Fibrin Sealant

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Introduction

The management of fistula-in-ano remains a difficult and frustrating problem for surgeons and patients alike. Although fistulotomy is the gold standard to which other therapies must be compared, preservation of continence is also an important goal of any operation for fistula-in-ano. Extensive laying open of anorectal fistulas places the patient at varying risks of incontinence, as documented in a number of studies [1–6]. Additionally, a layopen fistulotomy leaves the patient with an open wound to care for which, in addition to pain, can be a process that takes weeks or even months to fully heal. For these reasons surgeons have searched for alternative methods of treating fistula-in-ano. Setons (cutting or loose), staged division of the sphincters, endorectal advancement flaps, dermal advancement flaps, and ligation of the intersphincteric fistula tract (LIFT procedure) have all been used as alternatives to primary fistulotomy with variable success rates; however, each of these procedures carries risks of pain, wound healing complications, and incontinence [7–18]. The ideal objectives in the treatment of a fistula would effectively heal the fistula with minimal pain, preserve sphincter function, and at the same time provide an early return to activities of daily living. These objectives led to less invasive approaches, specifically fibrin glue in the management of anorectal fistulae.

Biology and Scientific Rationale

Fibrin glue (also referred to as fibrin tissue adhesive and fibrin sealant and used interchangeably in this chapter) is a tissue adhesive that simulates the terminal steps of the natural clotting cascade (Fig. 11.1). Part of the scientific rationale for the success of fibrin glue is not just its ability to provide air and fluid tightness through the polymerization of fibrinogen within the fistula tract, but also its ability to provide a scaffold into which fibroblasts can infiltrate. Furthermore, Factor XIII, which is present and essential for fibrin cross-linking to occur, has been shown to have a physiological role by stimulating fibroblast proliferation. Other components, such as fibronectin, thrombin, glycoproteins, and fibrinogen itself, also play a role in or contribute to fibroblast migration, attachment, re-epithelialization, and neovascularization [19, 20].

During the provisional matrix that forms in the wound during early healing, fibrin becomes coated with vitronectin from the serum and fibronectin derived from both serum and aggregating platelets. Fibronectins are a class of glycoproteins that facilitate the attachment of migrating fibroblasts as well as other cell types to the fibrin lattice. Because of its influence on cellular attachment, fibronectin is a key modulator of the migration of various cell types in the wound. Additionally, the fibrin-fibronectin lattice binds various cytokines released at the time of injury and serves as a reservoir for these factors in the later stages of healing [19, 20]. The theory behind the treatment of fistulae with fibrin sealant is twofold. First, occlusion of the fistula tract with sealant immediately halts the ongoing contamination of the tract with stool, mucus, blood, and pus. Second, the proteins contained within the sealant stimulate native tissue in-growth and provide biologic scaffolding for the wound-healing process. The sealant is degraded as the fibrotic reaction progresses, and ultimately the sealant is entirely replaced by native tissues. Thus, no foreign body persists and the tract simply scars closed [21]. Fibrin gluing of anal fistulas is simple and repeatable. These factors make it a highly desirable treatment option. The use of fibrin sealant has grown in popularity over the last one and a half decades, although its appeal may be waning because of the variable results published over time.

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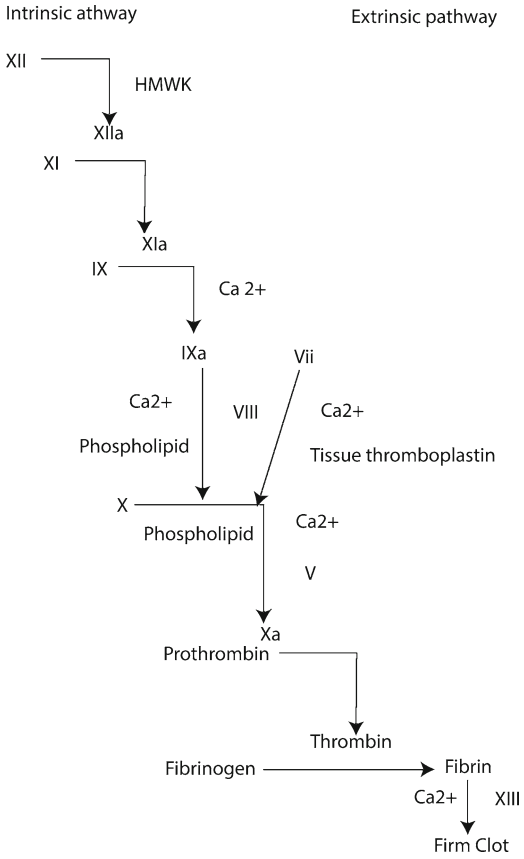

Fig. 11.1 Schematic of classic coagulation cascade

History

Fibrin tissue adhesive was first used successfully as a hemostatic agent in the early 1900s [19]. The efficacy of fibrin sealant was markedly improved through the addition of bovine thrombin to fibrinogen in 1944 [22]. Commercial plasma fractionation methods in the 1970s generated highly concentrated fibrinogen preparations that were made available in Europe in the late 1970s. Unfortunately, pooled fibrinogen concentrates were associated with an increased risk of viral transmission, especially hepatitis B and hepatitis C and later HIV. This led to license revocation in the United States by the Food and Drug Administration in 1978. Two decades later in 1998, the Food and Drug Administration relicensed the commercial preparation of fibrin sealant.

In the United States prior to 1998 fibrinogen was obtained primarily through autologous donation and "home-made" preparations. Implementation of viral inactivation procedures has made the use of commercial sealants quite safe and popular now and the preferred source of fibrin due to its ease of use and quick preparation, as evidenced by abundant clinical literature from throughout the world.

Autologous Fibrin Glue

The use of an autologous source to prepare fibrin glue minimizes the risk of disease transmission and provides a safe and simple method to treat anorectal fistulas. Abel et al. [23] published their results on the use of autologous fibrin glue in the treatment of rectovaginal and complex fistulas in ten patients and reported an overall success rate of 60 %. The authors combined autologous fibrinogen in cryoprecipitate (AFTA-C) with reconstituted bovine thrombin, thereby reproducing the final stage of the coagulation cascade. This process was reported to recover approximately 20–40 % of the fibrinogen in a unit of plasma that in total yielded approximately 10–35 mg/mL of fibrinogen concentrate. The fibrinogen concentrate is then combined with reconstituted thrombin (1,000 U/mL). Unfortunately, the process of autologous fibrinogen preparation through cryoprecipitation (AFTA-C) in the study by Abel et al. [23] took greater than 24 h to manufacture and required donation of a unit of blood. In addition, patients in the study by Abel et al. [23] underwent outpatient bowel preparation, received preoperative parenteral antibiotics, and stayed in the hospital taking nothing by mouth for 2 days postoperatively.

