A prospective randomized study comparing fibrin sealant to manual compression for the treatment of anastomotic suture-hole bleeding in expanded polytetrafluoroethylene grafts

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Objective: **The ideal hemostatic agent for treatment of suture-line bleeding at vascular anastomoses has not yet been established. This study evaluated whether the use of a fibrin sealant containing 500 IU/mL thrombin and synthetic aprotinin (FS; marketed in the United States under the name TISSEEL) is beneficial for treatment of challenging suture-line bleeding at vascular anastomoses of expanded polytetrafluoroethylene (ePTFE) grafts, including those further complicated by concomitant antiplatelet therapies.**

Methods: **Over a 1-year period ending in 2010, ePTFE graft prostheses, including arterio-arterial bypasses and arterio-venous shunts, were placed in 140 patients who experienced suture-line bleeding that required treatment after completion of anastomotic suturing. Across 24 US study sites, 70 patients were randomized and treated with FS and 70 with manual compression (control). The primary end point was the proportion of patients who achieved hemostasis at the study suture line at 4 minutes after start of application of FS or positioning of surgical gauze pads onto the study suture line.**

Results: **There was a statistically significant difference in the comparison of hemostasis rates at the study suture line at 4 minutes between FS (62.9%) and control (31.4%) patients ($P < .0001$), which was the primary end point. Similarly, hemostasis rates in the subgroup of patients on antiplatelet therapies were 64.7% (FS group) and 28.2% (control group). When analyzed by bleeding severity, the hemostatic advantage of FS over control at 4 minutes was similar (27.8% absolute improvement for moderate bleeding vs 32.8% for severe bleeding). Logistic regression analysis (accounting for gender, age, intervention type, bleeding severity, blood pressure, heparin coating of ePTFE graft, and antiplatelet therapies) found a statistically significant treatment effect in the odds ratio (OR) of meeting the primary end point between treatment groups (OR, 6.73; $P < .0001$), as well as statistically significant effects for intervention type (OR, 0.25; $P = .0055$) and bleeding severity (OR, 2.59; $P = .0209$). The safety profile of FS was excellent as indicated by the lack of any related serious adverse events.**

Conclusions: **The findings from this phase 3 study confirmed that FS is safe and its efficacy is superior to manual compression for hemostasis in patients with peripheral vascular ePTFE grafts. The data also suggest that FS promotes hemostasis independently of the patient's own coagulation system, as shown in a representative population of patients with vascular disease under single- or dual-antiplatelet therapies. (J Vasc Surg 2012;56:134-41.)**

Expanded polytetrafluoroethylene (ePTFE) graft placement can be complicated by prolonged anastomotic suture-hole bleeding, which increases operative time, overall blood loss, and risk of wound complications.[1,2] The intraoperative use of heparin for prevention of thromboses and perioperative use of platelet inhibitors can exacerbate the problem. In patients on dialysis, the underlying disease compromises the coagulation system and dialysis itself may lead to increased fibrinolysis.[3]

Suture-hole bleeding can be managed through the use of manual compression with surgical gauze pads, reversal of heparin, and topical hemostatic agents. Agents such as collagen, oxidized cellulose, gelatin alone or in combination with thrombin,[4-8] polyethylene glycol-based glues,[9] gelatin-resorcine-formol glues,[2] and cyanoacrylate glue[10] have been used with varying success.

Fibrin sealants contain the components necessary for the generation of a fibrin clot and can achieve hemostasis or sealing independently of the patient's coagulation system. They have shown beneficial results with respect to significantly shorter times to hemostasis than other commonly used agents/techniques in a variety of complex clinical situations[1,6-8,11-18] and with respect to significant decreases in mortality and morbidity in spleen and liver injuries.[19]

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Our prospective controlled study evaluated the efficacy and safety of a fibrin sealant containing 500 IU/mL thrombin and synthetic aprotinin (referred to herein as FS) for the treatment of anastomotic suture-hole bleeding that is not amenable to additional sutures during placement of ePTFE vascular grafts.

