Biologic Fistula Plugs

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Introduction

Sphincter-sparing procedures for the treatment of anal fistulae are the standard of care. Full resolution, however, may be challenging to achieve in patients with complex fistulae, defined as fistulae that involve greater than 30 % of the sphincter mechanism, fistulae in the setting of Crohn's disease or irradiation, in patients with a history of incontinence, and anterior fistulae in women [1, 2]. Historically cutting setons have been used in treating complex fistulae, however their efficacy has recently been called into question with up to a 60 % incontinence rate in some studies and significant pain caused by seton placement [3]. When simple fistulotomy is not an option, usually in the setting of a recurrent or complex fistulae, surgeons are turning to new biological agents as an option to achieve fistula closure while preserving continence.

Numerous biologic agents have been developed over the last 20 years for use in treating anal fistulae. Hjortrup et al. first described the use of fibrin glue to achieve closure of anal fistulae in 1991 [4]. Since then many other biologic agents have also been employed to this end, primarily in the form of plugs composed of either acellular biologic matrices or xenografted biologic tissue.

Surgical closure of a fistula consists primarily of two steps, closure of the internal opening and separation of the fistulous tract. Biologic agents have been used to achieve both of these ends and primarily work as a scaffolding to promote tissue ingrowth. Prior to placement of a biologic agent, the surgeon must first clear the acute septic episode and effective drainage must be achieved through either wide drainage or seton placement. At the time of the plug placement or glue injection the tract should be curetted to remove all granulation tissue and epithelialization. Interestingly, further obliteration of the fistula opening via endorectal advancement flap (ERAF) after either plug or fibrin glue placement has not been shown to improve results and therefore is not routinely recommended [5, 6].

While there are numerous biologic agents available for fistula therapy, the results thus far have been mixed and good results have not been reproducible. This is primarily because most studies to date have been too small to demonstrate significant results and few prospective studies have been performed. With time the data will likely improve, however the use of biologic agents in the treatment of anal fistulae is still in its infancy. Outlined here is a comprehensive list of the various agents which have been used for this purpose to date.

Injectable Glue

Fibrin Glue

Fibrin glue was the first biologic event described in the treatment of anal fistula in 1991 [4]. The glue, which is composed of fibrinogen and thrombin which when combined, form a fibrin clot, fills the fistula tract completely, adheres to local tissues, and acts as a scaffolding for ingrowth of healthy tissue. The procedure is noninvasive, only requiring removal of any granulation tissue or epithelialization prior to glue injection, and therefore has little impact on continence.

Initial reports were impressive, with a 75 % healing rate without loss of continence. More recent studies have been less promising, however, with cure rates between 40 and 54 % [7], with only one recent study, by Maralcan et al. in 2006 demonstrating a strong healing rate of 78 % [8]. Several recent meta-analyses of the literature have been published and demonstrate no advantage for the use of fibrin glue over conventional surgical therapies [7, 9]. However, because it is considered safe, with a minimal side-effect profile, and does not make future fistula repairs more difficult, fibrin glue can

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be considered as an adjunctive therapy to achieve closure in complex fistulae which may have failed previous attempts at closure.

Cryolife Bioglue

Bioglue is a combination of bovine serum albumin and glutaraldehyde which has been primarily used in achieving intraoperative hemostasis. It's use has been described in the treatment of anal fistulae, however, due to a low cure rate of 21 % at 60 months, an unacceptably high rate of acute sepsis necessitating repeat drainage, as well as demonstrably toxic serum levels of glutaraldehyde, it should not be used for this purpose [10–12].

Biologic Fistula Plugs

Numerous fistula plugs comprising a variety of biological agents have found their way to market over the last decade. Plugs are composed of a variety of acellular biologic materials and come in a variety of shapes and sizes. Placement usually involves identifying the fistula tract with a standard fistula probe followed by curettage. Once the probe has been placed through the tract, the plug can be tied to the probe with a silk tie and pulled through the tract. The plug should be trimmed at the level of the mucosa internally and sutured in place with an absorbable suture, usually in figure-of-8 fashion to prevent extrusion. The external end of the plug is also trimmed at the level of this skin for patient comfort and to prevent accidental removal of the plug. It is advised that some space be left at the external opening to allow for drainage of the tract, and for this reason the plug is not sewn in distally.