Autologous fibrin tissue adhesive made from a patient's own blood and based on ammonium sulfate precipitation (AFTA-A) is another method of producing autologous fibrin tissue adhesive. This tissue adhesive is biodegradable, is without side effects, and minimizes the risk of viral transmission. However, the bonding power of AFTA-A is significantly less than commercially produced fibrin tissue adhesives, hence limiting its effectiveness in cases where bonding power is essential such as in anorectal fistulas.

Another alternative method of producing autologous fibrin tissue adhesive uses a combination of ethanol and freezing to precipitate fibrinogen (AFTA-E). This method produces a biodegradable, autologous, and superior bonding power product than AFTA-A. AFTA-E is a third-generation autologous fibrin tissue adhesive developed after the first-generation (AFTA-C) and second-generation (AFTA-A) adhesives. The technical aspects of preparation of AFTA-E have been reported elsewhere [24]. Component one of AFTA-E is manufactured from 100 mL of a patient's blood. The fibrinogen is obtained via ethanol precipitation. Component two of the adhesive is prepared by combining a calcium chloride solution with thrombin and aminocaproic acid. The final thrombin concentration is 450 U/mL and the total preparation time for ATFA-E is 60 min. The results reported by Cintron et al. [25] using autologous fibrin glue parallel those of prior generation tissue adhesives [23]; however, several important differences should be pointed out. The use of a third-generation autologous fibrin tissue adhesive (AFTA-E) allows the manufacture of fibrin sealant within 1 h

of a scheduled operation in contrast to 24 h. In addition, the fibrinolytic inhibitor, aminocaproic acid, keeps AFTA-E present in vivo for over 40 days at the reported concentration [26]. Furthermore, a sufficient quantity of fibrinogen (3–4 mL) is precipitated from 100 mL of blood, which when combined with an equal volume of bovine thrombin adequately fills the fistula tracts. Thus, large blood donations are avoided. All procedures were done on an ambulatory basis, and bowel preparation, parenteral antibiotics, and fistula tract decontamination were not performed unlike the studies by Abel et al. [23] and Hjortrup et al. [27], respectively.

Commercial Fibrin Sealant

By the 1970s, highly concentrated fibrinogen became widely available, as did Factor XIII and aprotinin, which served to stabilize the fibrin clot. In 1978, however, the United States Food and Drug Administration (FDA) prohibited the use of fibrinogen concentrates derived from pooled donors because of the risk of viral transmission of hepatitis (and later HIV). As a result, surgeons in the United States were left to use single-donor fibrinogen products and bovine aprotinin. By 1998, donor screening, reliable testing methods, and viral deactivation techniques made pooled fibrinogen products safe again. The FDA subsequently approved the use of commercially produced products for patients. Since that time, the use of fibrin sealant has been described for nearly every organ system. The combination of the two components of fibrin sealant reproduces the final stage of the native clotting cascade. The two essential components are fibrinogen and thrombin. The thrombin converts the fibrinogen into active fibrin. One of the commercial products most widely used is Tisseel® VH fibrin sealant (Baxter Healthcare, Deerfield, IL). The sealant is available as a two-component system. One component contains a solution of fibrinogen, Factor XIII, and bovine aprotinin. The second contains thrombin and calcium, which acts as a cofactor. The two components are maintained in separate syringes until a specially designed dual syringe applicator (Duploject®, Baxter Healthcare) (Fig. 11.2) delivers the products to the surgical site. The two components remain separated until they are mixed at the tip of the applicator device. The fibrin clot begins to organize within seconds of the two components mixing. As with autologous fibrin glue the fibrin matrix contained within the clot also serves as scaffolding for tissue in-growth into the healing wound. The fibrin as well as the fibronectin and glycoproteins that migrate into the clot stimulate activate fibroblasts, collagen deposition, re-epithelialization, and neovascularization of the wound. In this way the sealant facilitates the wound healing process. The body's native plasminogen system will destabilize the clot, and within 2 weeks, the entire synthetic clot is destabilized and replaced by host tissues [19, 20].

Fig. 11.2 Duploject® catheter system

Fibrin Sealant as a Carrier or Delivery Vehicle

Fibrin sealant has also been utilized to deliver cytokines, biomaterials, and most recently stem cells to the site of anal fistulas [28–30]. Singer et al. [29] reported on the use of fibrin sealant as a delivery vehicle for transforming growth factor beta (TGF-β) in an acute and chronic wound model in rats. Transforming growth factor is known to stimulate the inflammatory cascade and the wound healing process. They concluded that although fibrin sealant was an adequate delivery vehicle for TGF-β, unfortunately, it did not result in any significant changes in the healing of acute or chronic wounds in rats. Hammond et al. [28] assessed the safety, feasibility, and efficacy of cross-linked collagen in two different formats to heal anal fistulae. At operation patients were randomized to receive a solid collagen implant vs. collagen fibers suspended in fibrin glue. At the end of 29 months 80 % of the patients who underwent collagen-fibrin glue treatment were healed compared to 54 % who received the collagen implant alone. Garcia-Olmo and colleagues [31] reported on a randomized controlled multicenter Phase II study looking at fibrin glue vs. fibrin glue with adipose-derived stem cells in the treatment of 49 patients with complex perianal fistulas. After a 1-year follow-up there was a 16 % success rate in patients receiving fibrin glue alone compared to 71 % for patients who received fibrin glue in combination with adipose-derived stem cells. Herreros et al. [30] subsequently reported their results from a multicenter, randomized, single blind phase III trial utilizing autologous-expanded adipose-derived stem cells for the treatment of complex cryptoglandular perianal fistulas. Patients underwent surgical closure of the internal opening and then were randomized to receive either stem cells alone, stem cells with fibrin glue, or fibrin glue alone. The authors concluded that healing rates of

approximately 40 % at 6 months were equivalent to fibrin glue alone and that when the three groups were compared no statistically significant differences were found. The utilization of fibrin sealant for these applications is still in its infancy and continues to evolve.