FS is currently licensed in the United States under the trade name TISSEEL (Baxter Healthcare Corporation, Westlake Village, Calif). This study was part of the manufacturer's clinical development program, which is aimed at broadening the indications for FS to include hemostasis in all surgical applications where control of bleeding by standard surgical techniques is ineffective or impractical.

METHODS

Study design. This prospective, controlled, randomized, subject-blinded, multicenter phase 3 study evaluated the efficacy and safety of FS for the treatment of anastomotic suture-hole bleeding during ePTFE graft placement as compared to manual compression with gauze pads, a valid standard of care technique. The requirement for a comparator therapy is specific to higher-risk surgical procedures where hemostasis/sealing and suture support, such as in vascular anastomoses, are critical.[20-22]

The study protocol was approved by the institutional review board at each of 24 US study sites.

Patients underwent graft placement on day 0, which was when hemostasis was assessed. Postoperative follow-up took place at discharge or on day 1 (whichever occurred first) and on days 14 and 30. The following surgical procedures were permitted: axillofemoral, axillobifemoral, aortobifemoral, iliofemoral, femorofemoral, iliopopliteal, femoropopliteal, femorotibial vessel bypass, and arteriovenous (AV) shunting for dialysis access in the upper and lower extremities.

The primary end point was the proportion of patients who achieved hemostasis at the study suture line of the graft at 4 minutes after the start of either a single application of FS or continuous manual compression with surgical gauze pads (control) and maintained it until closure of the surgical wound. The study suture line was defined as either the iliac or the femoral anastomosis in arterio-arterial bypasses; the last femoral anastomosis to be completed in axillobifemoral and in aortobifemoral bypasses; and the arterial anastomoses in AV shunts. Hemostasis was defined as no visible bleeding at the study suture line. Bleedings treated at the nonstudy suture line were not assessed for time to hemostasis. Patients were considered treatment failures if hemostasis was not achieved within the first 4 minutes or additional hemostatic treatment was administered (including the reapplication of FS), or if intraoperative rebleeding occurred after the first 4 minutes. This end point was considered appropriate to detect a clinically relevant reduction of time to hemostasis in treatment groups.

Secondary efficacy end points included the following:

- Proportion of patients who achieved hemostasis at the study suture line at 6 minutes after treatment application and maintained it until surgical closure.
- Proportion of patients who achieved hemostasis at the study suture line at 10 minutes after treatment application and maintained it until surgical closure.
- Incidence of intraoperative rebleeding at the study suture line after the achievement of hemostasis.
- Incidence of postoperative rebleeding at the study suture line requiring surgical re-exploration.

Overall safety was assessed by monitoring adverse events (AEs), including surgical site infections (SSIs) and graft occlusions, laboratory values, vital signs, and concomitant medications. We defined an AE as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with study treatment, regardless of the presumed causality between the event and treatment. SSIs were graded according to the Szilagyi classification system.[23] Graft occlusions were determined clinically and defined as absence of blood flow through the graft.

Patients. Upon provision of informed consent, all male and female patients scheduled for arterio-arterial bypasses or AV shunts with ePTFE grafts were eligible for inclusion in the study. Only patients with moderate or severe anastomotic suture-hole bleeding that could not be controlled with additional suturing were randomized to one of two treatment groups: FS or control.

Key exclusion criteria were other vascular procedures planned for the same surgical session, pregnant or lactating women, congenital coagulation disorders, prior kidney transplantation, heparin-induced thrombocytopenia, hypersensitivity to aprotinin or other components of FS, hypersensitivity to heparin, severe congenital or acquired immunodeficiency, prior radiation therapy to the operating field, and severe inflammation (ie, infection) at the operating field.

