

New innovations in anal fistula surgery

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ABSTRACT

The management of anal fistula remains a source of frustration for patients and surgeons alike. The continued challenge posed by this condition has led to considerable innovation and investigation with the ongoing refinement of surgical techniques, the development of new technologies, and the application of advanced biomaterials. This article will describe recent, ongoing, and future developments in the treatment of anal fistula.

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Introduction

Anal fistula, also known as fistula-in-ano, continues to pose considerable problems to patients and clinicians alike. The estimated incidence of anal fistula is approximately 1–2 per 10,000 per year and a significant number of individuals presenting with an initial anorectal abscess will ultimately develop an anal fistula.^{1–3} Fistulas can also develop in the setting of inflammatory bowel disease.

The Parks system, initially developed in 1976, remains widely used to classify anal fistula based on involvement of the sphincter complex.⁴ Fistulas may be classified as subcutaneous, intersphincteric, trans-sphincteric, supra-sphincteric, and extra-sphincteric. Alternatively, fistulas can be described more broadly as either “simple” or “complex”.⁵ Simple fistulas are subcutaneous, intersphincteric, or low trans-sphincteric (involving less than one third of the anal sphincter complex) with a single internal opening and no abscesses or secondary tracts. Fistulas are considered complex if they are high trans-sphincteric, supra-sphincteric, extra-sphincteric, have multiple external openings, or evidence of either a perianal abscess or rectovaginal fistula.

The principles underlying the surgical management of anal fistula are: 1) to eliminate infection, 2) to eradicate the fistula tract, and 3) to preserve continence. Achieving all of these sometimes challenging goals and preventing recurrence while preserving sphincter function requires thoughtful decision-making about the choice of the most appropriate treatment option for an individual patient. Fistulotomy, or “laying open” of the fistula tract, remains the standard treatment for simple fistulas with high rates of success and low rates of post-operative incontinence.⁶ Fistulotomy for complex fistulas poses a higher risk of damage to the sphincter mechanism with resultant incontinence and is thus not routinely recommended. In 2007, the

Association of Coloproctology of Great Britain and Ireland (ACPGBI) published a position statement regarding the treatment of anal fistula which identified seton placement, advancement flaps, fistula plugs, and fibrin glue as recommended treatment options for complex fistulas.⁷ The subsequent decade has seen significant advancement in nearly every dimension of anal fistula treatment. Novel operations, such as the Ligation of the Intersphincteric Fistula Tract (LIFT), have been developed and refined. Advances in technology have facilitated the adoption of video-assisted surgery (VAAFT), laser-based procedures, and other novel devices. Recent developments in stem cell technology and other biomaterials have been translated into clinical practice as new devices and new procedures. This review will provide an overview of these emerging options for the management of this still-difficult clinical problem.

Modifications of existing operations

The diverse range of procedures that have been developed for the management of complex anal fistula serves as a testament to the enduring challenge posed by this condition. The use of setons dates back to antiquity. Sphincter-sparing advancement flaps were first reported in the early 20th century.⁸ The LIFT procedure was initially developed and disseminated in the early 21st century. In the case of each of these procedures, the reported success and recurrence rates are highly variable.⁹ As such, while all of these procedures are still in use today, each has undergone iterative modifications to incorporate new techniques and technologies. This section will describe some of the more recently-reported modifications to these established procedures.

Seton placement

The seton is a versatile tool for the management of complex anal fistula and continues to be a mainstay of treatment. Broadly speaking

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setons can be described as “draining” or “cutting”. Draining setons are placed loosely and used to establish long-term drainage of a fistula, either as definitive management or to facilitate a staged procedure. Cutting setons are placed tightly and used to divide the sphincter muscle in the case of trans-sphincteric fistulas. A wide array of readily-available materials have been traditionally and continue to be used for this purpose, including vessel loops and sutures.¹⁰ This trend of using readily-available materials has continued with recent reports of the use of self-locking plastic cable ties as cutting setons.¹¹ In a 2011 study conducted in Pakistan, 79 patients with complex fistulas were managed with cable tie seton placement. Complete healing was achieved in a mean of 11 weeks with no reported incontinence and a 5% recurrence rate at one year.¹²