Technique

Although the operative procedure for fibrin glue injection of anal fistulas in the United States was performed with autologous fibrin sealant prior to 1998, most surgeons now utilize commercially prepared fibrin sealant when gluing anorectal fistulas. The reasons for this are multiple, including high fibrinogen concentrations with commercially prepared products, uniform production, advanced viral inactivation techniques, easy and quick preparation, no need for patient blood donation, greater quantities easily available, and consistent high bonding power. Operative procedures are typically performed as an outpatient. Preoperative mechanical bowel preparation is not required, other than an enema on the morning of surgery to evacuate the distal rectum. Oral and/or intravenous antibiotics are not necessary for this procedure. Patient positioning is at the discretion of the surgeon, provided that the primary and secondary openings of the fistula are easily accessible. The secondary or external opening is easily identified. Location of the primary or internal opening is essential in order to improve the success of the procedure. Occasionally hydrogen peroxide is utilized in order to inject the fistula tract in order to locate the primary opening. The tract should then be gently debrided without undue dilatation of the tract. Either an unfolded gauze sponge, a silk suture with a series of knots, a small curette, or a cytology brush works well (Fig. 11.3). Aggressive curettage or debridement should be avoided so as not to dilate the fistula tract. Dilation of the tract can lead to a greater quantity of sealant required to fill the fistula and to a higher risk of fibrin clot extrusion from the tract. After debridement the tract should be irrigated with saline or hydrogen peroxide to further cleanse the tract. Iodine irrigation of the tract should be avoided because iodine solutions can destabilize the fibrin clot. The fibrin sealant is prepared according to the manufacturer's instructions. A dual syringe applicator and dual lumen catheter is utilized containing the two components, which will mix together at the tip when injected. A variety of delivery systems are available. The author prefers a long, flexible catheter tip as seen in Fig. 11.2. Other delivery systems are available including malleable dual lumen catheters (Fig. 11.4). The dual lumen catheter is passed through the entirety of the fistula tract, at least up to the internal or primary opening and in most cases preferably through the internal opening. The catheter tip is first placed into the external orifice, through the tract, and into the anal canal towards the primary opening. This is usually accomplished by placing a tie/seton through the tract initially, which can then be secured to the catheter. The tie is then used to drag the dual lumen catheter with it and into the tract towards the primary opening (Fig. 11.5).

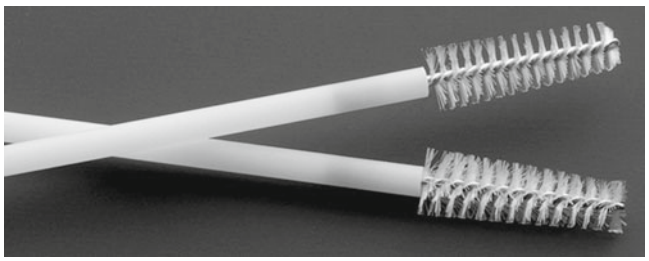

Fig. 11.3 Cytology brush used to debride fistula tract

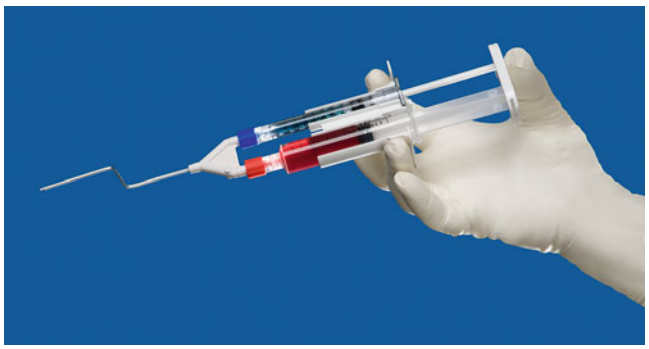

Fig. 11.4 First-generation Micromedics® malleable catheter system. With permission © Micromedics Inc., St. Paul, MN