Investigational product. FS is a two-component biological fibrin sealant that mimics the final stage of the blood coagulation cascade. The active ingredients of FS, fibrinogen and thrombin (500 IU/mL), are manufactured from pooled human plasma that is obtained via a strict screening program; two independent, virus inactivation/reduction manufacturing steps (vapor heat treatment and solvent/detergent treatment) further increase its viral safety margin.[20] Upon mixing of the two components, soluble fibrinogen is transformed into a fibrin matrix that adheres to the wound surface and achieves hemostasis and sealing/gluing of tissues. During the course of wound healing, the solidified FS is slowly lysed and completely resorbed within 10 to 15 days.[24]

Surgical procedure. The ePTFE graft placement was performed according to hospital standards. To avoid bias, study-related surgical procedures were standardized to the extent possible across treatment groups.

Before initial clamping, patients who had arterio-arterial bypass received 100 IU ± 10% heparin per kg body

weight, and patients who had AV shunts received 50 IU ± 10% heparin per kg body weight. Additional doses of heparin were administered at the discretion of the investigator. Heparin was reversed, if necessary, with protamine after the primary end point assessment. Sutures and needles were standardized for the graft anastomoses. For arterio-arterial anastomoses, 5-0 Prolene sutures and C-1 needles (Ethicon) were used. For AV shunts, 6-0 Prolene sutures and RB-2 needles were used.

After completion of anastomotic suturing, cross clamps were opened to determine if eligible suture-line bleeding that could not be controlled with additional suturing was present. If present, randomization was performed, as stratified by bleeding severity. Bleeding was defined as moderate if it affected >25% of the suture line, consisted of at least five suture-line bleeds, or consisted of one pulsatile suture-line bleed. Bleeding was considered severe if it covered >50% of the suture line, consisted of at least 10 suture-line bleeds, consisted of >1 pulsatile suture-line bleed, or consisted of at least one spurting (ie, continuous) suture-line bleed. Upon completion of the bleeding assessment, vessels were reclamped and randomization occurred.

In the FS group, a thin, continuous film of FS was applied with a blunt application needle to the study suture line, covering both the native vessel and ePTFE graft; arterial flow was re-established after 2 minutes of polymerization or setting of FS. In the control group, dry gauze pads were positioned to completely cover the study suture line; arterial flow was re-established immediately after gauze pads were positioned and manual compression was applied. The study suture line was inspected for bleeding at 4, 6, and 10 minutes after the start of application of FS or positioning of gauze pads. In the control group, gauze pads were momentarily lifted for inspection of the study suture line. During the observation period, additional hemostatic treatments on the study suture line were used only in cases of severe bleeding that jeopardized subject safety. The choice of alternative treatments was at the discretion of the investigator; however, in the FS group, no fibrin sealant other than FS was to be used, and in the control group, neither FS nor any other fibrin sealant was to be used. Furthermore, the perioperative administration of platelet inhibitors was allowed in this study.

Treatment of bleeds at the nonstudy suture line was to mirror that of bleeds at the study suture line; however, time to hemostasis was not recorded.

Statistical methods. Sample size calculations were based on the results of the previous phase 2 study.[25] The proportion of patients achieving hemostasis at 4 minutes for FS was expected to be about 60%, and the rate for control patients was expected to be about 35%. If the above assumptions held true, a per-group sample size of 70 randomized patients with valid assessments for the primary end point was considered sufficient to show a difference between treatment groups with a one-sided type one error of 2.5% and a power of approximately 85%.

The primary efficacy analysis was carried out on the intent-to-treat population (ie, all randomized patients), as well as on a subset who were administered platelet inhibitors perioperatively (post hoc analysis); this subset included patients who were under antiplatelet therapy preoperatively and either stopped therapy within <5 days before surgery or continued therapy perioperatively. For comparison of hemostasis rates between treatment groups, the likelihood ratio χ^2 test was carried out with a 2.5% one-sided significance level. In addition, the proportion of patients achieving hemostasis at 4 minutes in the treatment groups was analyzed using logistic regression, taking into account gender, age, type of intervention, severity of bleeding, systolic blood pressure, diastolic blood pressure, and heparin coating of the ePTFE graft, as well as platelet inhibitors in the post hoc analysis.