Ideally, the material from which the plug is composed should allow good tissue ingrowth as well as vascular ingrowth while being resistant to infection and extrusion. Plugs are an appealing therapeutic option because they do not require ligation of the fistula or division of the sphincters, both of which can lead to postoperative decrease in continence. Plug placement is also not particularly technically demanding, making their use more appealing than challenging procedures such as ERAF. To date, however, the data on their efficacy is mixed with closure rates ranging between 13 and 86 % [13, 14].

The reason for this lack of efficacy is not clear. Plug extrusion clearly accounts for a significant number of early postoperative failures with a 0–41 % extrusion rate reported in the literature [13, 15]. Extrusion is thought to be a technical failure from plug placement and rates are thought to decrease as one masters the learning curve. This however does not account for failure in patients who retained their plugs. Short tract length, less than 4 cm, was also shown to be a risk factor for plug failure in another study where longer tracts were shown to be three times as likely to achieve closure when compared to their shorter counterparts [16].

Ineffective clearance of the infectious process, failure to appropriately de-epithelialize the tract, and failure to optimize the patients' inherent ability to heal the fistula, such as diabetic control and smoking cessation, have all been implicated in further failures [17]. Several technical and postoperative considerations have been implicated in improving closure rates, including cleaning the tract with hydrogen peroxide, postoperative antibiotics, avoiding strenuous activities postoperatively, and the implementation of a clear liquid diet for several days, however none of these has been demonstrated to be effective in a study [18].

Cost is another consideration in plug placement. With most plugs costing around $1,000 significant expense can be added onto the procedure cost. Adamina et al. looked at the overall costs for patients receiving plugs vs. those receiving ERAF and found that when factoring in the need for reoperation and the length of stay, fistula plug placement saved the institution $1,588. This study was limited, however, by the fact that ERAF patients had a length of stay of 2.5 days vs. 1 day for plug patients since these procedures are both currently being done on an outpatient basis at most institutions. Results were also skewed by the poor cure rate of the ERAF group where 33 % achieved fistula closure vs. 50 % in the plug group. When hospital stay was controlled for the savings were $825, demonstrating a financial advantage for using fistula plugs [14].

Due to the expense and the overall scarcity of biologic materials, non-biologic absorbable plugs have been developed. These are less expensive and have demonstrated similar results in preliminary studies as their biologic counterparts, however little data is available to date on long-term outcomes and more research needs to be performed before they can be considered equivalent or better.

Xenograft

Xenograft materials are currently in use for a variety of applications, and have been a mainstay of treatment when mesh is required in contaminated surgical fields. These same materials have been repurposed for use in anal fistulae based on their ability to avoid vigorous host inflammatory reactions as well as maintain resistance to infection while being rapidly absorbed by host tissues after stimulating tissue ingrowth.

Xenograft tissues are readily available and less expensive than allografts. Their primary drawback is that since they are not human tissue, it is thought that their base components, collagen, elastin, and peptidoglycans may not be compatible

with human tissue ingrowth and may lead to increased plug rejection. This has not been demonstrated to be the case with the materials currently available on the market, however.

Cook Surgisis Plug

The Cook Surgisis plug was released in 2006 and was the first commercially available fistula plug. This plug consists of a lyophilized porcine small bowel submucosal matrix. It consists of 90 % collagen (primarily types I, III, and V). It has been demonstrated to be resistant to infection and to be resistant to giant cell foreign body reactions, both of which could potentially lead to plug failure. The plug is completely degraded by host tissues over a period of 3 months [19, 20].

Initial studies demonstrated an 83 % cure rate at 12 months with minimal morbidity or impact on continence [21]. Despite promising initial results, further studies failed to demonstrate the same efficacy with cure rates ranging from 24 to 78 % at 6 months [13, 22–24]. However, because this plug has been on the market the longest time, it is the plug for which most data is available.