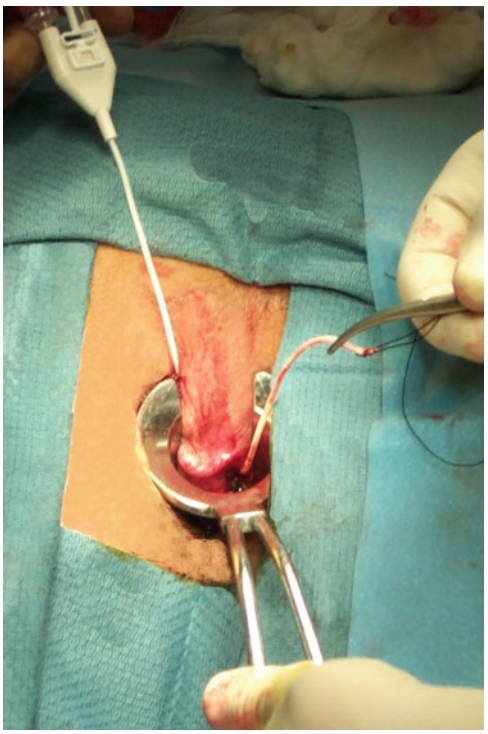

Fig. 11.5 Seton used to drag dual lumen flexible catheter through fistula tract

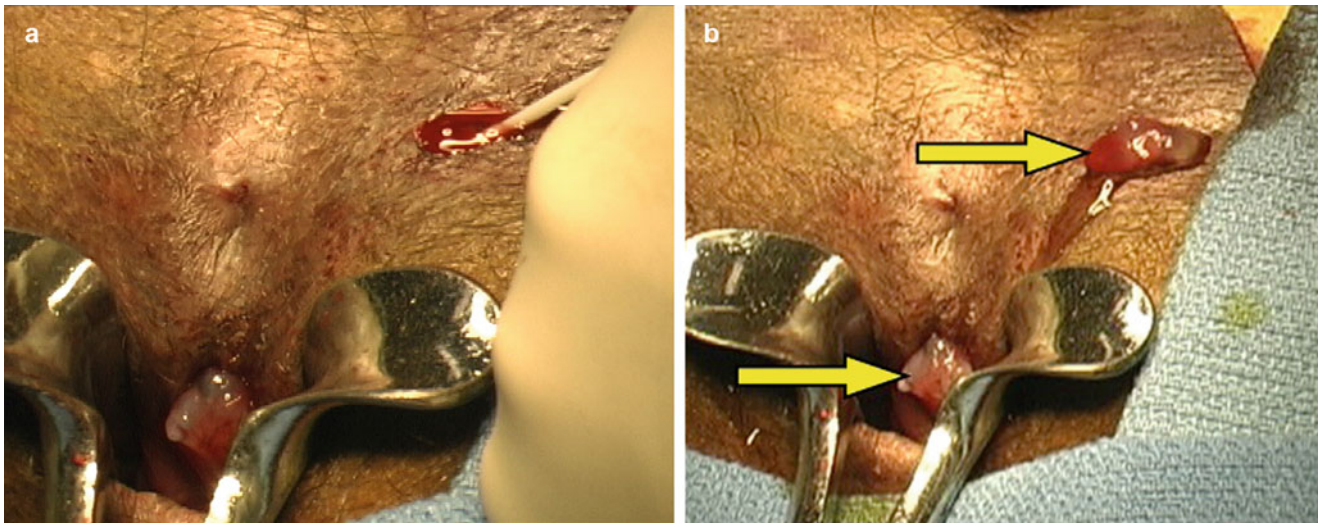

Fig. 11.6 (**a**) Dual lumen catheter trimmed and injection commenced occluding primary opening. (**b**) Completed injection demonstrating fibrin plugs present by arrows at primary and secondary fistula orifices (With permission Singer et al. [40])

The sealant is slowly injected at the internal opening and allowed to set (Fig. 11.6a). Once the clot stabilizes at the primary opening, the catheter is slowly withdrawn through the tract as sealant is being injected, thus obliterating the entire tract (Fig. 11.6b). The clot is allowed to solidify for 5–10 min. Figure 11.7a–c graphically demonstrates the injection process. The external orifice is then dressed with a non-adherent dressing. Patients are discharged home on the day of surgery, as there is minimal or no postoperative pain. Patients are instructed to avoid strenuous activity and are placed on a bowel regimen for approximately 2 weeks. Additionally, patients are instructed not to take Sitz or tub baths for 2 weeks, so as not to prematurely disrupt the fibrin clot. Showering is permitted. Complete obliteration of the tract and any of its side branches with sealant is the critical feature of the procedure. If an abscess is identified at the time of examination, it should be drained and a seton placed, and fibrin gluing deferred for a later date.

Complications Associated with Fibrin Sealant

One of the most common complications associated with the use of fibrin sealant for anorectal fistulas is the development of infection typically at the site of the external or secondary opening. This is reported in approximately 0–10 % of patients. It is important not to suture close the secondary opening at the time of gluing as this can lead to an increased incidence of infection. Other complications or side effects may be secondary to the components that constitute the product itself. These include but are not limited to hypersensitivity or allergic anaphylactoid reactions (bradycardia, tachycardia, hypotension, flushing, bronchospasm, wheezing, dyspnea, nausea, urticaria, angioedema, pruritus, erythema, paresthesias) as well as infectious risks. Anaphylactic reactions to the antifibrinolytic protein aprotinin have been reported especially in patients who have had prior exposure to aprotinin [32, 33]. Additionally, as the commercial sealants are manufactured from human plasma, there is always the risk that the plasma may contain infectious agents such as known viruses (parvovirus), emerging viruses, or other pathogens that can potentially transmit disease including Creutzfeldt–Jakob disease (CJD) that are not eliminated by current inactivation procedures [33].

In autologous preparations or in preparations in which bovine thrombin is used, there have been some reports regarding excessive bleeding following the use of bovine thrombin particularly after reexposure to thrombin [34, 35]. Some patients have been reported to develop acquired coagulation factor inhibitors in response to bovine thrombin exposure. This does not seem to be the case when patients are reexposed to recombinant human thrombin which is utilized with greater frequency today [36]. The antibodies to bovine Factor V have been shown to elicit cross-reactivity with human Factor V, which potentially can decrease the amount of Factor V available, with subsequent inhibition of the clotting cascade [37]. This reaction is minimized via lower thrombin concentrations and through the use of Factor V-depleted bovine thrombin preparations [38].

Literature Review

Over the past one and a half decades there have been an increased amount of publications on the topic of fibrin glue in the management of anal fistulas that corresponds to the period after the FDA approved commercial sealants for use

