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Research Paper

Randomized clinical trial comparing a small intestinal submucosa anal fistula plug to advancement flap for the repair of complex anal fistulas

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ABSTRACT

Introduction: Current treatments for complex anal fistulas are associated with substantial variability in healing, recurrence, and incontinence rates. This study compared the effectiveness and safety of the Biodesign anal fistula plug to the anorectal advancement flap in patients with transsphincteric anal fistulas.

Methods: A total of 82 patients attending coloproctology clinics in Germany were enrolled in this prospective, non-blinded, multicenter trial and randomized to the advancement flap or the plug. Study endpoints included healing rates, health-related quality of life, continence-related quality of life, pain, and safety at the time of surgery and 2 weeks, 3, 6, and 12 months following surgery.

Results: Follow-up at 12 months ($n = 82$) revealed healing rates of 67% for the plug and 76% for the flap ($p = 0.56$), with the noninferiority analysis confirming equivalence ($p = 0.47$). Fecal continence rates and the overall safety profile were similar between the two interventions. There were trends for lower pain scores at the time of surgery and 2 weeks postoperatively, and higher overall quality of life in the plug group. The surgical time required for the plug procedure was, on average, 34% shorter than the time required for the advancement flap. Regardless of treatment group, higher healing rates were observed in patients with a higher body mass index ($p = 0.03$), shorter fistula length ($p = 0.01$), and fewer previous colorectal surgeries ($p < 0.001$), while prior colorectal surgeries were associated with lower healing rates ($p = 0.026$).

Conclusions: The plug and advancement flap were equally effective treatments for complex anorectal fistula, with the plug associated with significantly less surgical time and a favorable safety profile.

Clinical trial registration: NCT00545441.

1. Introduction

Complex anal fistulas involve the upper two-thirds of the sphincter complex, affect significant portions of the sphincter musculature, have multiple tracts, and may be associated with radiation or inflammatory bowel disease [1,2]. Long-term healing and maintaining continence are the primary goals when treating complex anal fistulas, with one often achieved at the cost of the other [3–5].

Current treatments include seton placement; closure with fibrin glue; fistula plug insertion; closure with endorectal or dermal advancement flaps; ligation of the intersphincteric fistula tract; fistula laser closure; video-assisted anal fistula treatment (VAAFT); or treatment with novel biomaterials such as adipose-derived stem cells [2–4,6]. There is substantial variability between these interventions in healing, recurrence, and incontinence risk [2]. While the advancement flap remains a common operation for the treatment of

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complex fistulas [4] with success rates ranging from 60% to 80% [5,7,8], the risk of flatal or fecal incontinence can be significant [5,9].

The risk of incontinence has prompted clinicians to choose sphincter-sparing options such as fibrin glue [10], fistula plugs [11–13], or the LIFT [14] technique to minimize sphincter complex damage. Increasingly, clinicians now recognize that a single technique is unlikely to be appropriate for all patients due to the heterogeneity of fistula pathology and conflicting results [2–4,15].

Biodesign® is a complex, collagen-based extracellular matrix (ECM) material derived from porcine small intestinal submucosa (SIS) that consists of multiple collagen types and ECM components [16]. It provides a complete scaffold that supports new blood vessel growth and promotes cellular differentiation as well as deposition and maturation of host ECM components involved in tissue remodeling. The body gradually incorporates SIS during remodeling, eliminating the need for removal. Furthermore, the tissue-derived nature of the SIS material permits its use in contaminated operative fields, distinguishing it from synthetic materials that are contraindicated for use in contaminated settings [17].

Since its introduction in 2005, the Biodesign Anal Fistula Plug (Cook Medical, Bloomington, IN, USA) has undergone extensive clinical evaluation, with reported success rates ranging from 14% [18] to 87% [11,12,18,19], plug extrusion rates of 10%–20% [20], and postoperative sepsis affecting up to 29% of patients [21]. Recent systematic reviews and meta-analyses suggest that success rates for the plug range between 50% and 60% with low overall complications [1,20,22].

This prospective, randomized, multi-center clinical trial compared the effectiveness and safety of the AFP to the anorectal advancement flap for the treatment of primary transsphincteric, suprasphincteric, or extrasphincteric anal fistulae. Post-hoc analyses examined clinical and demographic predictors of treatment response.