In contrast to the repurposing of existing materials, the Comfort Drain (Agency for Medical Innovations, Feldkirch, Austria) was specifically designed to avoid local irritation and discomfort caused by the knots used to secure traditional setons. The device is a flexible drain with a knot-free closure system that creates a fully-closed ring when the two ends of the drain are connected (Fig. 1). An initial report of 5 patients treated with the Comfort Drain found that no patients had complications related to drain placement and 80% remained in place over an indeterminate follow-up period.¹³ In a follow-up study of 44 patients undergoing draining seton placement in preparation for definitive surgery or as definitive management of Crohn's related anal fistula, half were treated with the Comfort Drain and half with traditional setons. The Comfort Drain was associated with improvements in mental health and perianal comfort with no differences in complication rates or continence.¹⁴ Importantly, patients receiving the Comfort Drain had setons placed for approximately half the duration of traditional setons (185 vs. 378 days). However, the Comfort Drain more commonly required replacement due to a failure of the closure mechanism in early iterations of the device.

The use of separate irrigation catheters as an adjunct to draining setons has also recently been reported. For fistulas associated with large pararectal cavities a draining seton itself may be inadequate to ensure drainage of both the primary fistula tract and secondary cavities. A 2018 study from Sri Lanka described the placement of irrigation tubes into pararectal cavities through separate perianal stab incisions. Irrigation was performed three times per day until sonographic evidence of cavity resolution at which point conventional surgical treatment was performed.¹⁵ Complete healing of the fistula was seen in 28 of 32 patients with no recurrences in the healed group over a median follow-up of 6 months.

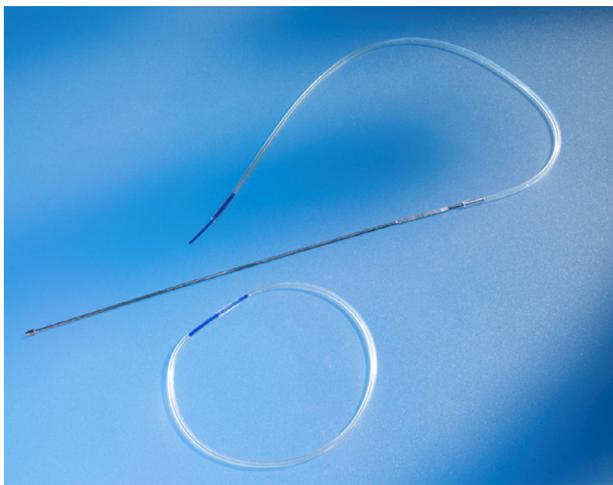


Fig. 1. The Comfort Drain (AMI, Feldkirch, Austria). The device is inserted over a probe and then made into a closed loop with a knot-free closure device. Reproduced with permission from Riss S et al. The Comfort Drain: a new device for treating complex anal fistula. *Tech Coloproctol.* 2014;18(11):1133–1135.

Ligation of intersphincteric fistula tract

The LIFT procedure was first reported in 2007 by Rojasasakul et al. and has subsequently been described in detail in previous editions of this journal.^{16,17} Briefly, this procedure entails the identification and dissection of the fistula tract in the intersphincteric plane using a curvilinear incision made in the intersphincteric groove. The intersphincteric tract is then divided, suture-ligated, and debrided to remove infected tissue followed by closure of any external sphincter defects. Although the initially reported success rates for this procedure were as high as 94%, healing rates in subsequent studies have been more variable. As such, in the decade since its first description several modifications to the original LIFT procedure have been reported. These include alternative surgical approaches to dissect the intersphincteric fistula tract and the use of biologic devices as adjuncts to surgical ligation and debridement.

