

Repair of Chronic Anorectal Fistulae Using Commercial Fibrin Sealant

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Hypothesis: Commercially produced fibrin sealant can be used to completely close both simple and complex fistulae in ano.

Methods: A 29-patient prospective nonrandomized clinical trial was performed. In the operating room, the patient underwent an examination with anesthesia and the primary and secondary fistula tract openings were attempted to be identified. The fistula tract was curetted and fibrin sealant was injected into the secondary fistula tract opening until fibrin sealant was seen coming from the primary opening. A petroleum jelly gauze was then applied over the secondary opening and the patient was sent home. Follow-up visits were scheduled for 1 week, 1 month, 3 months, and 1 year later.

Results: Twenty-nine consecutive patients received fibrin sealant injections for their fistulae in ano, with a mean follow-up of 6 months. Two patients had a history of Crohn disease (regional enteritis) and 2 patients had human immunodeficiency virus infection. Overall, 17 (68%)

of 25 patients have had successful closure of their fistula with 4 patients lost to follow-up. Two patients required reinjection with fibrin sealant, and neither of these subsequently had closure. One of the 2 patients with Crohn disease had closure, as well as 1 human immunodeficiency virus-positive patient. In addition, there has been no evidence of incontinence or complications related to the use of fibrin sealant in this procedure.

Conclusions: Initial results in the treatment of chronic anorectal fistulae using commercial fibrin sealant are optimistic, but require further support through longer follow-up data. Fibrin sealant treatment of anorectal fistulae offers a unique mode of management which is safe, simple, and easy for the surgeon to perform. By using fibrin sealant, the patient avoids the risk of fecal incontinence and the discomfort of prolonged wound healing that may be associated with fistulotomy.

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COMPLICATIONS from the repair of fistulae in ano can be devastating. While it is common practice to treat individuals with intersphincteric or low transsphincteric fistulae with fistulotomy, fecal incontinence in these patients has been reported.¹ Even more common, but often underreported, is permanent gas incontinence, which for many individuals is a source of great anxiety and embarrassment in social situations.²

Fistulotomy of high transsphincteric, suprasphincteric, or extrasphincteric fistulae is associated with high rates of incontinence and in most institutions, including our own, fistulotomy for these fistula types is contraindicated. Relative contraindications for fistulotomy include Crohn disease (regional enteritis)-related fistulae, anterior midline fistulae in female patients, previous fistulotomies, and poor sphincter tone in elderly patients.²

Over the years, many different methods for treating fistulae in ano, particularly fistulae in which fistulotomy is contraindicated, have been reported. Staged fistulotomy using a seton, mucosal advancement flaps, and island flap anoplasty have all been described.³⁻⁵ While these surgical modalities minimize incontinence compared with standard fistulotomy, their lower rates of efficacy, prolonged postoperative wound healing, and protracted pain have been problematic.

Over the past 2 years, our institution began repairing all types of anorectal fistulae using autologous fibrin tissue adhesive. In one study, 26 patients with fistulae in ano were treated using autologous fibrin tissue adhesive that used a combination of ethanol and freezing to precipitate fibrinogen (AFTA-E).⁶ Twenty-one (81%) of the 26 patients had success-

PATIENTS, MATERIALS, AND METHODS

Twenty-nine consecutive patients participated in our prospective nonrandomized clinical trial. These patients were selected from Cook County Hospital, The University of Illinois Hospital and Clinics, and the Westside Veterans Hospital, all located in Chicago. To maximize patient safety and comfort, our study was performed in the operating room with spinal anesthesia where appropriate evaluation of each patient's fistula could be performed. Patients did not receive preoperative mechanical bowel preparations or antibiotics, and patients were discharged home postoperatively on a general diet.

PARTICIPANTS

Twenty-nine consenting patients with fistulae in ano were offered treatment with fibrin sealant. Patients with human immunodeficiency virus (HIV) infection, Crohn disease, complex recurrent fistulae, and rectovaginal fistulae were also included in our study.

