A Polymeric Sealant Inhibits Anastomotic Suture Hole Bleeding More Rapidly Than Gelfoam/Thrombin

Results of a Randomized Controlled Trial

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Hypothesis: An experimental polymeric sealant (CoSeal [Cohesion Technologies, Palo Alto, Calif]) provides equivalent anastomotic sealing to Gelfoam (Upjohn, Kalamazoo, Mich)/thrombin during surgical placement of prosthetic vascular grafts.

Design: Randomized controlled trial.

Setting: Nine university-affiliated medical centers.

Patients: One hundred forty-eight patients scheduled for implantation of polytetrafluoroethylene grafts, mainly for infrainguinal revascularization procedures or the creation of dialysis access shunts, who were treated randomly with either an experimental intervention (n = 74) or control (n = 74).

Intervention: Following polytetrafluoroethylene graft placement, anastomotic suture hole bleeding was treated intraoperatively in all control subjects with Gelfoam/thrombin. Subjects in the experimental group had the polymeric sealant applied directly to the suture lines without concomitant manual compression.

Main Outcome Measures: Primary treatment success was defined as the proportion of subjects in each group that achieved complete anastomotic sealing within 10 minutes. The proportion of subjects that achieved immediate sealing and the time required to fully inhibit suture hole bleeding also were compared between treatment groups.

Results: Overall 10-minute sealing success was equivalent (86% vs 80%; P = .29) between experimental and control subjects, respectively. However, subjects treated with CoSeal achieved immediate anastomotic sealing at more than twice the rate of subjects treated with Gelfoam/thrombin (47% vs 20%; P < .001). Consequently, the median time needed to inhibit bleeding in control subjects was more than 10 times longer than for experimental subjects (16.5 seconds vs 189.0 seconds; P = .01). Strikingly similar findings for all comparisons were observed separately for subgroups of subjects having infrainguinal bypass grafting and for those undergoing placement of dialysis access shunts.

Conclusions: The experimental sealant offers equivalent anastomotic sealing performance compared with Gelfoam/thrombin, but it provides this desired effect in a significantly more rapid time frame.

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PATIENTS AND METHODS

PATIENTS

A multicenter randomized controlled trial was undertaken at 9 geographically dispersed US medical centers to determine the safety and effectiveness of a novel polymeric sealant compared with Gelfoam/thrombin for control of anastomotic suture hole bleeding during surgical placement of prosthetic vascular grafts. In all cases, PTFE grafts were implanted. This study was conducted under an investigational device exemption protocol approved by the Food and Drug Administration (Rockville, Md) with appropriate institutional review board approval at each clinical site. To qualify for inclusion, all male and nonpregnant female adult patients provided informed consent, supplied a medical history, and were scheduled for surgical placement of a PTFE vascular graft.

Fifty-five subjects (29 experimental, 26 control) with intermittent claudication underwent infrainguinal revascularization procedures to treat lower extremity ischemia almost exclusively via femoropopliteal PTFE bypass grafting. Eighty-seven subjects (43 experimental, 44 control) requiring long-term hemodialysis had arteriovenous PTFE grafts implanted to create an access shunt in the upper extremity either as a primary procedure where native vessels were deemed inadequate or as a secondary procedure in cases with unsalvageable autologous fistulae. Six subjects (2 experimental, 4 control) had PTFE patch grafting. Heparin was used in more than 90% of cases (137/148 [69 experimental, 68 control]), and approximately 50% of experimental subjects (n = 37) and controls (n = 38) had intraoperative heparin reversal with protamine.

RANDOMIZATION PROCEDURES

Treatment was assigned randomly to each subject on a 1:1 basis in blocks of 6 and randomization was stratified within each clinical site. Computer-generated randomization schedules of treatment group assignment placed in sealed envelopes were provided separately for each clinical site. The investigators and the sponsor were blinded to treatment assignment until the day of surgery, when a separate sealed envelope for each subject was opened once anastomotic bleeding was verified. All subjects remained blinded to treatment assignment throughout the course of this investigation.

Figure 1 shows the randomization procedure and patient throughput in addition to the specific reason(s) for excluding subjects from the analyses of sealing success. Approximately 97% of randomized patients (148/153) participated as study subjects, received treatment, and provided complete data with respect to the time required to achieve anastomotic sealing. Four of 5 patients who did not receive a study-related treatment had no evidence of bleeding along the suture line and in one patient, a decision was made intraoperatively not to implant a PTFE graft.