First reported in 2008, the Bio-LIFT utilizes a bioprosthetic graft (a collagen mesh such as Surgisis® Biodesign, Cook Surgical Inc, Bloomington, Indiana, USA) placed into the intersphincteric groove following tract ligation to reinforce the repair. Although this requires a more extensive dissection of the intersphincteric space the placement of the graft ensures separation of the two ends of the remaining fistula and, in theory, provides a mechanical barrier to recurrence. The first series describing this technique reported a primary success rate of 94% in 31 patients with a minimum of 12 months follow-up.¹⁸ A subsequent study exploring the use of Bio-LIFT for the management of recurrent fistulas following prior intervention demonstrated a more modest 68.8% success rate in 13 patients with no impairment of continence as measured subjectively or via manometry after the operation.¹⁹ This success rate is similar to the 63% reported in a 2013 study documenting the use of both LIFT and Bio-LIFT for management of complex fistulas, although the Bio-LIFT-specific success rates were not provided.²⁰ Importantly, none of these studies reported impairment of continence in any of the included patients despite the more extensive dissection in the intersphincteric space required for graft placement and the resultant theoretical increased risk for damage to the sphincters compared to traditional LIFT.

The LIFT-Plug is a technique that utilizes a bioprosthetic graft as a plug in the external component of the residual fistula tract following tract ligation and excision, unlike the Bio-LIFT which interposes the graft between the remaining sides of the fistula tract (Fig. 2). First described in 2012 in a cohort of 21 patients, this technique utilizing a human acellular dermal matrix (Qingyuanweiye Inc, Beijing, China) was demonstrated to have a 95% primary success rate with no

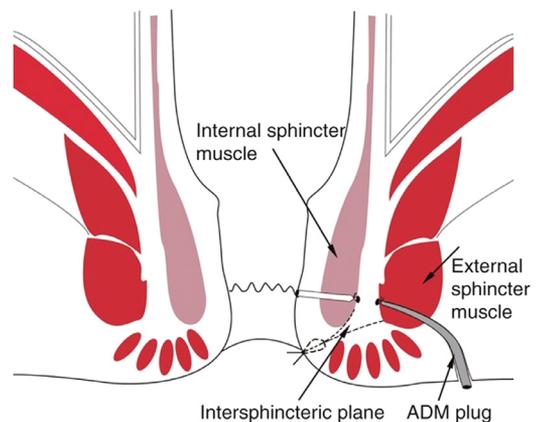


Fig. 2. Schematic demonstrating the concept of the ligation of the intersphincteric fistula tract (LIFT)-plug procedure. Reproduced with permission from Han JG, Yi BQ, Wang ZJ, et al. Ligation of the intersphincteric fistula tract plus a bioprosthetic anal fistula plug (LIFT-Plug): a new technique for fistula-in-ano. *Colorectal Dis.* 2013;15(5):582–586.

resultant fecal incontinence and one case of gas incontinence reported.²¹ This promising early data prompted a randomized control trial in which 235 patients were randomized to undergo either LIFT or LIFT-Plug using porcine small intestine submucosal extracellular matrix (Shaanxi Reshine Biotech Co. Ltd., Shaanxi, China).²² This demonstrated higher rates of primary success with the LIFT-Plug (94.0% vs. 83.9%) with no difference in recurrence or incontinence between groups over 6 months of follow-up. The durability of this repair was demonstrated in a retrospective study of the long-term outcomes of a cohort of 78 patients undergoing LIFT-Plug. Over a median of 30 months of follow-up, 96.2% of fistulas were successfully healed primarily and only 3% of patients sustained a recurrence.²³

Multiple alternative approaches to isolating the intersphincteric fistula tract have been reported. A 2015 study from the Swedish Medical Center described fully unroofing fistulas from their internal opening to the intersphincteric groove with division of the internal sphincter and ligation of the remaining tract at the level of the external sphincter. Amongst 66 patients undergoing this modified LIFT, a cure rate of 71.4% was achieved with no persistent fecal incontinence over 21 weeks of median follow-up.²⁴ Similar success rates were reported with a lateral approach to the LIFT which avoids a separate incision in the intersphincteric groove by circumferentially dissecting the entire fistula tract from the external opening to the intersphincteric plane. The fistula tract is ligated proximally through the incision created by this circumferential dissection and excised distally without division of the external sphincter muscle. The first description of this lateral approach to the LIFT reported an 80% success rate in 10 patients with no incontinence over a median of 7 months of follow-up. Subsequently a study of 28 patients undergoing this procedure reported a 75% success rate with no incontinence over a median follow-up of 16 months.^{25,26}