2. Methods

2.1. Study design and patients

This prospective, randomized, open-label, multicenter study was conducted at six clinical centers in Germany. The Ethics Committee of the University of Giessen approved the study, which was performed in full accordance with the international standards of Good Clinical Practice and the ethical principles outlined in the Declaration of Helsinki.

Eligible patients were 18 years or older with primary, persistent anal fistulas eligible for surgical repair. Those presenting with evidence of abscess, infection, or acute inflammation were excluded until the tract matured and the infection resolved. Also excluded were patients with Crohn's disease, ulcerative colitis, human immunodeficiency virus, other disorders of the immune system, collagen disease, and a history of anorectal radiation therapy. Patients with superficial fistulas conventionally treated with fistulotomy or fistulectomy, recurrent fistula tracts, J-pouch fistulas, and those with porcine allergies or religious or cultural objections to the use of pig tissue, also were ineligible.

Patients were serially recruited from the participating surgeons' practices and screened to confirm their eligibility for inclusion by physical exam and endoanal ultrasound (EAUS). All patients provided written informed consent before enrollment and randomization. Randomization was performed immediately before the operation so that the patient did not know prior to surgery their assignment. A computer-generated sequence using a random block size of 4 or 6 patients, blocked on clinical study site, was used to ensure relatively equal assignment of patients across all sites and both treatments. A contract research organization (MED Institute, West Lafayette, IN, USA) coordinated subject randomization, provided data management, and oversaw quality control and data monitoring.

2.2. Operative procedures

Patients in both groups received identical preoperative and postoperative care. A seton or vessel loop was placed in the fistula tract for a minimum of 6 weeks prior to surgery and all patients underwent a preoperative examination to confirm absence of infection. EAUS was performed at the beginning of the operation and was used to confirm the presence of any blind openings or pockets. Bowel preparation was performed according to standard of care at each site, and patients received a single, preoperative dose of cephalosporin and metronidazole.

2.3. Advancement flap technique

The internal fistula opening was excised and mobilization of the mucosa, submucosa, and a small number of muscular fibers from the internal sphincter complex was performed. A rectal flap with a 2–3 cm base was mobilized to completely cover the internal opening. The flap was sutured in the distal anal canal with polyglactin 3-0, the tract was curetted, and the external opening was left open to allow drainage to decrease the risk of fluid accumulation, infection, and abscess.

2.4. AFP insertion technique

The plug was rehydrated in sterile saline for 2–5 min immediately before insertion. The tract was irrigated with hydrogen peroxide and gentle curetting or brushing using the Cook® Fistula Brush until bleeding occurred. Efforts were made not to enlarge the tract diameter. A 2-0 polyglactin suture was secured to the narrow (tail) end of the plug to facilitate insertion. The plug was pulled tail-first into the internal opening until it securely blocked the tract. The plug was sutured deep to the internal sphincter muscle using a figure-of-eight 2-0 polyglactin suture. A small mucosal flap was mobilized to completely cover the plug and bury it within the fistula tract. Excess plug material was excised and the external opening was enlarged slightly to allow drainage, minimizing the risk for infection or abscess development.

2.5. Study withdrawal

Study participation was voluntary and patients could withdraw at any time with no negative impact on their ongoing clinical care. Patients with evidence of continued fistula drainage at the 6-month postoperative visit were withdrawn from the study. Those who declined follow-up examinations, patients treated with the plug in whom the plug dislodged, and those requiring additional surgical or nonsurgical interventions affected the treatment area were also withdrawn.

2.6. Data collection and endpoints

Patient demographic and clinical characteristics were recorded at baseline. Follow-up assessment of healing rates, pain, continence, and quality of life were collected at 2 weeks following surgery and at 3, 6, and 12 months postoperatively.

The primary study endpoint was the rate of fistula healing at the 12-month follow-up visit. Healing was prospectively defined as closure of the external opening with no evidence of abscess, drainage, or pain. Assessment of closure was made at each follow-up visit, with an initial determination of healing made at the 3-month follow-up evaluation. Patients who discontinued study participation due to fistula drainage at 6 months, technical failure, or other reasons were considered failures in the analysis of healing rates.