Multiple prospective, blinded studies have been carried out comparing the Surgisis plug to ERAF, and results have been disappointing. Van Kopernen et al. demonstrated in 60 patients a recurrence rate of 71 % in the plug arm with 52 % recurrence in patients receiving ERAF and there were no differences in preoperative or postoperative continence or soiling between the groups, nor were there any differences in quality of life [23]. These results however were not significant due to study size. Ortiz et al. however were forced to stop their trial early when 12 of the 15 patients accrued in the plug group recurred early while only demonstrating two recurrences in 16 patients treated with ERAF. These results were called into question, however, as it was felt that technical errors led to an unacceptably high extrusion rate which led to early plug failures [22].

Our own personal experience with the Surgisis plug has been mixed. We observed that over time the efficacy of plug closure decreased from 72.7 % closure rate at 8 weeks to 62.4 % at 12 weeks to 54.6 % at a median of 6.5 months with Crohn's disease patients doing significantly worse than non-Crohn's (26.6 % vs. 66.7 % closure rate long term). Also, interestingly, patients who received multiple plugs did significantly worse than those treated with a single plug (12.5 % vs. 63.9 %) indicating that multiple attempts at placement of a fistula plug is unlikely to prove effective [25]. Long-term follow-up of that same cohort demonstrated a 51 % closure rate at 24 months indicating that those fistulae that stayed closed at 6 months were likely to remain closed over the long term.

More recently, the Surgisis material has been employed in conjuncture with the LIFT procedure which has been termed the BioLIFT. In this procedure, a sheet of Surgisis is placed in the intersphincteric space following fistula tract ligation. Initial studies demonstrated a 94 % cure rate at 15 months with minimal postoperative morbidity [26]. Surgisis sheets have also been used as interposition material after rectovaginal fistula closure with success rates between 66 and 81% at 12 months [27, 28].

Covidien Permacol

Permacol is composed of cross-linked acellular dermal matrix (ADM) of porcine origin. It is approximately 95 % type I collagen with a small amount of elastin as well as type III collagen. It is manufactured in two constructs, a porous sheet and milled fibers in saline suspension [29, 30]. The fibrous suspension has been hypothesized to be more effective at filling irregular fistula tracts after injection, potentially improving cure rates. This hypothesis was tested, comparing Permacol strips sutured into fistula tracts to the milled fibers, suspended in fibrin glue, injected into the tracts. At a median of two and a half years the suspension group achieved an 80 % cure rate vs. 54 % in the Permacol sheet group, however these results were not statistically significant [31].

Other Xenografted Acellular Dermal Matrices

A variety of other porcine and bovine ADMs are being manufactured worldwide and there are several anecdotal reports of their use in the treatment of anal fistulae. One example of the work being done with these various ADMs come from a study from China where they examined the J-I type ADM which is manufactured similarly to the Surgisis plug. This prospective randomized trial demonstrated a significant improvement in fistula healing using this plug when compared to ERAF in 90 patients (82 % vs. 64 %) with no difference in incontinence or anal deformity rates between the two groups [32]. No individual ADM has yet to distinguish itself as superior to the rest and the vast majority of the available data is from individual case reports.

Allograft

Several types of allografts have been harvested from cadavers and employed as fistula plugs. Because they are composed of a variety of tissue types, including collagens, fibrin, elastin, and glycosaminoglycans [33, 34], it was initially thought that they would lead to improved fistula closure rates when compared to xenografted tissue. While this has not been demonstrated unequivocally, allografted tissues have demonstrated

acceptable closure rates with minimal incontinence. These grafts all lack any cellular component which could potentially lead to rejection.

The primary drawback associated with allograft use stems from the scarcity of the product due to the manner in which is harvested. Cadaveric tissue is donated by the deceased leading to a much greater cost when compared to easily acquired xenograft sources. Interestingly, studies have also demonstrated no difference in biocompatibility between porcine and human ADMs [35].

Ruinuo Human Acellular Dermal Matrix

The ADM plug is an allogenic tissue graft derived from donated human skin. This plug consists of collagen, elastin, and glucosaminoglycans. Cones are formed from thin sheets of ADM, pulled through the fistula tract, and sutured into the internal sphincter.