Proportions and corresponding 95% two-sided confidence intervals (CIs) based on the likelihood ratio χ^2 test were calculated for each treatment group for the secondary end points. These end points were also analyzed using the likelihood ratio χ^2 test for proportions, comparing treatment groups.

For the incidence of infections and graft occlusions, proportions and corresponding 95% two-sided CIs based on the likelihood ratio χ^2 test were calculated for each treatment group. These variables were also analyzed using the likelihood ratio χ^2 test for proportions, comparing treatment groups.

RESULTS

A total of 140 patients between 33 and 90 years of age were treated in this study: 70 with FS and 70 with control. The majority of patients underwent upper extremity AV shunt placement (31/70 FS patients [44.3%] and 40/70 control patients [57.1%]) and femoropopliteal arterio-arterial bypass (24/70 FS patients [34.3%] and 17/70 control patients [24.3%]; Table I). Demographic and baseline characteristics (Table II) and the number and type of surgical procedures performed were comparable between treatment groups.

The proportion of patients that achieved hemostasis at the study suture line at 4 minutes and maintained it was 62.9% (44/70; 95% CI, 51.2-73.6) in the FS group and 31.4% (22/70; 95% CI, 21.4-42.8) in the control group (Table III). The one-sided P value from the likelihood ratio χ^2 test indicated a statistically significant difference at the 2.5% one-sided level in the comparison of hemostasis rates between treatment groups ($P < .0001$).

Logistic regression was performed on the primary end point adjusted for factors influencing hemostasis, including platelet inhibitors. A statistically significant treatment effect at the 5% two-sided level was observed in the odds ratio (OR) of achieving hemostasis at 4 minutes between treatment groups (OR, 6.73; 95% CI, 2.65-17.11; $P < .0001$; Table IV). Statistically significant effects were also observed for the type of intervention (OR, 0.25; 95% CI, 0.10-0.67; $P = .0055$) and severity of bleeding (OR, 2.59; 95% CI, 1.16-5.81; $P = .0209$).

Table I. Surgical records

Surgical record	*Type/location*	*FS group n (%) (n = 70)*	*Control group n (%) (n = 70)*
Procedure			
Arterio-arterial bypass	Axillofemoral	2 (2.9)	1 (1.4)
	Axillobifemoral	1 (1.4)	0 (0.0)
	Aortobifemoral	5 (7.1)	5 (7.1)
	Iliofemoral	0 (0.0)	1 (1.4)
	Femorofemoral	4 (5.7)	2 (2.9)
	Iliopopliteal	2 (2.9)	0 (0.0)
	Femoropopliteal	24 (34.3)	17 (24.3)
	Femorotibial vessel bypass	1 (1.4)	2 (2.9)
Arteriovenous dialysis access shunt	Upper extremity	31 (44.3)	40 (57.1)
	Lower extremity	0 (0.0)	2 (2.9)
ePTFE prosthesis type			
	Heparin coated	33 (47.1)	33 (47.1)
	Not heparin coated	37 (52.9)	37 (52.9)
Suture type			
	Running	70 (100.0)	69 (98.6)
	Interrupted	0 (0.0)	1 (1.4)
Suture thickness			
	5.0	38 (54.3)	28 (40.0)
	6.0	32 (45.7)	42 (60.0)
Needle type			
	C1	38 (54.3)	28 (40.0)
	RB2	31 (44.3)	41 (58.6)
	BV1	1 (1.4)	1 (1.4)

ePTFE, Expanded polytetrafluoroethylene; *FS,* fibrin sealant containing 500 IU/mL thrombin and synthetic aprotinin.

