis, is shown in Table III. Results are shown by procedure and anastomotic site in Table I (online only). As prescribed in the protocol, all times to hemostasis longer than 10 minutes were replaced by 10 minutes, and for the 69 femoral bypass patients, the anastomotic site with the longest time to hemostasis was used. The primary efficacy analysis was a test of noninferiority of the time to hemostasis for patients treated with cyanoacrylate surgical sealant to within 1 minute of that of patients treated with the control. The test of noninferiority was rejected ($P < .001$), and a test for superiority was performed, which was also significant ($P < .001$). The mean time to hemostasis for all procedures was 284 seconds faster for patients treated with cyanoacrylate surgical sealant than for those treated with the control.

The time to hemostasis based on the type of procedure is also shown in Table III. For patients treated with cyanoacrylate surgical sealant, the mean time to hemostasis was 302 seconds faster than with the control for femoral bypass patients and was 269 seconds faster for AV access patients. For both groups, the mean time to hemostasis was faster for AV shunt procedures than for femoral bypass procedures.

An additional analysis was performed that included the 2-minute polymerization time for cyanoacrylate surgical sealant in the time to hemostasis. In this analysis, the mean time to hemostasis was 230.7 seconds with cyanoacrylate

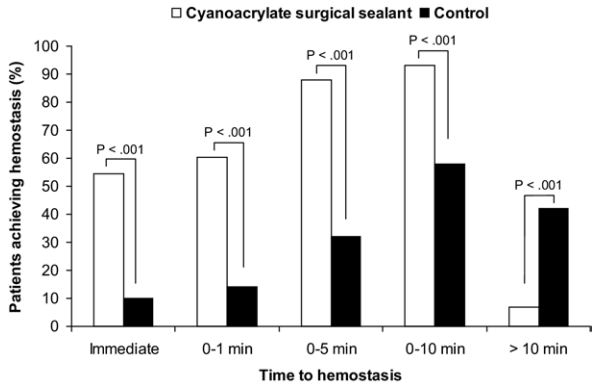

Fig. The percentage of patients achieving hemostasis at t = 0 (immediate), 1, 5, and 10 minutes after clamp release is shown for all procedures by treatment group.

surgical sealant and 422.0 seconds with the control. The analysis confirmed that time to hemostasis was significantly faster (191.4 seconds; 95% confidence interval, 139.4-243.4 seconds) with cyanoacrylate surgical sealant than with control ($P < .001$).

Secondary end points. The proportion of patients who achieved hemostasis within 0 (immediate), 1, 5, and 10 minutes after clamp release is reported by treatment group and procedure in the Figure and Table II (online only). The proportion of patients achieving hemostasis within each of the time intervals was significantly greater for patients treated with cyanoacrylate surgical sealant than for those receiving the control ($P < .001$). Immediate hemostasis was achieved in 54.5% of the patients in the cyanoacrylate surgical sealant group vs only 10% of those in the control group. As with the primary end point, the proportion of patients achieving immediate hemostasis was higher for AV shunt procedures than for femoral bypass procedures in both treatment groups.

The number of patients who required additional adjunctive agents to achieve hemostasis and the type of adjunctive agent used is reported in Table IV. Only the proportion of patients requiring an additional unit of the assigned treatment was significantly different between treatment groups (11% for cyanoacrylate surgical sealant and 30% for the control; $P < .001$). Similar results were observed when analysis was performed by procedure.

Safety assessment. All adverse events that occurred from the index procedure through the 12-week follow-up are reported by treatment in Table V. The only difference in event rates that achieved a nominal significance ($P < .05$) was hematoma, which occurred in 12% of the control patients and 2% of the cyanoacrylate surgical sealant patients. The occurrence of serious adverse events and device-related adverse events was not significantly different between treatment groups. The results of vascular assessments were similar in both treatment groups for both procedures.

Table IV. Use of additional adjunctive agents to achieve hemostasis (all patients and procedures)

Variable	*Cyanoacrylate surgical sealant (N = 101), n (%)*	*Control (N = 50), n (%)*	P *value**
Patients requiring ≥1 additional agent†	31 (30.7)	22 (44.0)	.08
Additional unit of assigned treatment	11 (10.9)	15 (30.0)	<.001
Stitches	7 (6.9)	7 (14.0)	.15
Pledgets	0 (0)	0 (0)	—
Protamine‡	7 (6.9)	8 (16.0)	.08
Other§	12 (11.9)	3 (6.0)	.22

*Adjusted for study center and procedure.
†The total number of individual agents may exceed the number of patients who had at least one agent used because patients may have had multiple agents used and because multiple anastomotic sites were treated in femoral bypass patients.
‡Protamine was to be administered only after clamp removal in cases of significant bleeding.
§For the cyanoacrylate surgical sealant group, other adjunctive agents included Surgicel (Johnson & Johnson, New Brunswick, NJ; n = 3), Surgicel Nu Knit (Johnson & Johnson; n = 4), Fibrillar (Johnson & Johnson; n = 1), Gelfoam and thrombin (Pharmacia & Upjohn, Kalamazoo, Mich; n = 1), and manual compression/pressure (n = 3). For the control group, other adjunctive agents included Gelfoam (n = 3), Fibrillar (n = 1), and Surgicel Nu Knit (n = 3).