INTERVENTIONS

Polytetrafluoroethylene vascular prostheses were surgically implanted in accordance with the standard practice of the investigative team at each clinical site using methods detailed previously and a 1:1 needle-to-thread ratio was employed preferentially along the anastomotic suture line.9,13,16,32 Following the anastomosis procedure, each graft was unclamped and primed with blood to verify bleeding and to estimate the degree of leakage, classified as oozing or brisk. The graft was then re-clamped for 1 minute and the appropriate randomly assigned treatment was applied to the suture line. When blood flow was restored, each treated suture line site was monitored by a trained study coordinator and the time required to achieve complete sealing was recorded with a stopwatch. Because of the distinct physical characteristics of each sealing agent, the coordinators also could not be blinded intraoperatively to treatment assignment. Subjects were considered treatment failures if suture line bleeding could not be controlled within 10 minutes or if additional interventions were required to achieve sealing within the same time frame. Thirty-two subjects (12 experimental, 20 control) had 1 suture line site treated and 116 subjects (62 experimental, 54 control) had 2 sites treated. Thus, 264 sites among 148 study subjects were treated with either experimental or control sealing agents. All subjects

Continued on next page
followed up for 6 weeks postsurgically to assess study-related adverse events and clinical complications. All control subjects had suture hole bleeding managed with Gelfoam soaked in a bovine thrombin solution (1000 U/mL). Subjects assigned to the experimental treatment received a single 8-mL maximum application of CoSeal surgical sealant (Cohesion Technologies, Palo Alto, Calif). CoSeal is comprised of 2 distinct polyethylene glycol polymers that rapidly form a biocompatible and strongly adherent hydrogel when admixed with their respective reconstitution buffers near the time of surgery. The experimental material is applied directly to the site using a specially designed delivery system, forming a cohesive matrix within seconds and resorbing during several weeks. CoSeal firmly binds to the bleeding site and concomitant manual compression is not required to achieve anastomotic sealing.

OUTCOMES

The time required to inhibit suture hole bleeding was recorded for all treated subjects. The primary end point, sealing success, was defined a priori as the cumulative rate for each treatment group to achieve complete anastomotic suture line sealing within 10 minutes of observation. This study was designed as an equivalency trial and the overall sample size provided adequate statistical power (1-β = .80) to detect a 20-percentage point difference between treatment groups, assuming both groups exhibited complete sealing rates of 70% (α = .05, 1-tailed). We also determined the proportion of subjects in each study group that achieved immediate sealing on restoration of blood flow and the overall time required to achieve sealing. Most analyses were repeated for subgroups of subjects having infrapopliteal revascularization bypass procedures or placement of dialysis access shunts separately. Treatment groups also were evaluated for sealing success based on whether the initial suture hole blood leakage was classified as oozing or brisk. Lastly, we estimated the total operating room time for all subjects, irrespective of treatment group, who exhibited immediate anastomotic sealing and compared this value with the operating time required for all cases in which any suture hole bleeding occurred on reestablishment of blood flow.

Between treatment groups (P = .51). A slightly higher proportion of controls (66/74 [89%]) were hypertensive compared with experimental subjects (38/74 [78%]) (P = .08), and diabetes was reported with exactly the same frequency in both treatment groups (39/74 [53%]; P > .99). Very similar proportions of subjects in the experimental (26/74 [35%]) and control (27/74 [36%]) (P = .86) groups also experienced a previous thromboembolic event.

The proportion of subjects achieving complete anastomotic suture hole sealing within the 10-minute period of observation (ie, treatment success) is presented in Table 1 for the entire sample of subjects as well as separately for subjects having infrapopliteal revascularization bypass procedures and for subjects undergoing implantation of prosthetic dialysis access shunts. Overall sealing success was equivalent (86% vs 80%; P = .29) between experimental and control subjects, respectively. Comparative 10-minute sealing success rates also were similar but slightly more pronounced in favor of treatment with CoSeal among separate subgroups of subjects, eg, bypass (79% vs 73%; P = .62) and dialysis (93% vs 84%; P = .14) (Table 1).