Novel procedures

The persistent difficulties in treating complex anal fistulas continues to drive the development of novel techniques, the creation of new devices, and the adaptation of existing technologies to this problem. This section will detail several such innovations, including endoscopic and laser-based procedures.

Laser ablation

Although the use of lasers for the treatment of anal fistulas was first reported in the 1980s this technology was not significantly explored until the more recent development of radial emitting laser probes such as FiLaC™ (Biolitec, Jena, Germany).²⁷ The first reported use of this technology for the treatment of anal fistula was in 2011. Fistula curettage and advancement flap closure and ablation of the fistula tract by continuous retraction of the FiLaC™ laser probe from the internal to external openings. Over a median of 7.4 months of follow-up, this treatment was successful in 81.8% of 11 patients included with only one case of incontinence successfully managed with rubber band ligation of hypertrophied mucosa.²⁸ 5-year follow-up data from this same institution demonstrated a 64.1% primary success rate with this combination of laser ablation and advancement flap closure of the internal opening.²⁹

The use of laser ablation as a stand-alone therapy has also been investigated. Giamundo et al. reported a 71.4% primary success rate and 5.8% recurrence rate in 35 patients over a median follow-up of 20 months.³⁰ Some of the patients in this pilot study underwent laser treatment at a wavelength of 980 nanometers (nm) while others underwent treatment at the more widely-used 1470 nm. A subsequent study from this group re-demonstrated this efficacy with a primary success rate of 71.1% over a median follow-up of 30 months amongst 45 patients treated with laser ablation at 1470 nm.³¹ Two more recent studies have demonstrated a more modest healing rate

of 40%.^{32,33} Indeed, evidence from a 2018 study by Lauretta et al. that the length of the fistula tract is a major predictor of successful laser ablation, with fistulas greater than 30 mm in length having a 16.6% healing rate compared with 58.3% in shorter fistulas.

Photodynamic ablation

Photodynamic ablation relies upon the use of a photosensitizing compound, such as 5-aminolevulinic acid (ALA) to induce cell damage following stimulation with light. A 2017 study from Spain described the use of photodynamic therapy in 10 patients with anal fistulas.³⁴ Each patient underwent suture closure of an identified fistula tract and instillation of 2% ALA into the sealed tract. After a two-hour incubation period the tract was then ablated with placement and continuous removal of a fiber emitting light at 630 nm. This produced primary success in eight patients with three developing recurrence during a median follow-up of 14.9 months.

Video-assisted anal fistula treatment

Video-assisted anal fistula treatment (VAAFT) utilizes a fistuloscope (Karl Storz, Tuttlingen, Germany) with an 8° angled eyepiece to interrogate the entirety of the fistula tract and eradicate it under direct visualization. The VAAFT procedure is divided into two phases: a diagnostic phase and a therapeutic phase. In the diagnostic phase the fistuloscope is inserted through the external opening and after a solution of glycine and mannitol is used to open the tract, the primary tract and any secondary extensions are identified. The therapeutic phase involves the destruction of the fistula tract by fulguration and debridement from the inside under direct visualization, irrigation of the tract to remove any debris, and the closure of the internal opening. Importantly, the specific closure utilized for the internal openings is variable between surgeons and studies. In some cases, including the initial report of this technique, sealants such as cyanoacrylate or fibrin glue are applied into the fistula tract.³⁵

