Fistula-in-ano: advances in treatment


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Abstract

BACKGROUND: Several techniques have been described for the management of fistula-in-ano, but all carry their own risks of recurrence and incontinence. Technology has evolved over the past 2 decades that may enable surgeons to deal with this troublesome issue with greater success. This review summarizes the history of fistula-in-ano management, the current techniques available, and describes new technologies.

METHODS: Medline searches were performed using the PubMed, Ovid, Embase, Cochrane, and Google Scholar databases to identify articles reporting on fistula-in-ano management using surgery alone, fibrin glues, and fistula plugs. Forty-one articles reporting on the history of fistula-in-ano management and the use of new technologies were included.

RESULTS: Conventional fistula surgery techniques have their place, but new technologies such as fibrin glues and the anal fistula plugs offer an alternative approach, with initial studies reporting good success rates.

CONCLUSIONS: New technologies provide promising alternatives to traditional methods of management. There is, however, a real need for high-quality randomized control trials.

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Fistula-in-ano has been a troublesome pathology to both patient and physician throughout surgical history. The estimated prevalence of nonspecific anal fistulae is 8.6 to 10/100,000 of the population per year, with a male to female ratio of 1.8:1.1 Optimal management is aimed at eradicating the fistula, preserving the anal sphincter, preventing recurrence, and allowing an early return to normal activity for the patient. Achieving these aims, however, represents a real challenge to the surgeon.

The disease and surgical instruments used in treating fistulae have been well documented historically. Probes were found among the ruins of Pompeii as part of a surgeon’s tool box, and the difficulty in managing the pathology was recognized by Hippocrates (460 BC). The English surgeon, John Arderne (1307–1390), wrote “Treatises of Fistula in Ano; Hemorrhoids, and Clysters” in 1376, which alludes to the current practice of probing, and laying open of fistulas, as well as the use of setons for more complicated fistulae. The French King Louis XIV underwent a surgical procedure performed by the famous French surgeon George Mareschal (1658–1736), who was ennobled for his services. In the late 19th and early 20th centuries, prominent physicians and surgeons such as Goodsall and Miles, Milligan and Morgan, Thompson, and Lockhart-Mummery made substantial contributions to the understanding and treatment of anal fistulae.

In modern times, advances in molecular biology and bioengineering have meant that we now have access to a number of new materials that may be used as adjuncts to
fistula closure. This article aims to review the literature and identify new technologies used in fistula management, the latest of which is the fibrin plug.

**Materials and Methods**

A literature search was performed using the PubMed, Ovid, Embase, Cochrane, and Google Scholar databases to identify articles reporting on the management of peri-anal fistulae. The following key words were used: fistula in ano, anal fistula, fibrin glue, anal fistula plug, and Crohn’s fistula. The most informative and recent articles reporting on results from a range of fistula management techniques were selected for this review. These 41 articles (26 prospective studies, 7 retrospective studies, 2 case reports, 3 randomized controlled trials, and 3 reviews) were used to formulate this review and are presented later.

**Comments**

**Traditional surgical management**

**Cryptoglandular fistulae.** Fistulae are thought to emerge in most cases as a consequence to a previous cryptoglandular perirectal abscess that was either drained surgically or spontaneously discharged. A remnant of that abscess cavity and tract from the drainage, consisting of granulation tissue, persists, giving rise to the fistula. The tract connects the primary opening in the rectum (which was the opening of the infected gland) to the secondary opening in the skin of the perianal area (which was the drainage site, be it spontaneous or surgical).

The classic techniques described throughout history, which still carry worldwide popularity, are the fistulotomy or the laying-open technique. The patient is positioned in the lithotomy position or prone jack-knife position according to preference for the purposes of an examination under general anesthesia. The secondary fistula opening is identified and then probed until the primary opening becomes apparent as the distal end of the probe emerges from it. This is performed sometimes under the aid of injecting methylène blue or hydrogen peroxide diluted solution in the secondary opening to see it come out of the primary opening, thus helping in identification of the latter. The use of transrectal ultrasound in assessing the tract and finding the primary opening sometimes is helpful, especially in conjunction with the use of peroxide, which delineates the tract on the ultrasound image. Magnetic resonance imaging also may be used to delineate complex fistula tracts, and especially those associated with supralever extension. If the fistula is low lying and under the anal sphincter musculature, or involves a small amount of sphincter, it is laid open, although the risk of altered continence exists and must be explained to the patient before any intervention. The objective in managing fistulae is to allow the fistula to heal with minimum surgical trauma to the skin and anal sphincter musculature. Fistulotomy wounds can take prolonged periods of time to heal, causing the patient significant discomfort and distress as well as contour defects around the anus. Simple low fistulas usually are treated adequately by this method, with reported recurrence rates of less than 8%, although some studies report incontinence to flatus in up to 50% of cases.

More complex fistulae and high fistulas traversing through or around the sphincter complex are treated in a step-wise manner. A seton, either loose or cutting, is inserted through the tract and the foreign body reaction enables the tract to mature into a more low-lying position, as is the case with cutting setons. This allows it to be laid open in a second-stage surgery, thus sparing the sphincter. Nevertheless, incontinence rates are still reported to be as high as 63% with this method. Another procedure being performed is the anodermal advancement flap. However, this also is associated with incontinence rates of up to 35% as a result of dissection around the anal sphincter.