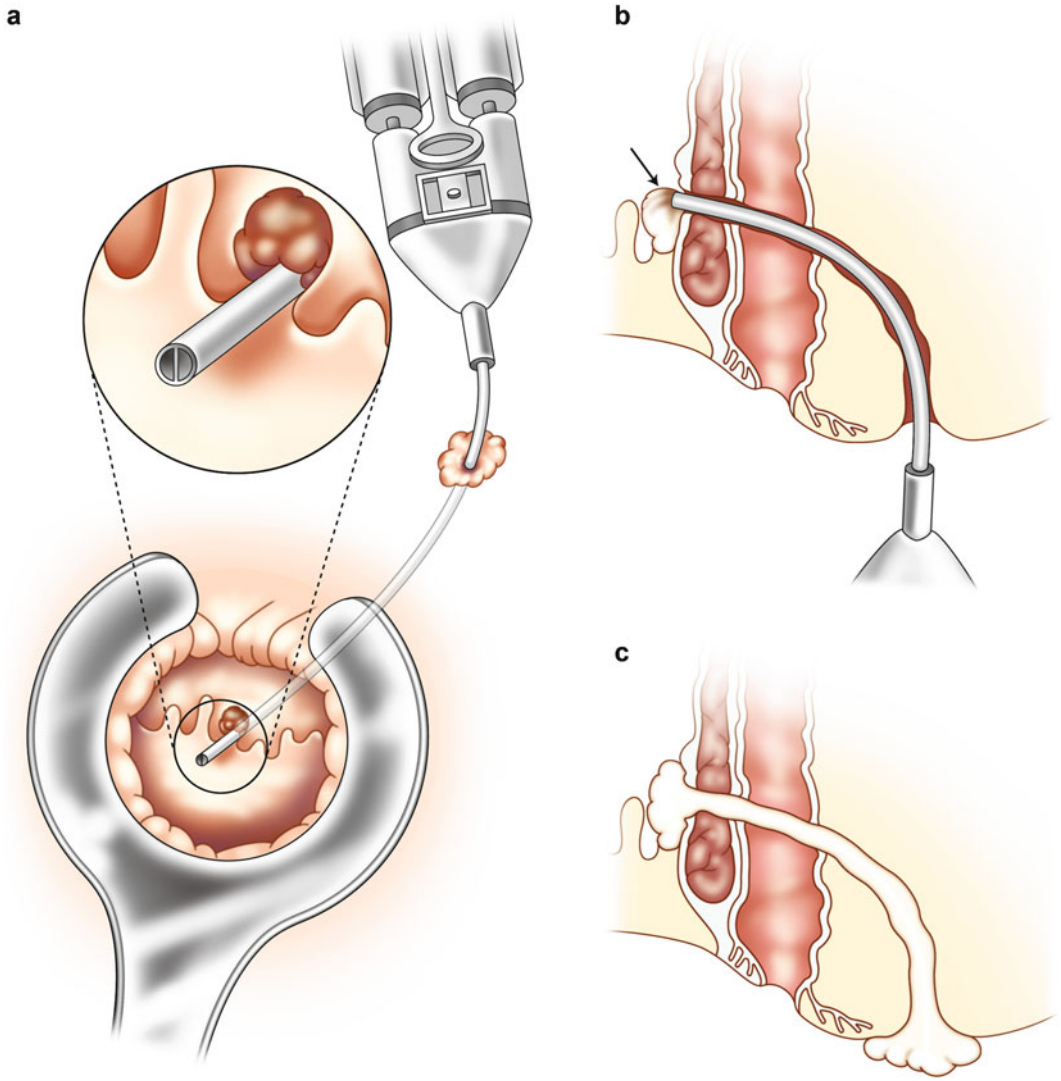

Fig. 11.7 (**a**) Dual lumen catheter system in place ready for fibrin sealant injection. (**b**) Fibrin sealant injection commenced with fibrin plug present at primary opening. (**c**) Fibrin sealant injection completed with entire tract sealed and plugs present at the primary and secondary openings (With permission Singer et al. [40])

in the United States, despite it being an off-label use for anal fistulas. The high variability regarding the design and methodology of reported studies makes comparison difficult. Few trials were initially prospective and randomized [39, 40], some were prospective and nonrandomized [23, 27, 41–48], while others were retrospective [49, 50]. The patients included in the majority of the trials were usually not standardized. They included patients who had acute and chronic fistulae, Crohn's disease, HIV-positive patients, postoperative patients, rectovaginal fistulae, and anastomotic fistulae. The commercial preparations of sealant are varied, and the intraoperative protocols differ in terms of preoperative preparation of the patient, management of the fistula in the operating room, and postoperative monitoring. The follow-up was relatively short in many of the trials, although several trials have reported long-term data as can be seen in Table 11.1. As previously described, it is critical to obliterate the entirety of the fistula and any attached branches. For this reason, some authors chose to exclude patients in whom additional tracts were identified [27, 39, 43, 46] or deferred the injection until adequate drainage was achieved [25, 40, 41, 48, 49, 51]. Other investigators chose to include these patients and make attempts to fill all tracts and cavities with sealant [23, 42, 44]. Preoperative antibiotic use was also highly variable in these studies. Authors administered parenteral antibiotics [23, 43, 47], enteral antibiotics [44], or refrained from antibiotic use [39, 41]. There is evidence to suggest that antibiotics mixed within the fibrin sealant will be slowly released from the matrix over 24–48 h [52]. Several studies attempted to improve healing rates based on

Table 11.1 Summary of data over the last 2 decades

Authors	Year	*N*	Etiology	Success (%)	Type glue	Follow-up	Remarks
Hjortrup et al. [27]	1991	23	Crypto, postoperative	74	Commercial	12–26 m	First series including fistula-in-ano in 8 pts, nonrandomized
Abel et al. [23]	1993	10	Crypto, RVF, HIV, Crohn's	60	AFTA-C	3–12 m	Safe and effective, nonrandomized
Venkatash et al. [47]	1999	30	Crypto, RVF, HIV, Crohn's, urethro-vesicorectal	60	AFTA-C	9–57 m	Only recurrent pts enrolled, prospective
Aitola et al. [42]	1999	10	Crypto	0	Commercial	6 m	Pilot study
Cintron et al. [25]	1999	26	Crypto, Crohn's	85	AFTA-E	3.5 m	Third-generation autologous
Nelson et al. [7]	2000	10	Crypto	50	Commercial and dermal advancement flap	28 (4–63)	Dermal advancement flap and glue odds ratio for recurrence 4.3
Cintron et al. [41]	2000	26—A 53—C	Crypto, HIV, RVF, Crohn's	54 64	Autologous or commercial	12	Less efficacy in complex fistulae, failure seen 11 m
Patrlj et al. [46]	2000	69	Crypto	74	Commercial and cefotaxime	18–36	More effective in tracts ≥3.5 cm
El-Shobaky et al. [45]	2000	30	Crypto	87	Autologous	?	
Sentovich [53]	2001	20	Crypto, Crohn's	85	Autologous/ commercial	10	
Lindsey et al. [39]	2002	19	Crypto, Crohn's	63	Commercial	3	Sealant better for complex fistulae Randomized, controlled
Chan et al. [44]	2002	10	Crypto	60	Commercial	6	Prospective nonrandomized
Tinay et al. [54]	2003	19	Crypto	78	Commercial	12	Prospective, nonrandomized
Sentovich et al. [48]	2003	48	Crypto, Crohn's,	69	Commercial	22 (6–46)	Better healing in shorter tracts, 89 % success if retreated, bowel preparation
Zmora et al. [49]	2003	24 (1°) 13 (flap and glue)	Crypto, Crohn's, postoperative	33-alone 54-flaps	Commercial	12.1 (1–36)	Retrospective, Sealant and flap yielded 54 % healing
Buchanan et al. [43]	2003	22	Crypto	14	Commercial	14	Prospective
Loungnarath et al. [50]	2004	42	Crypto, Crohn's postoperative	31	Commercial	26	Retrospective 3 pts lost to f/u
Jurczak et al. [55]	2004	31	Crypto	84	Commercial	9 (1–20)	
Gisbertz et al. [57]	2005	27	Crypto	33	Commercial	7	Complex fistulae excluded
Vitton et al. [58]	2005	14	Crohn's	57	Commercial	23 (12–26)	Similar success in Crohn's
Singer et al. [40]	2005	75	Crypto, HIV, Crohn's	35	Commercial ± Cefoxitin	27	Closure of internal opening and/or intra-adhesive cefoxitin not helpful
Zmora et al. [51]	2005	60	Complex crypto	53	Commercial (Quixil®) + ceftazidime	6	Prospective multicenter study + bowel preparation + IV cefonocid/ flagyl antibiotics 1,000 U/mL thrombin
Dietz [59]	2006	39	Crypto, Crohn's, postoperative	31	Commercial	23	
Maralcan et al. [60]	2006	36	Crypto	83	Commercial	13.5 (10–17.5)	+Bowel preparation + I.V. antibiotics
Johnson et al. [61]	2006	10	Crypto	40	Commercial	3	Prospective cohort study
Ellis et al. [62]	2006	28	Advancement flap ± sealant	54	Commercial	22 (12–36)	Randomized controlled Worse result w/glue
Witte et al. [63]	2007	34	Crypto, IBD, HIV	55	Commercial	7	
Tyler et al. [64]	2007	89	Crypto, IBD, HIV	70	Commercial seton used		Success includes re-glued pts