The first report of this technique described 98 patients treated with VAAFT and demonstrated a 73.5% primary healing rate within 2–3 months and with no self-reported worsening of continence.³⁶ A recent systematic review and meta-analysis demonstrated a similar overall success rate of 76.0% in eight studies including 786 patients with individual success rates varying from 52.5% to 92.5%.³⁷ The reported overall rate of minor complications was 16.2% with no major complications and no long-term impairment of continence reported. Another recent systematic review and meta-analysis including studies of patients with Crohn's-associated fistulas, reported a recurrence rate of 14.2% over a median follow-up of 9 months with the additional finding that the method of closing the internal opening, specifically the use of an advancement flap instead of stapling or sutures, was associated with fistula recurrence.³⁵

Fistula clips

The OTSC® Proctology system (Ovesco AG, Tuebingen, Germany) allows for the transanal deployment of a nitinol clip to compress the internal opening of a fistula tract. This clip can be removed following resolution of the fistula or earlier if necessary due to patient discomfort or clip migration. In 2016 Prosst et al. published their experience with 100 consecutive cases using the OTSC® system on both primary and recurrent fistulas, reporting a 65% overall primary success rate at 6 months after surgery, as defined by resolution of fistula signs and symptoms.³⁸ Importantly this overall success rate was driven in large part by a 79% success rate as initial treatment compared with a 26% success rate when used as salvage therapy. In 14 cases the nitinol clip was explanted, either due to failed healing, discomfort, dislocation, or patient preference. A similar success rate of 60% was reported in a 2018 case series of ten patients.³⁹ Although a recent small randomized

control trial in which patients received either OTSC® application or fistulectomy for trans-sphincteric fistulas reported a 93.3% success rate amongst 15 patients undergoing clip application, the majority of the data suggest that this procedure has a modest success rate as a first-line therapy for anal fistula.⁴⁰

BioHealx

BioHealx (Signum Surgical, Galway, Ireland) is a novel device, yet to be tested in humans, that delivers an absorbable coil-shaped implant around the internal opening of an anal fistula in combination with an absorbable drain into the rest of the fistula tract.⁴¹ The implant, which provides circumferential compression of the internal opening of the fistula tract and is intended to preserve sphincter function, is delivered using a disposable delivery device that inserts the implant to the correct depth automatically limiting user-to-user variation (Fig. 3). Clinical testing of this device is expected to begin in human patients in 2019.

Biologic agents and biomaterials

Although the use of biologic agents and biomaterials in anal fistula is not new, with the first use of fibrin glue being reported in the 1980s, this remains a robust area of investigation and development. Biologic agents are particularly attractive for this purpose given the persistent inflammation and failure of healing that is central to the pathophysiology of anal fistulas as well as the high potential for recurrent infection. Although many specific agents, including several commercially-available products, have been studied they can be broadly classified into the categories of acellular matrices, stem cell therapies, and plasma or growth factor treatments.

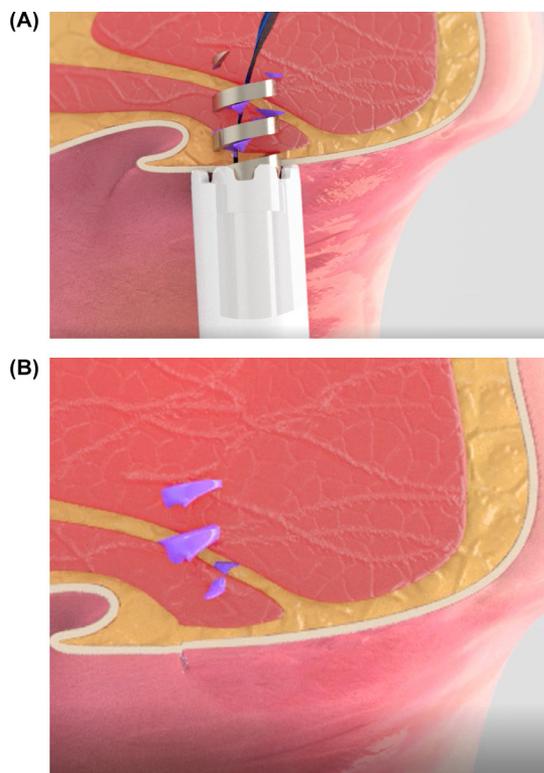


Fig. 3. BioHealx (Signum Surgical, Galway, Ireland). A. The disposable delivery device places a bioabsorbable implant around the internal opening of the fistula. B. The implant and drain both absorb over time. Reproduced with permission of Signum Surgical (Galway, Ireland).