Table II. Demographic and baseline characteristics

Parameter	*FS group n (%) (n = 70)*	*Control group n (%) (n = 70)*
Gender		
Male	30 (42.9)	37 (52.9)
Female	40 (57.1)	33 (47.1)
Race		
White	40 (57.1)	41 (58.6)
Black or African American	28 (40.0)	27 (38.6)
Asian	1 (1.4)	0 (0.0)
American Indian or Alaska native	1 (1.4)	2 (2.9)
Ethnicity		
Hispanic or Latino	4 (5.7)	6 (8.6)
Non-Hispanic or Latino	66 (94.3)	64 (91.4)
Age, years		
Mean	62.5	66.3
SD	12.6	11.5
Median	63.5	68.0
Range	33-88	43-90

FS, Fibrin sealant containing 500 IU/mL thrombin and synthetic aprotinin.

Hemostasis rates at 4 minutes in patients on platelet inhibitors, including aspirin, cilostazol, dipyridamole, dipyridamole with aspirin, and clopidogrel, were comparable to those in patients not on platelet inhibitors (Table V): 64.7% (FS group) and 28.2% (control group) vs 61.1% (FS group) and 35.5% (control group).

Hemostasis rates at 4 minutes were higher for moderate bleeders than severe bleeders in both treatment groups. Hemostasis rates were 75.9% (22/29; 95% CI, 58.5-88.8) in the FS group vs 48.1% (13/27; 95% CI, 30.1-66.5) in the control group for moderate bleeders, and 53.7% (22/41; 95% CI, 38.5-68.4) in the FS group vs 20.9% (9/43; 95% CI, 10.7-34.6) in the control group for severe bleeders. It is important to note that FS is not indicated for treatment of massive and brisk arterial bleeding.

Differences were also observed in hemostasis rates at 6 and 10 minutes: 71.4% (50/70; 95% CI, 60.2-81.1) for the FS group vs 42.9% (30/70; 95% CI, 31.7-54.6) for the control group ($P = .001$), and 75.7% (53/70; 95% CI, 64.9-84.7) for the FS group vs 55.7% (39/70; 95% CI, 44.0-67.0) for the control group ($P = .012$), respectively.

The overall incidence of intraoperative rebleeding at the study suture line was low (4/70 FS patients [5.7%] and 1/70 control patients [1.4%]). Treatment of intraoperative rebleeding included reapplication of FS, manual compression, additional sutures, thrombin-soaked Gelfoam, Surgicel, and other topical hemostatic agents such as Fibrillar and FloSeal. None of the treated patients had postoperative rebleeding.

The evaluation of safety showed no remarkable differences between treatment groups in the occurrence of and risk of experiencing all AEs (serious and non-serious), serious adverse events (SAEs), and non-serious AEs during or after treatment (Table VI).

None of the 26 SAEs that occurred in 20 of 70 FS patients (28.6%) and none of the 23 SAEs in 18 of 70 patients (25.7%) were considered related to study treatment.

Table III. Summary of hemostasis at 4 minutes after treatment

Study group	*Hemostasis achieved at 4 minutes*[a] *n (%) (n = 70)*	*Additional treatment required to achieve hemostasis n (%) (n = 70)*	*Intraoperative rebleeding after primary hemostasis n (%) (n = 70)*	*Hemostasis achieved at 4 minutes and maintained until surgical closure*[b] *n (%) (n = 70)*
FS	47 (67.1)	13 (18.6)	4 (5.7)	44 (62.9)
Control	22 (31.4)	28 (40.0)	1 (1.4)	22 (31.4)

FS, Fibrin sealant containing 500 IU/mL thrombin and synthetic aprotinin.
[a]Includes patients who achieved hemostasis at 4 minutes but required additional treatment and/or experienced intraoperative rebleeding.
[b]Primary efficacy end point.