Table 1 also presents the proportion of subjects who achieved immediate sealing. Overall, subjects treated with CoSeal achieved immediate sealing at more than twice the rate of subjects treated with Gelfoam/thrombin (47% vs 20%; P < .001). This robust treatment effect also was realized among bypass (45% vs 12%; P = .003) and dialysis (51% vs 23%; P = .002) subjects, separately.

The marked difference between treatment groups in immediate sealing rates contributed, in part, to a substantially reduced overall time required to inhibit suture hole bleeding (Table 2). For example, the median time to complete sealing in subjects treated with Gelfoam/thrombin was more than 10 times longer than in experimental subjects (16.5 seconds for the CoSeal group vs 30.1 seconds for the control group).
Table 1. Anastomotic Sealing Success*

<table>
<thead>
<tr>
<th></th>
<th>CoSeal†</th>
<th>Control</th>
<th>P†</th>
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<tbody>
<tr>
<td>10-Minute sealing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>64/74 (86)</td>
<td>59/74 (80)</td>
<td>.29</td>
</tr>
<tr>
<td>Infrainguinal bypass graft</td>
<td>23/29 (79)</td>
<td>19/26 (73)</td>
<td>.62</td>
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<tr>
<td>Dialysis access shunt</td>
<td>40/43 (93)</td>
<td>37/44 (84)</td>
<td>.14</td>
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<tr>
<td>Immediate sealing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>35/74 (47)</td>
<td>15/74 (20)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Infrainguinal bypass graft</td>
<td>13/29 (45)</td>
<td>3/26 (12)</td>
<td>.003</td>
</tr>
<tr>
<td>Dialysis access shunt</td>
<td>22/43 (51)</td>
<td>10/44 (23)</td>
<td>.002</td>
</tr>
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*Data are given as number (percentage) unless otherwise indicated. †CoSeal is manufactured by Cohesion Technologies, Palo Alto, Calif. ‡Significance levels computed with the Cochran-Mantel-Haenszel χ² test for sealing success rates.

189.0 seconds for the control group; P = .01). Differences in the median time to complete sealing in favor of treatment with CoSeal also were detected among separate subgroups of subjects; however, lack of adequate sample size among the bypass group did not provide sufficient power to achieve statistical significance (Table 2). Inspection of Table 2 and Figure 2 further illustrates the enhanced speed of anastomotic sealing offered by the experimental intervention. Within 3 minutes, more than 70% of experimental subjects had achieved complete inhibition of suture hole bleeding. In contrast, less than one half of control subjects had sealing by 3 minutes. Comparison of categorized sealing times strongly favored treatment with CoSeal (P = .009) (Table 2). Figures 3 and 4 show cumulative sealing success for bypass and dialysis subjects separately, reflecting similar findings to the overall study group. Likewise, comparison of categorized sealing times favored treatment with CoSeal for both bypass (P = .04) and dialysis (P = .08) subjects (data not provided).

There was a very similar proportion of sites classified as experiencing oozing (97/136 [71%] vs 94/128 [73%]) and brisk (39/136 [29%] vs 34/128 [27%]) bleeding on pretreatment graft priming for experimental and control subjects, respectively. The 10-minute sealing success rates among sites with oozing bleeding was noticeably higher than among sites with brisk bleeding irrespective of treatment group, eg, CoSeal (oozing: 91%, brisk: 74%), control (oozing: 88%, brisk: 74%). Differences between treatment groups in 10-minute sealing success were not significantly different among sites classified as having oozing (P = .47) or brisk (P = .58) bleeding. However, a noteworthy improvement in the immediate sealing rate was accomplished for experimental subjects compared with controls when sites were classified as having either oozing (48/97 [50%] vs 24/94 [26%]; P < .001) or brisk (16/39 [41%] vs 1/34 [3%]; P < .001) bleeding.

Twenty-nine subjects (21 CoSeal, 8 control) exhibited immediate suture hole sealing at any and all sites. The remaining subjects (n = 119) bled at 1 or both sites. The mean operative time among subjects with uniform immediate sealing was approximately 30 minutes less than for subjects with some bleeding along the suture line irrespective of treatment type (1.9 ± 1.0 hours vs 2.4 ± 1.4 hours) and this difference was statistically significant (P = .03).
Two control subjects died during the 6-week post-surgical follow-up period but these events were judged to be definitely not related to the treatment material. There were no adverse events related to the experimental sealing agent in this study.