DISCUSSION

The results of this study demonstrate that the family of cyanoacrylate hemostatic agents, which have proven their safety and efficacy in topical use,[11,12] have now produced a safe and effective absorbable surgical sealant for internal use. The data show that the time from clamp release to complete hemostasis with cyanoacrylate surgical sealant is shorter than that with oxidized cellulose. In addition, immediate hemostasis was achieved in 55% of the cyanoacrylate surgical sealant patients, compared with only 10% of the control patients. Similar safety profiles in both groups confirm that cyanoacrylate surgical sealant is safe for use in femoral bypass procedures and AV shunt procedures.

In general, medical risk factors that can affect bleeding time and hemostasis, such as hypertension and a history of cerebrovascular accidents, chronic liver disease, or renal failure, were similar in the two groups at baseline. In the control group, the proportion with diabetes was marginally significantly higher, and pre-enrollment use of aspirin and anti–vitamin K anticoagulants was nominally significantly higher. However, additional statistical analyses revealed that these variables did not have a significant effect on the primary end point and that adjusting for these items actually increased the difference in time to hemostasis between groups.

The two potential safety issues that are raised with cyanoacrylates include carcinogenicity and toxicity. The issue of carcinogenicity has already been addressed in studies evaluating the use of internally placed nonabsorbable cyanoacrylates.[16] The cyanoacrylate surgical sealant used in this study was designed to be absorbed in a controlled

Table V. All adverse events occurring from the index procedure through the 12-week follow-up

Variable	*Cyanoacrylate surgical sealant (N = 101), n (%)*	*Control (N = 50), n (%)*	P *value*
No. patients with 1 adverse event	69 (68.3)	35 (70.0)	.83
Bleeding complication			
Bleeding, procedure	2 (2.0)	0 (0)	1.0
Bleeding, postprocedure	2 (2.0)	1 (2.0)	1.0
Coagulopathy	1 (1.0)	0 (0)	1.0
Hematoma	2 (2.0)	6 (12.0)	.016
Pulmonary complication			
Atelectasis/pneumonia	0 (0)	1 (2.0)	.33
Respiratory failure	2 (2.0)	0 (0)	1.0
Cardiac complication			
Arrhythmia	0 (0)	1 (2.0)	.33
Myocardial infarction	2 (2.0)	0 (0)	1.0
Renal function complication			
Renal failure	4 (4.0)	1 (2.0)	1.0
Renal insufficiency	0 (0)	1 (2.0)	.33
Wound complication*			
Dehiscence	5 (5.0)	0 (0)	.17
Lymphocele/lymph fistula	3 (3.0)	0 (0)	.55
Wound infection	8 (7.9)	2 (4.0)	.50
Neurologic complication			
Cerebrovascular accident	0 (0)	1 (2.0)	.33
Paraplegia/paraparesis	0 (0)	1 (2.0)	.33
Vascular complication			
Edema	5 (5.0)	4 (8.0)	.48
Occlusion of graft/vessel	12 (11.9)	8 (16.0)	.48
Thrombosis	5 (5.0)	3 (6.0)	1.0
Other complication			
Death†	4 (4.0)	1 (2.0)	1.0
Increased temperature	2 (2.0)	4 (8.0)	.09
Erythema	7 (6.9)	1 (2.0)	.27
Infection	10 (9.9)	5 (10.0)	1.0
Pain	9 (8.9)	5 (10.0)	1.0
Other	43 (42.6)‡	14 (28.0)§	.11

*Refers to wound complications occurring at the site of the surgical incision, not the site where cyanoacrylate surgical sealant or the control was applied. The incidence of any wound complication was 13.9% in the cyanoacrylate surgical sealant group and 4% in the control group; the difference between groups was not statistically significant ($P = .091$).

†None of the deaths was reported to be device related.

‡Others were noted as diarrhea, anemia, hyperkalemia, bradycardia, vascular steal syndrome, amputation due to tissue loss, vagal dizziness, nausea/vomiting, constipation, visual deficit, ischemic hand, steal syndrome, seroma, intensive care unit psychosis, gastrointestinal distress, reddened buttock, epileptic seizure, severe hypoglycemia, cellulitis, redness/warmth at incision site, gastrointestinal bleeding, hyperglycemia, severe ischemic steal, blister reaction to surgical tape, skin graft right foot, ischemic colitis, pulmonary edema, colon cancer, stenosis of venous anastomosis, cholelithiasis, nonhealing wound, contralateral infection, chest pain, and excessive bleeding.