DATA

Participants completed multiple questionnaires. The first questionnaire was given at the time of initial presentation. Questions included age, medical history (including whether the patient had a history of Crohn disease or HIV infection), the duration of the fistula, and whether the fistula was a recurrence. The second questionnaire was given at each follow-up visit. Questions included whether they had perirectal drainage, pain, or evidence of failed fistula closure. Physical examinations were also conducted with each subsequent clinic visit and included inspection of the wound for closure and the presence of drainage. Follow-up clinic visits occurred 1 week, 1 month, 3 months, and 1 year after the operation. Patients were instructed to notify their physician if they suspected a recurrence anytime during their postoperative course.

MATERIALS

Multiple commercial fibrin sealant preparations were available. For our study, ViGuard-F.S. was used because of availability. ViGuard-F.S. (Vitex Pharmaceuticals, New York, NY) is made from 2 virally inactivated components that are mixed in equal amounts at the time of gluing. Component 1 is purified fibrinogen (65 mg fibrinogen/mL H₂O) and component 2 is human thrombin (25 US U/mL H₂O). Fibrinogen is prepared from pooled human plasma essentially by Cohn fractionation of plasma and subsequently virally inactivated. Details of the viral inactivation procedures and viral kill results with various lipid and nonlipid enveloped viruses have been reported elsewhere.^{9,10} Thrombin was also prepared from pooled blood and subjected to similar viral elimination steps.

APPLICATION

Our study was performed in the operating room. Spinal anesthesia was given and the patient was placed in the prone jackknife position. The primary and secondary fistula tract openings were identified. The fistula tract was then thoroughly cleaned using a blunt curette or gauze strip that was threaded through the tract. Components 1 and 2 were then siphoned into 2 tuberculin syringes and connected to a dual-chamber applicator and tip (Micromedic Applicator Tip; Micromedic Inc, Eagan, Minn). The 2 components were then injected simultaneously into the secondary fistula tract opening until fibrin sealant was seen coming from the primary tract opening. A petroleum jelly gauze dressing was then applied over the secondary fistula opening and the patient was sent home. Follow-up visits occurred 1 week, 1 month, 3 months, and 1 year later.

If an abscess was identified during the examination, the fibrin tissue adhesive was discarded, and a seton was placed to drain the abscess. The patient was then brought back to the operating room after the abscess was drained. At that time, the seton was removed, the tract was cleaned using a curette, and newly made fibrin tissue adhesive was injected. Follow-up visits also occurred 1 week, 1 month, 3 months, and 1 year later.

ful closure of their fistula after a 4-month follow-up. Two of the 5 failures were reinjected a second time and 1 closed, giving an overall successful closure rate of 85% (22 of 26 patients). Of the 5 patients with closure failure, the mean time to failure was 3.8 weeks. In addition, there was no evidence of infection or complications related to the procedure.

In 1998, commercially produced fibrin sealants became available for use in the United States. Fibrin sealants differ from autologous preparations in many ways. First, the bonding power of fibrin sealant is stronger and more consistent than "home-brewed" autologous mixtures, since the fibrinogen concentration is greater and standardized.⁷⁻¹¹ Second, commercial sealants can be prepared prior to surgery within minutes, whereas the average preparation time for an autologous fibrin tissue adhesive is 90 minutes. We surmised that because fibrin sealants bond stronger and more consistently than autologous preparations, the use of fibrin

sealant to repair fistulae in ano should be as effective, if not greater, than fistulae repair using autologous fibrin tissue adhesive. Therefore, our goal was to determine if commercially produced fibrin sealant could also be used to completely close both simple and complex fistulae in ano.

RESULTS

Twenty-nine individuals (17 men) participated in our study. The average age of our patients was 41.5 years (SD, 12.9 years). Patients waited an average of 48 months before seeking medical attention for their draining fistula. Patient fistula types are listed in **Table 1**. Follow-up ranged from 4 to 8 months, with a mean of 6 months. To date, 4 patients have been lost to follow-up. Data collection is ongoing.