One of the larger studies on any type of plug use comes from China and employs this ADM. Retrospective analysis of a prospective database demonstrated that 54.4 % of 114 patients achieved fistula closure at 6 months with only two reported cases on incontinence at this time. Factors associated with plug success included nonsmoking, longer duration of fistula, anterior location of fistula, short length of fistula, and procedure performed by an "expert" surgeon [36].

Recently, a variant of the LIFT procedure called the "LIFT-Plug" was also described using this ADM. The authors described closure of the internal opening of the fistula coupled with intrasphincteric ligation of the tract and placement of an ADM plug into the remaining external component of the tract. Healing rate for this procedure was reported at 95 % at a median of 14 months with a mean time to resolution of approximately 2 weeks, however it is unclear from this preliminary study whether this procedure is better than the LIFT alone as the authors did not compare the two [37].

Lifecell Alloderm

Alloderm is the most widely available ADM in the United States. No large studies have been performed to date employing Alloderm in closing complex anal fistulae, however several case reports have been published in which Alloderm sheets were used interpositionally in a layered closure in treating rectovaginal fistulae with good short-term results [38, 39]. Due to its similarity to other allograft ADMs, Alloderm should be used similarly when it is the only available ADM and an allograft is desired.

Considerations

Crohn's Disease

Managing perineal Crohn's disease can be very complicated, requiring multiple interventions, and often exhausting the armamentarium of a skilled colorectal surgeon. By definition all of these fistulae are complex and each proves a unique challenge in treating. Few studies have looked specifically at patients with Crohn's, however, a recent meta-analysis pooled similarly matched patients with and without Crohn's and demonstrated similar fistula closure rates in both groups with usage of the Surgisis plug (54.8 % vs. 54.3 %) with minimal impact on fecal continence between the groups [15]. This study was, however, limited by the number of Crohn's patients included, with only 42 of 530 total patients having Crohn's disease from 20 separate studies.

Head-to-Head Comparisons

Rarely have fistula plugs been compared head to head, but in one recent study, Buchberg et al. retrospectively analyzed their results from their use of both the Surgisis plug and the non-biologic, absorbable Gore Bio-A plug. They demonstrated that in their hands 6 of 11 patients treated with the Gore plug had successful closure of their fistulae while only 2 of 16 patients treated with the Surgisis plug achieved this outcome [40]. This ultimately demonstrates the limitations of the data demonstrated to this point as this study was very small, retrospective, and poor overall closure rates were demonstrated in both arms. More prospective head-to-head comparisons are needed to determine which plugs may be the most efficacious; however there has always been resistance by industry to put forth these studies.

Conclusions

Despite mixed results thus far, the use of biologic agents, such as fibrin glue or fistula plugs have demonstrated some success. While it is unlikely that one of the currently available plugs is vastly better than any other, further studies need to be performed, including head-to-head studies to identify superiority. This is a constantly evolving field and new plugs and new biologic agents are becoming available for use on a regular basis.

Despite the variability of the results, there is currently a place in the colorectal surgeon's armamentarium for these devices as they do offer another method to encourage fistula closure with minimal morbidity. That place is likely in the

patient who has a complex fistula or who has failed multiple other attempts at fistula closure. This is a therapy in its infancy and many more studies, particularly prospective and randomized studies, need to be carried out to truly demonstrate the efficacy and long-term results achievable by each agent.

Summary

1. Numerous biologic agents have been employed in the closure of complex anal fistulae, including fibrin glue, allograft plugs, and xenograft plugs with mixed results.
2. To achieve effective fistula closure with the use of biologic agents, the fistula tract must first be drained with a seton. The procedure-involving placement of the plug must then include closure of the internal opening and ligation of the tract.
3. The ideal fistula plug should be composed of material, which allows good tissue and vascular ingrowth while being resistant to infection and extrusion.
4. While there is some promising data to date, most data is mixed. Prospective and head-to-head studies are necessary to determine optimal material selection for use in fistula plugs.
5. Fistula plugs are a viable option in recurrent and hard-to-treat complex anal fistulae.

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