**Crohn’s disease fistulae**

Fistulae from Crohn’s disease are a more perplexing problem to manage and are resistant to many of the traditional management strategies offered. The pathogenesis of Crohn’s fistulae is thought to be different from cryptoglandular fistulae. It is thought to originate as a deep penetrating ulcer in the anorectum, which then is plugged with fecal material. With time and the ensuing high pressure produced by the anorectum, the ulcer finds its way through the skin and transforms into a fistula. Alternatively, it has been suggested that the fistula originates from a cryptoglandular infection that heals poorly as a result of the inflammatory nature of the primary pathology, finally leading to fistula formation. In either case, the transmural involvement of rectum in Crohn’s disease is a major contributory factor.

Several medical modalities for the conservative treatment of Crohn’s fistulae have been described in the literature. Antibiotic therapy alone has been documented by several series. Closure rates of up to 50% have been reported in some studies; however, there is a high incidence of recurrence after antibiotic therapy is discontinued. The use of 6-mercaptopurine and azathioprine for control of active Crohn’s disease and closure of fistulae in 54% of cases has been described. The adverse effects of these chemotherapeutic agents are significant drawbacks for patients, with the most common being leukopenia, hepatitis, pancreatitis, and various allergic reactions and infections.

Infliximab, a murine and human chimeric monoclonal antibody to tumor necrosis factor α, has been used with successful closure of up to 62% of fistulae. Adverse effects of infliximab include allergic reactions, delayed hypersensitivity reactions, and drug-induced lupus. Other therapies such as cyclosporine and tacrolimus also have been described, with initial response rates reported to be high.
However, the recurrence rates tend to be higher when the therapies are discontinued. Elemental diets, bowel rest, and parenteral nutrition have been cited sporadically in the literature but do not carry evidence to back their efficacy. Surgery for Crohn’s fistulae has to be individualized to the patient’s medical condition, the degree of activity of proctocolitis, together with the location and type of fistula. The healing rate of fistulotomy for simple low-lying fistulae in Crohn’s patients with silent disease is reported to be as high as 93% in some series, as compared with 27% in series describing the healing rate of low-lying fistulae in patients with active proctocolitis. It is therefore the general practice that patients with active proctocolitis should have a noncutting seton inserted rather than a fistulotomy performed because of the poor healing associated with the advanced form of the disease that will unlikely allow closure of an open fistulotomy. Medical therapy then can be instituted to inactivate the underlying disease if possible. This is then followed by re-examination under anesthesia to change the seton or to lay open that fistula in the setting of silent disease.

Complex fistulae consisting of high trans-sphincteric, suprasphincteric, and extrasphincteric fistulae in patients with Crohn’s proctocolitis should be treated more conservatively to avoid the risk of incontinence. Seton placement is the rule in these cases and this helps the fistula to heal and allows continued drainage without forming an abscess. The use of permanent setons until the disease subsides in Crohn’s patients is not an uncommon practice to preserve sphincter function and drain the tract. Medical therapy should be offered in conjunction with surgical intervention to help in suppressing the underlying disease. Rates as high as 85% for closure of complex Crohn’s fistula above the pubic symphysis have been reported. Recurrence rates as high as 40%, however, have been reported when there was no adjunctive medical therapy initiated with the surgical treatment.

Fibrin glue

This novel approach to fistula-in-ano management was published in 1991 by Hjortup and Kjaergard and was the result of a pioneering series of treatments for perianal fistulae with fibrin glue. It describes a method that stimulates healing of fistulae with preservation of the sphincter mechanism because it involves no surgical interference with the musculature of the sphincter mechanism. Early results were encouraging, but as the procedure gained wide acceptance, reports showed conflicting data with a very wide range of success from as low as 14% to as high as 74%. The use of fibrin was first documented in World War I, when the use of packs and tampons impregnated with fibrin were used to stop the bleeding from parenchymatous organs. In World War II, Cronkite and Deaver showed that fibrin could be used as a sealant in skin-grafting surgeries, but this was associated with a high failure rate. The use of fibrin glue was abandoned until 1972 when it re-emerged for surgical use only to be revoked again by the Federal Drugs Agency for its hazard in transmitting blood-borne viruses. As the technology of virus elimination in blood plasma progressed in the 1980s and 1990s, the Federal Drugs Agency re-approved the use of fibrin sealant for limited surgical procedures.

Fibrin glue was first described for plugging fistulae in 1982 by Hedelin et al. Its use was not exclusively for fistula-in-ano but all perineal fistulae postoperatively. The mode of action is thought to be by stimulating the growth of fibroblasts and pluripotent endothelial cells into the fistula tract to seal it off. This is achieved by using the fibronectin and collagen present in the mixture as a matrix for the cells to integrate into. These cells then lay collagen and extracellular matrix in the next stage of wound healing. The glue is deployed after curettage of the tract. Also, before application the primary opening is inspected to ensure that it is not closed and that it does not lie in the high-pressure zone of the anorectum. This results in the glue being pushed out of the fistula tract.