Secondary endpoints included changes in overall patient-reported quality of life and quality of life correlated with continence at the 3-, 6-, and 12-month assessments. The EuroQual-5D (EQ-5D), including the graduated visual analogue scale (VAS) and five dimensions of health [23] assessed overall quality of life. The Fecal Incontinence Quality of Life (FIQL) [24] evaluated patient-reported quality of life associated with incontinence. The Fecal Incontinence Severity Index (FISI) [25] assessed changes in the severity of fecal incontinence.

Additional secondary endpoints were healing rates at the 6-month evaluation, operating theatre time, and pain. Patients recorded pain on a VAS ranging from 0 to 100, with 0 indicating no pain and 100 the worst pain. Recordings were obtained at baseline, the day of surgery, at discharge, 2 weeks postoperatively, and at each scheduled follow-up visit. Adverse events (AEs) were collected from initiation of the surgical intervention through each patient's final follow-up assessment. Adverse events included in the primary safety endpoint were allergic reaction, infection, assessment of continence, and the need for additional procedures.

2.7. Statistical analysis and power calculations

Historical data provided by the six study sites provided an aggregate success rate of 70% for the plug and 55% for the advancement flap. Sample size calculation was performed using SAS version 9.2 (SAS Institute, Cary, NC). Two groups of 47 patients each were required to demonstrate a 25% difference between the interventions, with $\alpha = 0.05$, $\beta = 0.80$, and a noninferiority margin of 10%. The total enrollment target was 106 patients (53 per group) based on the assumption of a 12% attrition rate.

Descriptive statistics were calculated for all variables, including frequencies, percent responses, and 95% confidence intervals (CI) for categorical variables. Means, standard deviations (SD), and 95% CI were calculated for continuous variables. When calculating descriptive statistics, the maximum sample available for each variable was used.

The 12-month healing rate between groups was compared with an F-test (two-tailed $\alpha = 0.05$). A Z-test of noninferiority of the plug to the advancement flap procedure was performed using a 10% noninferiority bound. Healing rates were compared by baseline demographic, clinical, and fistula characteristics, with an F-test for normally distributed continuous variables, the Wilcoxon signed-rank test for non-normal continuous variables, and Fisher's exact test for categorical data (2-sided $\alpha = 0.05$).

All primary and secondary endpoints were analyzed. Statistical analyses were performed with SAS version 9.4 [26].

3. Results

Between April 2008 and February 2012, 82 patients were randomly assigned to a treatment group. Study enrollment was stopped early due to difficulties in patient recruitment. Forty-three patients were randomized to the plug group and 39 to the advancement flap group (Fig. 1). There were no intra-operative complications. Technical failures occurred in 2 (5.1%) patients in the advancement flap group, with no failures