§Others were noted as diarrhea, vascular steal syndrome, seroma, subclavian steal, blisters, syncopal episodes, urinary tract infection, itching without rash, nonfunctioning hemodialysis catheter, confusion, hyperkalemia, trauma—fall, severe nose bleed, serous drainage, increased international normalized ratio, right femoral-popliteal bypass, and infection.

manner to minimize any toxicity concerns. The safety of this product for internal use has been demonstrated in a pilot study[13] and now in this larger multicenter study.

This study demonstrates the superiority of cyanoacrylate surgical sealant to oxidized cellulose, which remains the standard of care; however, it is also interesting to see how it compares with fibrin sealant or another synthetic sealant. On the basis of published trials in a similar group of patients, cyanoacrylate surgical sealant seems to be at least as effective as these sealants. In a study that compared fibrin sealant and oxidized cellulose or pressure alone in patients undergoing AV shunt procedures, the mean time to hemostasis reported for fibrin sealant was 56.3 seconds, and the proportion of patients achieving immediate hemostasis was 54%.[17] For AV access patients treated with cyanoacrylate surgical sealant in this study, we observed a similar unadjusted mean time to hemostasis (45.7 seconds) and a higher percentage of patients achieving immediate hemostasis (73%). Similarly, in a study comparing a polyethylene glycol sealant with Gelfoam/thrombin (Pharmacia & Upjohn, Kalamazoo, Mich) in AV access and infra-inguinal bypass procedures, the proportion of patients achieving immediate hemostasis with this sealant was 47%,[9] which is lower than the 55% observed with cyanoacrylate surgical sealant in this study.

Cyanoacrylate surgical sealant has some potential advantages over fibrin sealants with regard to safety. Fibrin sealants contain derivatives from human plasma and, there-

fore, have a potential viral risk.[18] In addition, most fibrin sealants contain a bovine thrombin component, which can be immunogenic.[18] Although the potential risk is low, use of a synthetic sealant such as cyanoacrylate surgical sealant eliminates the risk. There is also a potential issue with patency of the anastomosis. There is evidence that sealants containing thrombin can adversely affect the patency of microvascular anastomoses; therefore, sealants that do not contain thrombin are recommended.[19] This could also apply to the patency of nonmicrovascular grafts, and the potential risk could be avoided by using non–thrombin-containing sealants, such as cyanoacrylate surgical sealant. For AV dialysis grafts, there is already a concern about thrombosis and anastomotic stenosis when ePTFE grafts are used, and additional risk could be avoided by using a sealant without thrombin.[20,21]

Cyanoacrylate surgical sealant has some characteristics that make it particularly useful and reliable for the surgeon. It can be stored at room temperature, can be easily and rapidly prepared in the applicator device, and is easy to apply. In addition, the sealant is mechanical and functions independently of the body's clotting mechanism. The availability of an effective surgical sealant such as cyanoacrylate surgical sealant means that vascular surgery is moving toward the ideal situation in which anastomotic bleeding is an unnecessary, unacceptable consequence of joining an ePTFE graft to an artery and leads to the possibility of performing sutureless anastomoses. Future uses of cyanoacrylate surgical sealant could include other areas of vascular surgery where there is a critical need for good hemostatic control, such as carotid endarterectomy and abdominal aortic aneurysm repair, especially with ePTFE grafts. It could also be used to give added security to the surgeon when the vascular procedure is being undertaken laparoscopically, as is increasingly becoming the case. Beyond the vascular anastomosis field, a strong effective surgical sealant could also be useful in other areas such as glue aortoplasty or surgery to repair complicated cardiac defects.

CONCLUSION

This study demonstrates that cyanoacrylate surgical sealant is highly effective at reducing the time to hemostasis in AV shunt and femoral bypass procedures and is safe for internal use. Immediate hemostasis was achieved in more than 50% of the patients, and the need for additional adjunctive agents was reduced. Cyanoacrylate surgical sealant is an easy-to-use vascular sealant with good safety and efficacy that significantly decreases anastomotic bleeding in vascular surgery.

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Final approval of the article: ABL, ERH
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INVITED COMMENTARY

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Experienced vascular surgeons recognize the value of topical hemostatic agents to treat anastomotic bleeding. Regardless of whether these agents actually contribute to local hemostasis or merely allow time for full heparin reversal and activation of the patient's own clotting factors, we all use them. Numerous options are currently available, and every surgeon has a favorite. However, no agent has emerged as clearly superior in terms of rapid hemostasis, ease of use, low cost, and minimal toxicity.