Our results are listed in **Table 2**. Our initial success rate was 68% (17/25). Four patients were lost to fol-

Table 1. Incidence of Fistula Types and Success Rates With Fibrin Sealant

Fistula Type	No. (%)	
	Incidence	Success Rate per Fistula Type
Transsphincteric	15/29 (52)	12/15* (80)
Intersphincteric	4/29 (14)	3/4 (75)
Extrasphincteric	3/29 (10)	2/3 (67)
Rectovaginal	3/29 (10)	1/3 (33)
Crohn related	2/29 (7)	1/2 (50)
HIV† related	2/29 (7)	1/2* (50)

*Including patients lost to follow-up.
 †HIV indicates human immunodeficiency virus.

Table 2. Summary of Patient, Fistula, and Operative Data

Patient No./ Sex/Age, y	Fistula Duration, mo	Previous Operations	Fistula Type	Results
1*/M/54	3	No	Transsphincteric	Healed
2/F/42	3	No	Transsphincteric	Failed
3*/F/49	36	No	Transsphincteric	Healed
4/M/32	7	No	Transsphincteric	Healed
5/M/33	168	No	Transsphincteric	Healed
6/M/41	4	No	HIV† related	Healed
7/F/34	24	No	Rectovaginal	Failed
8/M/79	24	No	Extrasphincteric	Failed
9/F/38	24	Yes	Crohn related	Failed
10/M/36	4	No	Transsphincteric	Healed
11/F/46	3	No	Intersphincteric	Healed
12/F/26	5	Yes	Rectovaginal	Failed
13/M/31	4	No	Intersphincteric	Failed
14/F/26	36	No	Rectovaginal	Healed
15/M/31	36	No	Transsphincteric	Healed
16/M/72	7	No	Extrasphincteric	Healed
17/M/69	7	No	Extrasphincteric	Healed
18/M/37	3	No	Crohn related	Healed
19/M/44	144	No	Intersphincteric	Healed
20/F/44	96	Yes	Transsphincteric	Failed
21/M/48	36	Yes	Transsphincteric	Healed
22/F/33	12	No	Intersphincteric	Healed
23/F/33	84	No	Transsphincteric	Healed
24/M/41	10	No	Transsphincteric	Healed
25/M/42	10	No	Transsphincteric	Failed
26/F/50	48	Yes	Transsphincteric	Healed
27/M/30	3	No	Transsphincteric	Healed
28*/F/32	192	No	HIV related	Failed
29*/M/38	360	Yes	Transsphincteric	Healed

*Lost to follow-up.
 †HIV indicates human immunodeficiency virus.

low-up, but not prior to them being examined postoperatively (Table 2). Of the 8 patients in whom fibrin sealant injection failed, 1 had Crohn disease, 1 had HIV infection, 1 had an extrasphincteric fistula from an anastomotic leak originating from a low-anterior resection anastomosis, 2 had rectovaginal fistulae, and 3 had transsphincteric fistulae.

Success rates per fistula type are shown in Table 1. Transsphincteric and intersphincteric fistulae had greater than 70% closure rates with fibrin glue injection, whereas fibrin glue repair of Crohn-related, HIV-related, and rec-

tovaginal fistulae was ineffective. Average time before fistula recurrence (failure) was 2.63 months (SD, 1.06 months). However, 2 of 8 patients experienced recurrence immediately.

Six of 29 patients had had previous surgical attempts at fistula closure. The success rate for patients with previous operations was 50% (3/6), whereas the success rate for patients with no previous operations was 74% (14/19).

COMMENT

In 1978 the Food and Drug Administration restricted commercial fibrin sealant use in the United States for fear of viral transmission with HIV, hepatitis B, or hepatitis C, since all commercial sealants use pooled blood. Since that time, viral elimination protocols have been implemented that have practically eliminated the risk of viral contamination. In 1998, the Food and Drug Administration relicensed fibrin sealant for limited operative indications.

When our institution initially began using autologous fibrin tissue adhesive to treat anorectal fistulae, manufacturing AFTA-E was time-consuming, inconvenient, and required experienced technicians. These factors limited the use of AFTA-E to only elective procedures. With the availability of commercial fibrin sealants, treating fistulae in ano with fibrin glue became more convenient. However, efficacy still needed to be determined.