Acellular matrices

Acellular matrices facilitate wound healing by providing a biocompatible scaffold that encourages the ingrowth of native tissues. These have been used in a variety of clinical applications requiring the management of chronic wounds, including anal fistula. Several products are currently commercially available. These are available either as sheets of material that can be modified by the surgeon for a specific purpose or as fistula plugs which can be fixed within the tract and can be used with or without additional concurrent procedures. These products can be further classified by the source from which they are derived. Allogeneic products are derived from human donors whereas xenogeneic products are derived from non-human animals, often porcine or bovine sources.⁴²

Available human allogeneic matrices are derived from the dermis of cadaveric skin and are composed of multiple extracellular matrix proteins including collagen, elastin, and glycosaminoglycans. Several such products are commercially available and were discussed previously in this article. A 2011 study from China utilizing an acellular dermal matrix, fashioned into a plug and suture-fixed at the internal opening, found a 54.4% primary success rate in 114 patients followed for at least 6 months.⁴³ Despite these promising results preclinical comparisons of allogeneic and xenogeneic matrices have not shown a difference in either the histology or biocompatibility of these products.⁴⁴

Xenogeneic products, unlike allogeneic materials, are not limited by the scarcity of human donors and can be made from a number of different tissues in multiple different species. The use of products derived from porcine submucosa, bovine dermis, and porcine urinary bladder have been reported with similar efficacy and safety profiles.^{45–47} The Surgisis bioprosthesis device, discussed earlier in this article, is derived from porcine submucosa and has been studied as both a stand-alone anal fistula plug and as an adjunct to the LIFT procedure in both sheet (Bio-LIFT) and plug (LIFT-plug) forms.⁴⁸

Permacol® (Medtronic, Dublin, Ireland), derived from cross-linked porcine dermis, differs from other bioprosthesis devices in that it is available as both an implantable sheet and as a suspension of milled fibers. The suspension form of this product offers the theoretical benefit of more complete filling of a fistula tract and improved healing. This was borne out by an initial study in 29 patients demonstrating healing in 80% of patients treated with a paste of the Permacol® suspension and fibrin glue compared to 53.8% of those treated with the solid implant.⁴⁹ A 2012 study described the use of Permacol paste in combination with an advancement flap procedure and reported an overall healing rate of 75.0% in 24 patients, including several patients with IBD-associated fistulas.⁵⁰ Subsequently a multicenter prospective observational study, the MASERATI 100 study, was conducted in Europe to evaluate the efficacy of Permacol® paste. A total of 100 patients underwent injection of Permacol® paste into fistula tracts and suture-closure of the internal opening of the fistula tract with follow-up for 12 months.⁵¹ This study demonstrated a 56.7% healing rate at 6 months that was durable to 12 months in 53.5% of all patients and with 73.0% patient satisfaction with the procedure.⁵² These findings were re-demonstrated in a subsequent prospective study of 30 patients managed with Permacol paste injection, including several patients with fistulas due to Crohn's disease, where a 57% overall healing rate was noted at 6 months.⁵³

Stem cell therapies

The use of autogenous stem cells to facilitate healing of anal fistulas has become an increasing area of focus. This is particularly true in the setting of fistulizing Crohn's disease where favorable results have been obtained following treatment with bone-marrow derived mesenchymal stem cells.⁵⁴ The majority of the work in this field has focused instead on the use of autologous adipose-derived stem cells