Swinscoe et al. reviewed the literature regarding simple fistula treatment outcomes using fibrin glue. The reported healing rates were variable and ranged from 10% to 74%, with a mean of 50%. The investigators stressed that long-term follow-up evaluation is very important when using this method of treatment because later follow-up evaluation revealed that healing rates decreased markedly. Sensito et al., Citron et al., and Buchanan et al. reported a decrease in healing from 85%, 81%, and 77%, to 60%, 61%, and 14%, respectively, with long-term follow-up evaluation at 2 years. In their review, Swinscoe et al. showed that studies dealing with simple fistulae reported a higher rate of healing, ranging from 60% to 78%, while those reporting exclusively complex fistulae had lower reported success rates, ranging from 14% to 50%. Shorter fistulae (<3.5 cm) tend to recur more often than longer fistulae (>3.5 cm), with rates of 54% as compared with 11%, respectively, the reason being that shorter fistulae do not hold the glue as well as longer-tract fistulae do.

Continence seems to be unaffected when the patient is treated with fibrin glue and this is logical because there is no trauma to the sphincter musculature. In a comparative matched retrospective study, El-Shobaky et al. showed that patients treated with fibrin glue had 0% incontinence whereas 10% of patients treated with the conventional surgical techniques incurred some form of incontinence. In a randomized comparative trial Lindsey et al. reported that patients treated with fibrin glue showed no evidence of incontinence whereas 15% of patients managed with traditional surgical techniques suffered postoperative incontinence. A few studies have reported the success rate of applying fibrin glue to the closure of Crohn’s fistulas as ranging from 31% to 57%, explained by the nature of the inflammatory disease. The complications of fibrin glue for treatment of both types of fistulae include formation of abscesses and new fistulae tracts.
Three studies,\textsuperscript{30,27,31} have reported these complications with a combined incidence of 3%.

### The anal fistula plug

Recently, a new technology, Surgisis (Cook Surgical Inc., Bloomington, IN), has become available. This is an advanced biomaterial that is derived from swine small intestinal submucosa.\textsuperscript{34} It is a strong, pliable tissue taken from porcine small intestine that provides a scaffold for host cells to replace and repair damaged tissue. Small intestinal submucosa is a naturally occurring, complex matrix that is easy to handle, yet strong enough to hold sutures and provide support for weakened tissue. Through processing it is denuded of cells and is biocompatible and safe for human use as well as sterile and pathogen free. Surgisis has been documented to have an inherent resistance to infection in contaminated abdominal wounds in 2 series.\textsuperscript{35,36} Its initial use was intended for bridging large tissue defects in the abdominal or chest walls. A group of surgeons\textsuperscript{34} rolled it into a cone and inserted it into anal fistulae in an attempt to achieve closure. The idea was to bridge the defect of the fistula with a biocompatible material that would act as a scaffold for the patient's own fibroblasts to come in and promote tissue healing in the fistula tract.

Further advances have been made by the construction of a purposely made anal fistula conical plug using the same material. The technique of plug deployment is as follows: the tract is explored, probed, and irrigated gently with hydrogen peroxide. Then the apex of the plug is tied to the probe from the internal opening and the plug is dragged through to the external opening. It is then cut to fit and secured in the internal opening using a figure-of-eight suture incorporating it with the mucosa of the anorectum to close the internal opening.

Johnson et al\textsuperscript{39} published a series comparing 2 prospective cohort groups of patients undergoing plug closure versus patients undergoing fibrin glue closure. They reported an 87% closure rate for the plug group versus a 40% closure rate for the glue group. Closure rates of 65% using the plug have been presented by Robb et al. in the 2004 Annual Meeting of the American Society of Colon and Rectal Surgeons. Recurrence rates are variable between 12% and 59% in most recent literature published by Ellis\textsuperscript{37} and van Koperen et al.,\textsuperscript{38} however, larger series by Champagne et al\textsuperscript{39} reported better success rates of 85% in cryptoglandular fistulae and 80% in Crohn’s fistulae\textsuperscript{40} management by the earlier-described technique.

### Conclusions

To the colorectal surgeon, fistula-in-ano remains a challenging condition to manage despite the best of technologic advances. The treatment objective remains the eradication of perianal sepsis, effective fistula healing, alleviation of symptoms, prevention of recurrence, preservation of the anal sphincter, and rapid patient recovery. Conventional fistula surgery has its role, and although technologies such as fibrin glue have promised to improve results, the reported success in the literature has decreased with increasing lengths of patient follow-up evaluation. That said, it is important to note that there is only one randomized controlled clinical trial available comparing fibrin glue with the classic techniques.\textsuperscript{31} The advent of the anal fistula plug and early evaluation\textsuperscript{34} seems superior to fibrin glue because it eradicates the problem of slippage of the material from the fistula tract. There is also the added benefit of the plug acting as a good bridging medium or matrix for human tissue regeneration. Definitive evidence of the advantages of the new technologies compared with traditional interventions relies on future randomized control studies being conducted.

### References