Table IV. Logistic regression: factors influencing hemostasis at 4 minutes after treatment

Factor	*OR*	*95% CI for OR*	P *value*[a]
FS vs control	6.73	2.65-17.11	<.0001
Gender (male vs female)	0.60	0.26-1.38	.2257
Age, years	0.99	0.95-1.03	.5276
Type of intervention (arterio-arterial bypass vs arteriovenous shunt)	0.25	0.10-0.67	.0055
Severity of bleeding (moderate vs severe)	2.59	1.16-5.81	.0209
Systolic blood pressure, mm Hg	0.98	0.96-1.00	.1208
Diastolic blood pressure, mm Hg	1.04	1.00-1.08	.0662
Heparin coating of the ePTFE prosthesis (yes vs no)	0.90	0.40-2.02	.8045
Platelet inhibitors (yes vs no)[b]	1.50	0.65-3.48	.3465

CI, Confidence interval; *ePTFE,* expanded polytetrafluoroethylene; *FS,* fibrin sealant containing 500 IU/mL thrombin and synthetic aprotinin; *OR,* odds ratio.
Platelet inhibitor = yes, if start date of the respective medication was before surgery date (for an unknown start date, it is assumed that the start date was before surgery date) and (1) in case the stop date of medication is ongoing or (2) in case the stop date of medication is after surgery date or (3) in case less than 5 full days are between stop date of medication and surgery date or (4) in case stop date of medication is unknown and not ongoing.
[a]Odds ratios, CIs, and *P* values were estimated from the logistic model accounting for the effects mentioned in the "Factor" column.
[b]Platelet inhibitors: aspirin, cilostazol, dipyridamole, dipyridamole with aspirin, and clopidogrel.

Table V. Primary efficacy end point for patients on antiplatelets

Platelet inhibitors	*FS group n of n (%)*	*Control group n of n (%)*
Yes	22 of 34 (64.7)	11 of 39 (28.2)
No	22 of 36 (61.1)	11 of 31 (35.5)

FS, Fibrin sealant containing 500 IU/mL thrombin and synthetic aprotinin.
Platelet inhibitor = yes, if start date of the respective medication was before surgery date (for an unknown start date, it is assumed that the start date was before surgery date) and (1) in case the stop date of medication is ongoing or (2) in case the stop date of medication is after surgery date or (3) in case less than 5 full days are between stop date of medication and surgery date or (4) in case stop date of medication is unknown and not ongoing.

Of the 125 non-serious AEs that occurred in 46 of 70 FS patients (65.7%), one was considered by the investigator to be possibly related to FS; and of the 119 non-serious AEs that occurred in 40 of 70 control patients (57.1%), one was considered possibly related to control. One FS patient underwent a femoropopliteal bypass and experienced severe bleeding at the study suture line. FS was applied, resulting in hemostasis at 6 minutes. During closure of the wound, the investigator noticed an area of blood welling up and seeping from under the application of FS at the study suture line. FS was removed, additional sutures were placed, and 2 mL of FS as well as Gelfoam and thrombin were applied to achieve hemostasis. The event was mild in severity and resolved the same day. One control patient underwent a femorofemoral bypass and experienced severe bleeding at the study suture line. Manual compression and Surgicel were applied, resulting in hemostasis at 10 minutes. On postoperative day 15, the patient experienced a 3-cm right groin hematoma. The event was moderate in severity and resolved after 9 days.

In the FS group, five of 70 patients (7.1%) experienced graft occlusions and seven of 70 patients (10.0%) experienced SSIs. Of the seven patients with SSIs, five patients (7.1%) experienced grade I (only dermis affected) infections, whereas two patients (2.9%) experienced grade II (infection invades subcutaneous region but not the arterial implant); no arterial implant infections occurred (Table VII). None of the SSIs or graft occlusions that occurred during the study was considered related to FS.

In the control group, eight of 70 patients (11.4%) experienced graft occlusions and five of 70 patients (7.1%) experienced SSIs. In the control group, three patients (4.3%) experienced grade I infections; one patient (1.4%) experienced a grade II infection; and one patient (1.4%) experienced a grade III infection (arterial implant infected; Table VIII).