(continued)

Table 11.1 (continued)

Authors	Year	*N*	Etiology	Success (%)	Type glue	Follow-up	Remarks
van Koperen et al. [65]	2008	26	Crypto	44 (1°) 59 (2°)	Commercial + Flap	13 (13–127)	Retrospective Outcome worse w/glue vs. flap alone
Adams et al. [66]	2008	36	Crypto	44	Commercial + closure 1° opening	40 (12–67)	Retrospective, long-term outcome
Hadzhiev [67]	2008	34	Crypto	74	Commercial	6	Retrospective, complex excluded, bowel preparation
Garcia-Olmo et al. [31]	2009	25 24	Crypto, Crohn's	16 71	Commercial [25] Commercial + adipose-derived stem cells [24]	12	Phase II multicenter randomized controlled
Chung et al. [68]	2009	23	Crypto	39	Commercial + closure 1° opening	3	Retrospective
Jurczak et al. [56]	2009	45	Crypto-complex	?	Commercial	67	
Damin et al. [69]	2009	32	Crypto	9	Commercial	12	Most failures w/in 3 m
de Parades et al. [70]	2010	30	Crypto-complex, Crohn's	50	Commercial Seton 8 weeks	11.7	Prospective nonrandomized Patients done under regional better outcome vs. general anesthesia
Grimaud et al. [71]	2010	36	Crohn's	38	Commercial	2	Multicenter, open label, randomized, controlled
Hammond et al. [28]	2011	16	Crypto	80	Commercial + collagen fibers	29	Prospective solid collagen implant vs. glue w/collagen fibers
Haim et al. [72]	2011	60	Crypto-complex	53 (32/60)–short 74 (17/23)–long	Commercial	78	Retrospective Recurrence 4.1 years postoperative 28 % lost to long-term f/u
Maralcan et al. [73]	2011	46	Crypto	87 (40/46) short-term 63 (29/46) long-term	Commercial	54	Prospective long-term study
de Oca et al. [74]	2012	28	Crypto	68	Commercial	20.6 (3–60)	Seton preoperative Recurrence 3–27 m
Herreros et al. [30]	2012	59 60	Crypto	37 52	Commercial + 1° closure vs. Commercial + adipose-derived stem cells	12	Phase III trial multicenter, randomized

AFTA-C autologous fibrin tissue adhesive-cryoprecipitate, *AFTA-E* autologous fibrin tissue adhesive-ethanol, *Crypto* cryptoglandular, *Pts* patients, *HIV* human immunodeficiency virus, *RVF* rectovaginal fistula, *f/u* follow-up, *IBD* inflammatory bowel disease

this laboratory data by including antibiotics within the sealant itself [40, 46]. Table 11.1 contains a summary of available data. Because of the variability in design, a formal systematic review or meta-analysis, although attempted, has not really provided useful information. Nonetheless, a review of the literature is warranted. The world literature review that follows primarily involves studies in which ten or greater patients had some form of fibrin glue treatment. Additionally, on occasion statistics may differ slightly as I thought it would be appropriate to not always dismiss patients who were lost to follow-up but include them on an intention to treat fashion.

In 1991 Hjortrup and colleagues [27] in Europe described the first cohort of patients successfully treated with a commercial sealant. This was a nonrandomized study of 23 patients of which only eight patients had fistula-in-ano, the remaining patients having postoperative persistent perineal sinuses. Although this series was small, it provided the first available data suggesting safety and efficacy for anal fistulas. Abel et al. [23] reported on a cohort of ten patients demonstrating safety and efficacy utilizing autologous fibrin glue. They reported a 60 % success with a mixed group of patients that included five patients who had rectovaginal fistulae, four of whom were successfully treated. Venkatesh and Ramanujam [47] reported results from 30 patients, all of whom had recurrent fistulae from various etiologies utilizing autologous fibrin glue. With a follow-up range from 9 to