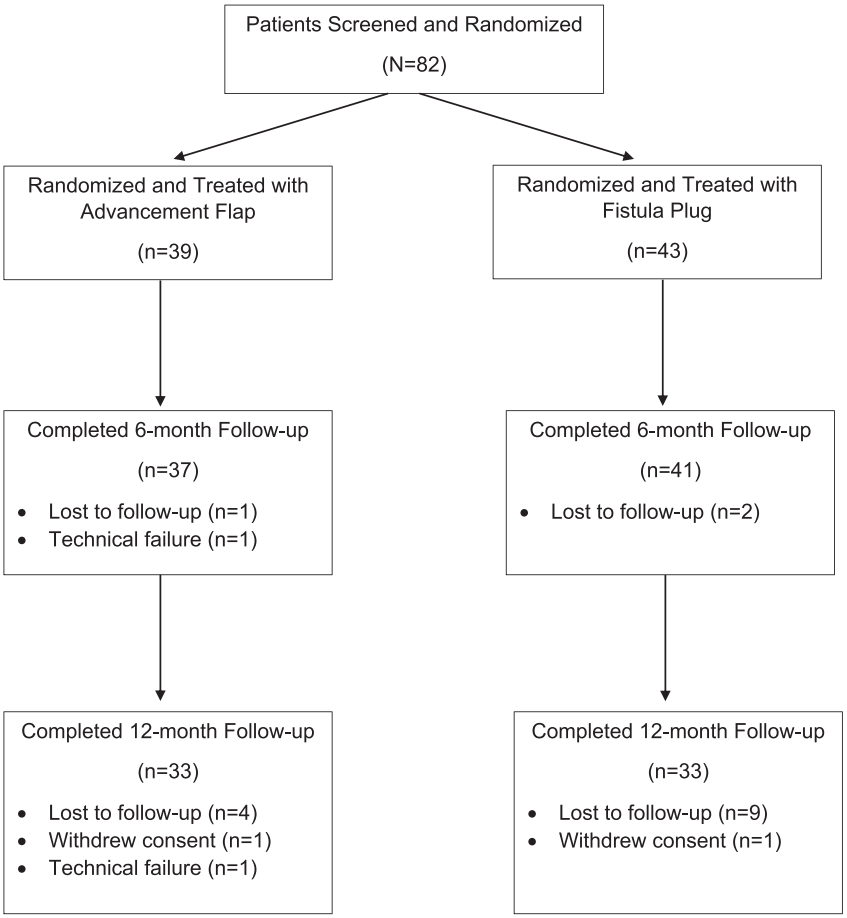

Fig. 1. Flow diagram indicating the disposition of patients from time of screening and randomization at study enrollment to the final 12-month follow-up, including the number of patients who withdrew, were technical failures, or were lost to follow-up.

reported in the plug group. There were no significant differences between the two groups in demographic, clinical, or fistula characteristics (Table 1).

3.1. Healing rate

The 6-month healing rate was not statistically different between the two groups. Similar results were observed at the 12-month assessment, with a healing rate of 75.8% in the advancement flap group and 66.7% in the plug group (Fig. 2). The noninferiority analysis confirmed that the healing rate for patients treated with the plug met the 10% margin of equivalence (P = 0.47), with evidence of equivalence also observed at the 6-month evaluation (P = 0.67).

Patients in the plug group had a significantly shorter duration of surgery at 19.6 (6.3) minutes compared to 29.8 (10.1) minutes for those in the advancement flap group (P < 0.001).

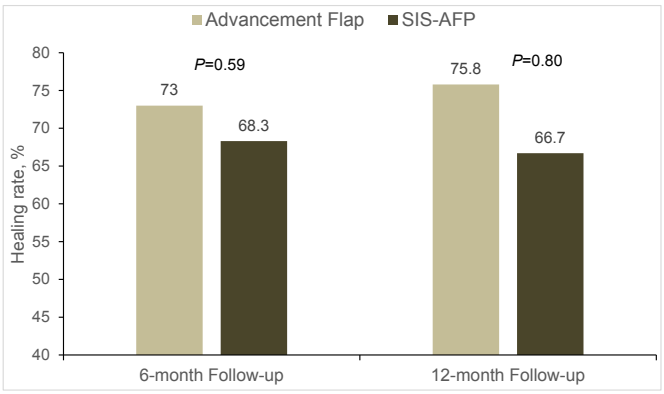

Fig. 2. Bar chart indicating the 6- and 12-month fistula healing rates for patients randomized to the advancement flap and the anal fistula plug groups.

3.2. Predictors of healing

Pooled analyses revealed no differences in healing rates associated with age, sex, tobacco use, or fistula duration at the time of the initial visit. However, healing rates were significantly better for patients with a higher body mass index (BMI) (P = 0.03), shorter fistula length (P = 0.01), and no previous colorectal surgeries (P < 0.001), regardless of treatment group (Table 2). Statistical comparison of healing rates by treatment group and demographic or clinical characteristics revealed no significant differences between men and women, or between patients who were current, former, or never smokers (data not shown).

3.3. Quality of life

Examination of EQ-5D scores during the study revealed no statistically significant differences between treatment groups, although there was a trend towards improved ratings in the plug group (Fig. 3). Ratings were consistently more positive for the five dimensions of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression in the plug group (data not shown). Examination of patient-reported mean scores on the four FIQL scales at baseline and the 3-, 6-, and 12-month assessments revealed no statistically significant differences between groups at any assessment, with all scores ranging from 3.5 to 3.9. There were no

Table 1
Baseline demographic, clinical, and fistula characteristics by treatment group.