Suspected anaphylactic or anaphylactoid reactions to FS and virus transmission were not reported in any of the patients treated with FS.

Table VI. Patients with AEs that occurred during/after treatment

	Study group	*n (%) (n = 70)*	*FS vs control*	
			RR	*95% CI of RR*
All AEs	FS	48 (68.6%)	1.115	0.875-1.420
	Control	43 (61.4%)	NA	NA
SAEs	FS	20 (28.6%)	1.108	0.649 to 1.892
	Control	18 (25.7%)	NA	NA
Non-serious AEs	FS	46 (65.7%)	1.148	0.884 to 1.492
	Control	40 (57.1%)	NA	NA

AEs, Adverse events; *CI,* confidence interval; *FS,* fibrin sealant containing 500 IU/mL thrombin and synthetic aprotinin; *NA,* not applicable; *RR,* risk ratio; *SAEs,* serious adverse events.

Table VII. SSIs and graft occlusions in FS patients

Reported term	*Relationship to treatment with FS*	*SSI grade*[a]
SSIs		
Postoperative surgical site infection with *Morganella morganii*	Not related	II
Methicillin-sensitive *Staphylococcus aureus* at right groin surgical site	Not related	II
Superficial wound infection	Not related	I
Superficial (dermal) cellulitis left groin surgical site	Not related	I
Cellulitis to right groin incision	Not related	I
Infection at left popliteal incision	Not related	I
Wound infection postoperative	Not related	I
Graft occlusions		
Clotted left AV graft	Not related	
Loop graft thrombosis-left arm	Not related	
Loop graft thrombosis-left arm	Not related	
Occluded graft	Not related	
Failed right forearm straight AV graft	Not related	
Failed right forearm straight AV graft	Not related	
Stricture compression of vein left arm	Not related	
Stricture compression of artery left arm	Not related	

AV, Arteriovenous; *FS,* fibrin sealant containing 500 IU/mL thrombin and synthetic aprotinin; *SSIs,* surgical site infections.
[a]Szilagyi DE, Smith RF, Elliott JP, Vrandecic MP. Infection in arterial reconstruction with synthetic grafts. Ann Surg 1972;176:321-33.

DISCUSSION

The ideal hemostatic agent for suture-line bleeding during vascular reconstructive surgery using ePTFE grafts should be both effective and fast-acting because perioperative blood loss poses significant health risks and can lengthen operating times and consequently increase costs. Clinical data on hemostatic agents in this type of application are limited, and, therefore, the ideal hemostatic agent has not yet been established.[26]

The main objectives of this study were to investigate whether the use of FS is beneficial for the treatment of anastomotic suture-hole bleeds that are not amenable to additional sutures, including those further complicated by concomitant platelet inhibitors.

The hemostatic advantages of FS over manual compression, as observed in the previous phase 2 study,[25] were confirmed in the present study. A statistically significant difference was observed between treatment groups in the proportion of patients that achieved hemostasis at the study suture line at 4 minutes and maintained it until surgical closure: 62.9% in the FS group vs 31.4% in the control group ($P < .0001$). This difference is confirmed by the logistic regression analysis, which indicated a statistically significant treatment effect ($P < .0001$) in the OR of achieving hemostasis at 4 minutes between the treatment groups. The odds of achieving hemostasis at 4 minutes was 6.30 times higher for FS patients than control patients, which is consistent with the results of a number of clinical studies comparing fibrin sealants to manual compression for hemostasis in vascular surgery.[6,7,11] When analyzed by bleeding severity, the hemostatic advantage of FS over control at 4 minutes was similar (27.8% absolute improvement for moderate bleeding vs 32.8% for severe bleeding).