Enter cyanoacrylate, the holy grail of topical sealants. As shown in the present study, this agent stops anastomotic bleeding at the source, just like a self-sealing tire. By creating a mechanical seal at leak sites, cyanoacrylate works independently of the patient's ability to form clot. Compared with the popular oxidized cellulose alternative, cyanoacrylate achieves more rapid hemostasis at all time intervals after clamp release. And it does this without any measurable increase in complications.

Based on the elegant methods and statistical support of the present study, the evidence for the superiority of cyanoacrylate seems irrefutable. However, there are a number of problems with the study design that should temper our enthusiasm beyond the fact the agent is not currently on the market. The first issue is that the study groups may not have been adequately matched. Significantly more controls received aspirin, and more controls had taken anti-vitamin K antagonists before the trial. Although the anticoagulation effects of warfarin should have resolved within the 4 days of discontinuation mandated by the inclusion criteria, we do not know how many subjects were over-anticoagulated, and we have no tests to ensure the absence of a residual anticoagulation effect.

A second concern is that the procedures were not standardized. Expanded polytetrafluoroethylene grafts were not uniform, and we do not know, for example, how many patients received standard-wall vs thin-wall grafts. Intraoperative heparin dosing was not standardized, nor was it monitored with the activated clotting time. The use of protamine was left entirely up to the decision of the surgeon, who was not blinded to the type of agent being used. Although patients receiving cyanoacrylate had a mandatory 2-minute wait time before clamps were removed, this was not the case for the controls. A 2-minute exposure to microscopic amounts of blood may have improved the hemostatic action of the control agent.

Despite these criticisms, there is much to commend this study. It is prospective, randomized, and adequately powered. The results are clear: to treat anastomotic bleeding, cyanoacrylate achieves faster hemostasis than oxidized cellulose. Cyanoacrylate is easy to apply and appears to have low toxicity. The present analysis is certainly provocative, and the study agent is very promising; however, further experience with cyanoacrylate is needed before we can say that it is superior to other agents.

Table I, online only. Time from clamp release to hemostasis by procedure and anastomotic site

*Time to hemostasis**	*Cyanoacrylate surgical sealant*	*Control*
Femoral bypass: proximal site (n)	45†	23
Mean ± SD (s)	174.4 ± 223.7	426.6 ± 199.6
Range (s)	0-600	0-600
Femoral bypass: distal site (n)	44†	23
Mean ± SD (s)	37.6 ± 72.6	323.2 ± 261.3
Range (s)	0-273	0-600
Femoral bypass: second distal site (n)	5	2
Mean ± SD (s)	42.2 ± 74.1	510.0 ± 127.3
Range (s)	0-171	420-600
Femoral bypass: site with longest time (n)	46	23
Mean ± SD (s)	194.4 ± 212.8	505.0 ± 152.3
Range (s)	0-600	70-600
AV access for hemodialysis (n)	55	27
Mean ± SD (s)	45.7 ± 105.2	298.0 ± 231.1
Range (s)	0-600	0-600

AV, Arteriovenous.
*All times >10 minutes were replaced by 10 minutes.
†One patient had no proximal site treated but had two distal sites treated, and two patients had one proximal site treated and no distal site.

Table II, online only. Proportion of patients achieving hemostasis in minute intervals by treatment group and procedure

Variable	*Cyanoacrylate surgical sealant (n = 101)*	*Control (n = 50)*	P *value**
AV shunt†			
0 (immediate)	40 (72.7)	5 (18.5)	<.001
0-1 min	43 (78.2)	7 (25.9)	<.001
0-5 min	53 (96.4)	13 (48.2)	<.001
0-10 min	54 (98.2)	21 (77.8)	<.001
>10 min	1 (1.8)	6 (22.2)	<.001
Femoral bypass†			
0 (immediate)	15 (32.6)	0 (0)	.003
0-1 min	18 (39.1)	0 (0)	<.001
0-5 min	36 (78.3)	3 (13.0)	<.001
0-10 min	40 (87.0)	8 (34.8)	<.001
>10 min	6 (13.0)	15 (65.2)	<.001
All patients			
0 (immediate)	55 (54.5)	5 (10.0)	<.001
0-1 min	61 (60.4)	7 (14.0)	<.001
0-5 min	89 (88.1)	16 (32.0)	<.001
0-10 min	94 (93.1)	29 (58.0)	<.001
>10 min	7 (6.9)	21 (42.0)	<.001

AV, Arteriovenous.
Data are n (%).
*Adjusted for study center.
†The anastomotic site with the longest time was used for femoral bypass patients with multiple sites treated.