57 months their overall success was 60 % in this complicated group, despite the variety of diagnoses and previous treatment failures. Aitola et al. [42] reported on their pilot study using commercial sealant with cryptoglandular fistulas over a 6-month follow-up. They reported zero success over the monitoring period. Cintron et al. [25] reported on a pilot study that enrolled 26 patients. The fistulas were of various etiologies and the fibrin adhesive was a third-generation autologous glue prepared via ethanol precipitation. Although reporting an 85 % success rate, follow-up was short at only 3.5 months. They subsequently published their long-term follow-up in a mixed cohort of patients utilizing autologous or commercial sealant in a prospective group of 79 patients [41]. Twenty-six patients were treated with autologous glue and 53 patients were treated with commercial sealant. Their follow-up was 12 months. There was a 54 % success rate in the autologous group and 64 % success in the commercial sealant group with an overall success at 61 %. More importantly, they recognized that recurrences occurred as late as 11 months in their study and urging even longer follow-up. Nelson and colleagues [7] published their results looking at derma island-flap anoplasty in a group of 65 patients. From that group commercial fibrin sealant was used in conjunction with a dermal island-flap anoplasty in ten patients with transphincteric fistulas. The anal fistulas were of cryptoglandular etiology and they reported a 50 % success rate over a 28-month follow-up on those patients who underwent concomitant fibrin glue injection. Of note, there was a higher failure rate when fibrin sealant was used in conjunction with dermal advancement flap with an odds ratio of 4.3. Although numbers were small, simultaneous use of fibrin glue was not advised. Patrlj et al. [46] enrolled 69 patients in a prospective study in which anal fistulae were treated with sealant that contained intra-adhesive cefotaxime. Their follow-up ranged from 18 to 36 months. They lavaged all fistula tracts with an antibiotic solution. Overall healing was 74 % and there was greater efficacy in patients whose fistula tract was ≥3.5 cm in length. This was the first study suggesting that intra-adhesive antibiotics may augment fistula healing. El-Shobaky et al. [45] presented at the Association of Coloproctology of Great Britain and Ireland their results with a series of 30 patients utilizing autologous fibrin glue in fistulas of cryptoglandular etiology. Although follow-up was not reported in their abstract, their patients enjoyed an 87 % success rate. Sentovich's [53] first report consisted of a cohort of 20 patients in 2001 utilizing autologous or commercial sealant with an 85 % success rate over a 10-month follow-up. His subsequent study in 2003 involved 48 patients utilizing commercial sealant only with a 69 % success rate with long-term follow-up of 22 months [48]. All patients were initially drained with setons and subsequently injected with sealant in a delayed fashion so as to insure adequate clearance of any perianal pus. Lindsey [39] described 19 patients in which a commercial sealant was used to treat anal fistulae. This was the first randomized controlled trial published involving fibrin sealants with fistula-in-ano. They compared fibrin glue with conventional surgical treatments. Patients with rectovaginal fistulas or fistulas with side branches were excluded. They offered retreatment if initial injection failed. This strategy of reinjection brought initial healing rates of 42 % up to 63 % overall. This confirmed that retreatment is a reasonable option in patients failing their initial injection, although follow-up was short in their study. Additionally, they found sealant to be more efficacious in patients with complex fistulas compared to simple fistulas. Chan et al. [44] published their preliminary experience with commercial sealants for fistula-in-ano. They included ten patients in their study and also performed magnetic resonance imaging (MRI) monitoring. Overall success was 60 % over a 6-month follow-up. Additionally, they noted that MRI demonstrated a variable decrease in signal on STIR (Short Tau Inversion Recovery) images in those patients who had success. Tinay and El-Bakry [54] reported their results in 19 patients with a total of 21 fistulae from the Kingdom of Saudi Arabia. Three of their patients were lost to follow-up and 14 out of 18 had successful closure for an overall healing of 78 % with 1-year follow-up. Zmora and coworkers [49] performed a review of their experience with complex fistulae (high transsphincteric, suprasphincteric, high rectovaginal, and Crohn's fistulae) in 37 patients. Sealant alone afforded only a 33 % healing rate; however, when combined with a simultaneous endorectal advancement flap, healing was 54 %. The same author subsequently presented a prospective multicenter study enrolling 60 patients [51]. They utilized a concentrated commercial fibrin sealant with added ceftazidime. Additionally, the thrombin concentration was significantly enhanced. These patients had a 53 % success rate after 6-month follow-up. Buchanan et al. [43] from St. Marks presented their prospective trial with commercial fibrin sealant in conjunction with dynamic contrast-enhanced MRI combined with STIR imaging over a median 14-month follow-up. The majority of their patients consisted of transsphincteric fistulas. Despite the presence of healing of the secondary skin opening in 77 % of patients at 2 weeks, only 14 % remained healed at 16-month follow-up. This outcome was predicted with excellent accuracy when dynamic contrast-enhanced MRI with STIR was performed. Loungnarath and colleagues [50] in St. Louis published their retrospective study on a total of 42 patients utilizing commercial sealant with a median follow-up of 26 months. They found that durable healing was achieved in only 31 % of patients, but due to its low morbidity and simplicity should still be considered in patients with complex fistulas. Jurczak et al. [55] published their results with commercial sealant in 31 consecutive patients with a mean follow-up of 9 months. They achieved a healing rate of 84 %. Their long-term follow-up paper in 2009 with 45 patients demonstrates that

all recurrences in their group occurred during the first 6 months and that durability of the procedure was present with a mean follow-up of 67 months [56]. Gisbertz et al. [57] reported on a pilot study in 27 patients. They excluded patients with complex fistulae. After a 6-month follow-up the overall success rate was 33 %. Patients with recurrent fistulae had a poorer outcome. Singer and colleagues [40] performed a randomized prospective study in the treatment of fistula-in-ano with commercial sealant. Seventy-five patients were randomized to sealant with cefoxitin, sealant with closure of the internal opening, or a combined arm. There were no significant differences between groups, with healing rates of 25 %, 44 %, and 35 %, respectively. Vitton and coworkers [58] published their results using commercial fibrin glue with modified aprotinin concentration in Crohn's disease fistulas in 14 patients. After 3 months there was a 71 % success rate. At the end of the follow-up period of almost 2 years the success rate was 57 %. In a varied cohort of patients Dietz [59] reported a 31 % success rate in 39 patients over a 2-year period utilizing a commercial sealant. Maralcan et al. [60] reported their results in a prospective study of 36 patients using commercial sealant. All their patients underwent preoperative mechanical bowel preparation and received intravenous antibiotics. After a mean follow-up of 54 weeks, they reported a 77.8 % success. Johnson et al. [61] reported on a trial comparing fibrin glue vs. anal fistula plug in a cohort of 25 patients. Of the 25 patients enrolled 10 were treated with a commercial fibrin sealant. There was a 40 % success rate after 3 months in the fibrin sealant group vs. 87 % in the anal fistula plug group. Ellis and Clark [62] reported a prospective randomized study comparing a flap procedure (mucosal advancement flap or anodermal advancement flap) to a flap procedure combined with fibrin glue obliteration of the fistula tract. With a median follow-up of 22 months, success was 80 % in those patients treated by advancement flap alone vs. 54 % in those treated by advancement flap in combination with fibrin glue injection. Witte et al. [63] reported their results with commercial sealant in complex and simple fistulas in 34 patients. They offered repeat injections to 8 of their 34 patients. Overall, closure after a median follow-up of 7 months was 55 % and success was similar in simple as well as complex fistulas. In a retrospective study, Tyler et al. [64] reported on 137 patients who underwent superficial fistulotomy vs. seton and glue, vs. seton and flap. The majority of these patients had a fistula of cryptoglandular etiology (116/137). The success rates were 100 %, 62 %, and 100 %, respectively. van Koperen and colleagues [65] published a retrospective study comparing advancement flap in conjunction with commercial sealant to advancement flap alone. Twenty-six patients underwent advancement flap combined with fibrin glue. After a median follow-up of 67 months the success rate in the group with fibrin glue was 44 % without any prior fistula surgery and 59 % with prior fistula surgery. The patients who underwent flap without glue had 87 % and 77 % success rates, respectively. The authors concluded that using glue in combination with advancement flap led to worse outcomes. Adams et al. [66] retrospectively reviewed their results with commercial fibrin sealant in combination with suture closure of the primary opening in a cohort of 36 patients with cryptoglandular transsphincteric fistulas. Their overall success rate was 66 % at 3-month (short-term) follow-up (22/33). Of the patients that had successful closure at 3 months ($n=22$) and who were available for follow-up ($n=17$), 94 % (16/17) remained closed at 40-month follow-up. If you take the known long-term successes and consider intention to treat (16/36) then their overall long-term success was 44 %. Hadzhiev and colleagues [67] reported their retrospective review on 34 patients with non-complex fistulas of cryptoglandular etiology. Patients had an overall 74 % success after a 6-month follow-up; however, those patients with a history of recurrent fistula at the time of gluing had only a 50 % success rate. Chung et al. [68] retrospectively reviewed their treatment of patients with high transsphincteric fistulas. Of the 23 patients who underwent fibrin glue injection in combination with closure of the primary opening, their success rate after a 3-month follow-up was 39 %. Patients who underwent either anal fistula plug or advancement flap treatment had a better outcome in their study. Damin et al. [69] reported on 32 patients with cryptoglandular fistulas who underwent fibrin glue injection. Out of 32 patients who were glued only three healed for a 9 % success rate over a 12-month follow-up. de Parades et al. [70] prospectively studied 30 patients glued after an 8-week seton period. They included complex cryptoglandular fistulas and Crohn's fistulas. They reported a 50 % success rate over a 12-month follow-up. Additionally, for unclear reasons patients who underwent regional anesthesia had better outcomes than those patients done under general anesthesia. Grimaud et al. [71] published a multicenter open label randomized controlled trial in 36 patients with Crohn's fistulas involving the anus, low rectum, perineum, vulva, or vagina. Patients were randomized to commercial fibrin sealant injection ($n=36$) vs. observation ($n=41$) after removal of their setons. They reported a 38 % remission vs. 16 % remission in patients glued vs. those patients in the observation arm. Hammond et al. [28] reported their experience using fibrin glue in combination with suspended cross-linked collagen fibrils compared to a solid collagen implant alone in the treatment of anal fistulas of cryptoglandular etiology. Of 16 patients undergoing injection with fibrin glue and collagen fibrils, there was an 80 % success rate after a 29-month follow-up. Haim et al. [72] retrospectively reported on 60 patients who underwent fibrin sealant injection for complex fistulas of cryptoglandular etiology. Their short-term (6 months) success was 53 % and their long-term (6.5 years) success was 74 %. Most importantly, they reported a mean recurrence of