The primary efficacy analysis should be interpreted in light of the following challenges in the study design: the exclusion of all mild bleedings from the analysis, only one application of FS at the study suture line, only ePTFE vascular grafts, heparinization and the administration of protamine for reversal of heparin after primary end point assessment, inclusion of perioperative administration of platelet inhibitors (common in high-risk settings for pre-

Table VIII. SSIs and graft occlusions in control patients

Reported term	*Relationship to treatment with control*	*SSI grade*[a]
SSIs		
Right lower extremity cellulitis along surgical site	Not related	II
Right surgical site groin infection	Not related	II
Surgical wound/incision infection in the right groin	Not related	I
Left upper arm graft infection due to MRSA sepsis	Not related	III
Cellulitis at right groin incision	Not related	I
Right groin cellulitis at incision site	Not related	I
Graft occlusions		
Thrombosed AV graft	Not related	
Thrombosis of AV graft	Not related	
Occluded right AV graft	Not related	
Graft thrombosis	Not related	
Occluded left femoropopliteal bypass graft	Not related	
Graft occlusion secondary to thrombosis	Not related	
Graft occlusion	Not related	
Graft occlusion	Not related	
Graft occlusion	Not related	

AV, Arteriovenous; *MRSA,* methicillin-resistant *Staphylococcus aureus*; *SSIs,* surgical site infections.
[a]Szilagyi DE, Smith RF, Elliott JP, Vrandecic MP. Infection in arterial reconstruction with synthetic grafts. Ann Surg 1972;176:321-33.

vention of bleeding-related complications[27,28]), and inclusion of various types of arterial bypasses. Recently released evidence-based guidelines and literature suggest that the practice of withdrawing platelet inhibitors 5 to 10 days before intermediate-risk to high-risk surgical procedures may increase thrombotic risk.[29-31] It is important to note that the hemostatic success rate at 4 minutes in the subset of patients on platelet inhibitors was approximately two times higher in the FS group than the control group, which is similar to the trend observed in patients not on platelet inhibitors and thereby confirms the effectiveness of FS independent of the patients' coagulation status.

In all, the significant difference observed for the primary end point and the statistically significant treatment effect demonstrate that FS is superior to manual compression for hemostasis in patients receiving peripheral vascular ePTFE grafts, including arterio-arterial bypasses and AV shunts.

In patients undergoing arterio-arterial bypass grafting, as well as AV shunting, generally, the aim is to create a graft that is durable, to have minimal risk of infection, and to require few interventions to maintain patency. The results of this phase 3 study validate the safety profile of FS in vascular surgery. None of the SAEs that occurred in this study was considered related to FS. The AEs most frequently reported in both treatment groups are expected in patients undergoing vascular surgery without the use of fibrin sealant.[32,33] Several factors may influence the rate of graft occlusions and infections, including patients' underlying disease and their progression, comorbidities, surgical technique, history of previous graft placement, graft materials used, anatomic features, antibiotic prophylaxis, and wound management.[23,34,35] The occurrence of graft occlusions and SSIs was similar between treatment groups and consistent with published literature, confirming that wound infections are a common cause of morbidity in open surgery for vascular disease.[36]

No evidence to support concerns relating to hypersensitivity/allergic reactions and suspected viral transmission as a result of FS use was found in this study or other published reports on fibrin sealants as hemostatic agents.[1,37-39]

Overall, there was no apparent frequency of certain types of AEs and no differences in the risk of experiencing AEs between treatment groups.

CONCLUSIONS

The findings from this study demonstrate that FS is safe and its efficacy is superior to manual compression for hemostasis in patients with peripheral vascular ePTFE grafts. The data also suggest that FS promotes hemostasis independently of the patient's own coagulation system, as shown in a representative population of patients with vascular disease under single- or dual-antiplatelet therapies.

AUTHOR CONTRIBUTIONS

Conception and design: BP, IP
Analysis and interpretation: SS, SM, WS, JD, AG, BP, IP, AG
Data collection: SS, SM, WS, JD
Writing the article: AG, BP, IP, AG
Critical revision of the article: SS, SM, WS, JD, AG, BP, IP, AG
Final approval of the article: SS, SM, WS, JD, AG, BP, IP, AG
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