The findings of this randomized controlled trial demonstrate that CoSeal surgical sealant provides equivalent inhibition of anastomotic suture hole bleeding compared with an active control intervention (Gelfoam/thrombin) after 10 minutes of intraoperative observation. These results are particularly encouraging because of the well-recognized propensity of PTFE vascular grafts to bleed at the anastomoses following reestablishment of circulation. Indeed, of the 153 randomized patients in this study, only 4 cases (3%) failed to demonstrate anastomotic bleeding when primed pre-treatment.

The 10-minute primary efficacy end point of this study, although somewhat arbitrary, was selected as a safety trigger to initiate alternative treatment if either study intervention failed to provide adequate suture hole sealing. However, it is questionable whether this end point has any clinical relevance or correlate. More impressive was the marked differences observed between treatment groups in the rate of immediate sealing and, commensurately, in the overall time required to inhibit bleeding. Clearly, treatment with CoSeal demonstrated a consistently and significantly more rapid sealing effect than Gelfoam/thrombin overall and within separate subgroups of subjects. Although this study was not designed to evaluate the clinical relevance or cost reduction associated with immediate sealing, we estimate that approximately 30 minutes of operative time can be saved if no additional treatment is required when circulation is restored. This time savings equates to about one quarter of the duration necessary to complete the entire operative intervention.

The experimental sealant evaluated in this study differs fundamentally from the control treatment and other commonly used interventions because it does not exhibit its effect via traditional hemostatic mechanisms to induce clot formation. This explains, in large part, the differences observed between treatment groups in the immediate and early sealing rates. On application, CoSeal forms a cohesive anastomotic seal within seconds that adheres strongly to the applied tissue site, effectively providing a mechanical barrier to blood flow without the need to induce coagulation. This contrasts with fibrin sealant, for example, which has been reported to have rather poor adhesive qualities when applied to prosthetic grafts. Even when sealing is not immediate with CoSeal, residual suture hole bleeding is generally so minor and intermittent that complete inhibition occurs rapidly. Hence, greater than 70% of the experimental subjects exhibited complete sealing within 3 minutes of application (Table 2, Figure 2). Importantly, unlike other polymeric agents, CoSeal does not produce an adverse tissue response and resorbs fully during several weeks.

We employed conservative methods in evaluating the results of this trial by having each subject contribute a single datum in each of the primary statistical analyses; ie, the patient was the sampling unit. For subjects that had 2 anastomotic sites treated, we randomly selected 1 of the sites for inclusion. Thus, 148 subjects contributed 148 outcomes. This approach is preferred because statistical methods that are based on common probability distributions assume independent observations. Additionally, including all sites (n=264) in the primary analyses would have falsely inflated the sample size, thereby increasing the possibility of detecting a significant difference between treatments where one might not exist. We did reexamine our findings using all treated sites, the first and second treated site separately, as outcomes and found strikingly similar results to those reported herein using randomly selected sites.

The participating surgeons in this study could not be blinded intraoperatively to treatment assignment because of the distinct nature of each material, thereby allowing for possible bias of results. However, the sealing effectiveness of the experimental treatment, especially with respect to immediate sealing, was observed consistently across all 9 clinical centers. In addition, the duration of bleeding was monitored and recorded by an independent study coordinator. While not blinded to treatment assignment, this coordinator provided an extra level of verification to the data collection process and likely reduced any potential investigator bias. Finally, this trial...
used an independent data management firm and all source data obtained from case report forms, data verification, cleanup efforts, and statistical analyses were subject to Food and Drug Administration inspection and audit. Consequently, any bias that may have entered the study or data analysis process was sufficiently small and most likely could not account for the consistent results obtained with CoSeal.

In summary, the experimental sealant evaluated in this randomized controlled trial offers equivalent anastomotic leakage performance compared with Gelfoam/thrombin, but it provides this desired effect in a significantly more rapid time frame. These results are encouraging considering that anastomotic leakage with PTFE vascular grafts is ubiquitous and often times brisk. We advocate the use of this novel polymeric sealant for treating suture lines among patients undergoing PTFE vascular grafting, including infranigual revascularization procedures and placement of hemodialysis access shunts.

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REFERENCES