4.1 years postoperatively with recurrence as late as 6 years postoperatively. Maralcan et al. [73] prospectively reported their long-term results in 46 patients treated with fibrin sealant for cryptoglandular fistulas over a mean follow-up of 4.5 years. They reported a 63 % success rate over the long-term. Furthermore, patients with tracts greater than 4 cm and without side branches were more likely to have a positive outcome. de Oca et al. [74] reported their long-term results in 28 patients with cryptoglandular fistulas. They had a 68 % success rate after a mean follow-up of 20.6 months. Disease-free curves from their study demonstrated that the highest probability of recurrence occurred in the first 2 years after fibrin glue injection.

Meta-analysis and Cochrane

Cirocchi et al. [75] performed a meta-analysis of fibrin glue vs. surgery for the treatment of fistula-in-ano. Their aim was to evaluate recurrence and fecal incontinence rates in fibrin glue vs. surgical treatment (fistulotomy, cutting seton, non-cutting seton, mucosal advancement flap). The lack of homogeneity of results between studies did not allow the authors to perform any secondary outcome analysis. Of two randomized controlled trials (RCTs) and one non-randomized study, statistical analysis did not detect any significant difference for recurrence or anal incontinence between fibrin glue treatment and conventional surgical treatment. Jacob et al. [76] performed a Cochrane Review for surgical intervention of anorectal fistula. In their analysis there were no significant differences in recurrence rates or incontinence rates except in the case of advancement flaps. Although there was a low incontinence rate when glue was used in combination with a flap, this was offset by a higher recurrence rate when fibrin glue was used in combination with an advancement flap in comparison to advancement flap alone. Hence, favoring a flap-only technique.

Conclusion

Fistulotomy remains one of the most reliable methods of treating most fistulae; however, the incontinence rates make it prohibitive in many scenarios: high internal opening, anterior fistulae in women, prior anorectal surgery, and patients who either have disturbances of continence already or who have preexisting risk of incontinence (Crohn's, HIV+, elderly). Fibrin sealant injection carries essentially no risk of incontinence as there is no division of sphincter muscle. Additionally, there is very little postoperative pain, the procedure is easily repeatable, and most importantly it does not preclude any further surgical options later in the patient's treatment. In these respects, fibrin sealant is an ideal procedure for anal fistulae; however, the available data even in the long-term suggest that the success rate is moderate at best. As previously explained, the data is highly variable, and the inconsistent trial design makes formal statistical analysis of the data difficult if not impossible. The operative procedure is technically simple; however, meticulous attention to the examination remains fundamental to its success. If there is any significant un-drained pus or unfilled side branches of the fistula, failure is likely to occur. Setons or drains should be used liberally, and injection delayed if pus is identified. The relationships between healing rates, fistula etiology, anatomy, tract length, antibiotic use, bowel preparation, and many other variables are not completely understood. Well-designed clinical trials may be required to properly evaluate these factors. Given its safety profile, ease of application, and repeatability, fibrin sealant injection should be in the armamentarium of the surgical specialist treating fistula-in-ano. Patients must be informed of its moderate success rate. Fistula-in-ano remains a complex disease that has evolved to include a variety of sphincter-preserving techniques [77]. Surgeons should become familiar with various surgical techniques including fibrin sealant injection in order that the treatment can be tailored to the patient.

Summary

1. Fibrin sealants simulate the terminal steps of the body's natural clotting cascade.
2. Fibrin sealants are safe, moderately effective, repeatable, and easy to use for the treatment of anal fistulas.
3. Fibrin sealants can be used as a carrier or delivery vehicle for other substances.
4. The outcomes of anal advancement flaps in the management of anal fistulas are worsened with the use of concomitant fibrin sealants.
5. The use of fibrin tissue adhesives continues to evolve and further randomized, prospective studies are needed.

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