Fibrin glue in the treatment of fistulae in ano has been previously explored. Abel et al¹² used cryoprecipitate-based autologous fibrin tissue adhesive (AFTA-C) to treat rectovaginal and complex fistulae in 10 patients and reported an overall success rate of 60%. Hjortrup et al¹³ from Denmark reported the use of a commercial fibrin sealant (Beriplast; Behringwerke, Marburg, Germany) in the treatment of 15 patients with persistent perineal sinus after proctectomy and 8 patients with abscess fistulae. They reported an overall closure rate of 74% (17/23); however, 5 patients (22%) required 2 or 3 attempts at sealant closure. Results of our original study,⁶ which used ethanol-based autologous fibrin tissue adhesive (AFTA-E), and our present study are similar to those of previous reported studies. Our surgical protocol differs, however, from other studies in that we do not treat our patients preoperatively with bowel preparations or antibiotics, and our patients are not hospitalized and are sent home postoperatively on a general diet. One consistent finding among all studies was the poor results found in patients with Crohn disease, rectovaginal, and HIV-related fistulae.

A criticism of our study, and of those that have been performed at other institutions, is that the treatment arm was not randomized against a control group nor was a long-term follow-up performed. Therefore, further investigation is still indicated.

In conclusion, use of fibrin sealant to treat chronic fistulae in ano is safe and provides an effective alternative or adjunctive therapy for complex anorectal disease.

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Factors Correlated With Progression-Free Survival After High-Dose Chemotherapy and Hematopoietic Stem Cell Transplantation for Metastatic Breast Cancer

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Context: Women with breast cancer are the most frequent recipients of high-dose chemotherapy followed by autologous hematopoietic stem cell transplantation (autotransplants) in North America. Despite widespread use, controversy exists about the benefits of and appropriate patients for this therapy.

Objective: To determine factors associated with disease progression or death after autotransplantation in women with metastatic breast cancer.

Design: Analysis of data collected retrospectively (January 1989 to 1992) and prospectively (1992 through January 1995) for the Autologous Blood and Marrow Transplant Registry.

Setting: Sixty-three hospitals in North America, Brazil, and Russia.

Participants: A total of 1188 consecutive women aged 18 to 70 years receiving autotransplants for metastatic or locally recurrent breast cancer, with a median follow-up of 29½ months.

Main Outcome Measure: Time to treatment failure (disease progression, disease recurrence, or death) after autotransplantation.

Results: Factors associated with significantly ($P < .05$) increased risk of treatment failure in a Cox multivariate analysis included age older than 45 years (relative hazard, 1.17; 95% confidence interval [CI], 1.02-1.33), Karnofsky performance score less than 90% (1.27; 95% CI, 1.07-1.51), absence of hormone receptors (1.31; 95% CI, 1.15-1.51), prior use of adjuvant chemotherapy (1.31; 95% CI, 1.10-1.56), initial disease-free survival interval after adjuvant treatment of no more than 18 months (1.99; 95% CI, 1.62-2.43), metastases in the liver (1.47; 95% CI, 1.20-1.80) or central nervous system (1.56; 95% CI, 0.99-2.46 [approaches significance]) vs soft tissue, bone, or lung, 3 or more sites of metastatic disease (1.32; 95% CI, 1.13-1.54), and incomplete response vs complete response to standard-dose chemotherapy (1.65; 95% CI, 1.36-1.99). Receiving tamoxifen posttransplantation was associated with a reduced risk of treatment failure in women with hormone receptor-positive tumors (relative hazard, 0.60; 95% CI, 0.47-0.87). Women with no risk factors ($n = 38$) had a 3-year probability of progression-free survival of 43% (95% CI, 27%-61%) vs 4% (95% CI, 2%-8%) for women with more than 3 risk factors ($n = 343$).

Conclusion: These data indicate that some women are unlikely to benefit from autotransplantation and should receive this treatment only after being provided with prognostic information and in the context of clinical trials attempting to improve outcome. (1999;282:1335-1343) www.jama.com

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