(ASCs) which are easily harvested through liposuction or biopsy of subcutaneous fat and can be extracted through the stromal vascular fraction and expanded in vitro as needed.⁵⁵ The first randomized control trial utilizing ASCs to treat anal fistulas was conducted on 49 patients, 14 of whom had Crohn's disease. Patients underwent either an injection of ASCs into the fistula tract followed tract closure with fibrin glue or tract closure with fibrin glue alone.⁵⁶ Both groups underwent suture closure of the internal fistula opening. Although initial healing rates of 71% and 16% were reported for ASC-treated and fibrin glue only groups respectively eight weeks following the procedure follow-up data found that this response was of limited durability despite a favorable safety profile.⁵⁷ A subsequent phase III trial comparing patients treated with ASCs alone, fibrin glue alone, or both ASCs and fibrin glue demonstrated more modest healing rates of 26.6%, 38.3%, and 15.6% respectively 12 weeks after treatment.⁵⁸ Ultimately there was found to be no significant difference in primary healing between groups at 24–26 weeks or one year following the procedure. This protocol has also been used in the management of recurrent fistulas, including fistulas associated with Crohn's disease, with a durable one-year healing rate of 60% being reported amongst ten patients.⁵⁹

Additional studies utilizing variations in ASC processing and administration have echoed the results of the initial studies in this field, with reported success rates between 69.2% and 71.4%.^{60,61} A recent phase I trial reported the use of a commercially-available anal fistula plug loaded with ASCs. Amongst 15 patients treated with this hybrid technique only 20% achieved complete clinic healing at 6 months although an additional 53.3% reported significantly improved symptoms following the procedure.⁶² Ultimately, although this strategy has demonstrated efficacy and merits further investigation, the need for a separate staged procedure for ASC isolation and enrichment remains a limitation of this approach.

Platelet-rich plasma and growth factors

Another area of recent focus has been on the use of either platelet-rich plasma or recombinant growth factors as a treatment for anal fistula. A 2010 study from Japan reported the use of basic fibroblast growth factor spray (bFGF, Trafermin, Kaken Co Ltd, Tokyo, Japan) as a stand-alone treatment for anal fistula in nine pediatric patients (mean age 5.1 months). Primary healing was noted in seven of nine patients with a second treatment with bFGF spray providing resolution of the fistula in the remaining two cases.⁶³ Despite these promising early results, no additional studies using this treatment or extending the use of this to adult populations have been reported.

Platelets are known to be a significant source of multiple growth factors and play a central role in the early stages of wound healing. In contrast to autologous ASCs, platelet-rich plasma can be readily isolated from the peripheral circulation and prepared by centrifugation to increase the platelet concentration. This ease of preparation has led to increasing focus on this as a potential therapeutic modality for anal fistulas. A 2011 study from the Netherlands reported on a group of 10 patients each of whom received local advancement flaps with concurrent intra-tract administration of autologous platelet-rich plasma, activated by thrombin to induce platelet degranulation.⁶⁴ Over a median follow-up of 26 months only one patient developed a recurrent fistula. A subsequent study utilizing a combination of advancement flap and thrombin-activated PRP in 25 patients with anal fistulas reported a similar 17% recurrence rate over a median of 27 months of follow-up.⁶⁵

More recently a phase II clinical trial was conducted in Spain utilizing a combination of suture-closure of the internal fistula opening with injection of platelet rich plasma into the internal opening and tract wall with subsequent sealing of the fistula tract using platelet-poor plasma through the external opening.⁶⁶ Amongst 36 patients included in this study 44.4% were symptom-free at one year with 33.3% achieving complete healing. Although the healing rates seen in

this study were significantly lower than early trials had been this did provide evidence that the use of platelet rich plasma is safe despite variation in surgical techniques.

Conclusions

Anal fistula remains a challenging clinical problem as well as an area of ongoing innovation across multiple domains. Several recent innovations, including novel biomaterials, the use of autologous stem cells, and laser ablation or video-assisted fistula treatment, have shown promising early results but all require further study before broad application can be recommended. It can be anticipated that this will continue to be an active area of investigation and that new techniques and technologies will continue to be developed and refined.

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