Treatment group			
Demographic and clinical characteristics	Advancement flap (n = 39)	Fistula plug (n = 43)	p-value
Age, years			
Mean (SD)	49.5 (13.2)	45.1 (13.1)	0.14
Min, max	20, 76	20, 69	
Sex, n (%)			
Female	16 (41.0)	10 (23.3)	0.1
Male	23 (59.0)	33 (76.7)	
BMI, kg/m^2			
Mean (SD)	28.4 (7.1)	28.3 (5.9)	0.95
Min, max	18.8, 55.8	18, 44.1	
Tobacco use, n (%)			
Current smoker	15 (38.5)	22 (51.2)	0.15
Previous smoker	10 (25.6)	14 (32.6)	
Never smoked	14 (35.9)	7 (16.3)	
Fistula characteristics	Advancement flap (n = 39)	Fistula plug (n = 43)	
Duration of fistula at initial clinical visits (months)			
Mean (SD)	4.7 (4.9)	5.6 (5.9)	0.45
Min, max	0, 18	1, 30	
Prior colorectal surgeries, n (%)			
No	23 (59.0)	23 (53.5)	0.4
Yes	16 (41.0)	20 (46.5)	
Prior colorectal surgeries			
Mean (SD)	0.9 (1.7)	0.7 (0.9)	0.4
Min, max	0, 9	0, 4	
Fistula length, cm			
Mean (SD)	4.0 (1.1)	4.3 (1.2)	0.18
Min, max	2, 7.8	3, 6.8	
Missing, n	1	0	
Fistula type, n (%)			
Branching	1 (2.6)	2 (4.7)	>0.99
Hemi-horseshoe	1 (2.6)	2 (4.7)	
Radial	37 (94.9)	39 (90.7)	

BMI, body mass index; Max, maximum; min, minimum; SD, standard deviation.

Table 2
Pooled healing rates at the 12-month follow-up by selected demographic, clinical, and fistula characteristics.

Healing outcome			
Variable	Success (n = 47)	Failure (n = 19)	*P*-value
Age			
Median	48.0	52.0	0.42
Min, max	20, 75	38, 76	
Sex			
Female	14 (29.8)	9 (47.4)	0.25
Male	33 (70.2)	10 (52.6)	
Tobacco use			
Current smoker	17 (36.2)	10 (52.6)	0.35
Previous smoker	15 (31.9)	6 (31.6)	
Never smoked	15 (31.9)	3 (15.8)	
Body mass index, kg/m^2			
Median	28.0	25.7	0.03
Min, max	18.8, 55.8	22.3, 47.9	
Duration of fistula at initial clinic visit, months			
Median	3.0	4.0	0.96
Min, max	1, 18	0, 30	
Number of prior colorectal surgeries			
Median	0	1	0.66
Min, max	0, 4	0, 9	
Fistula length, cm			
Median	4.0	4.8	0.01
Min, max	3, 7.8	3, 6.5	

Fisher's exact *t*-test for categorical variables; Wilcoxon *t*-test for continuous variables. Max, maximum; min, minimum.

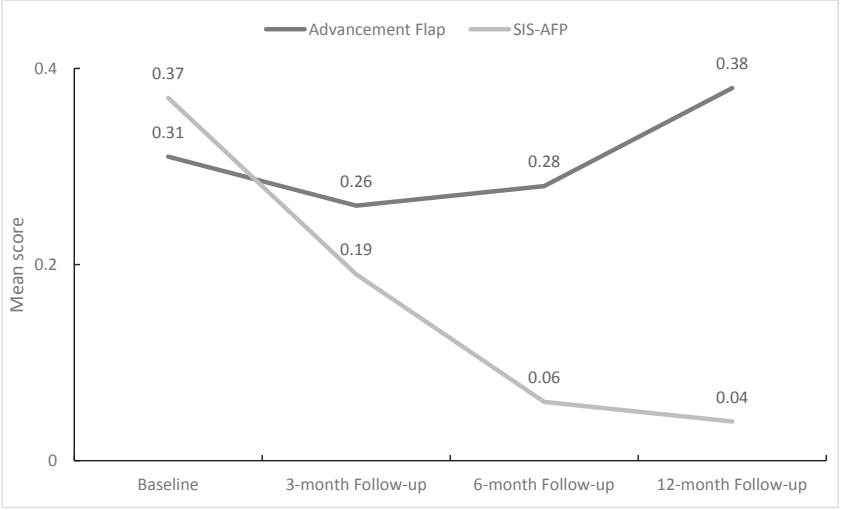

Fig. 3. Differences between the advancement flap and plug groups in the overall quality of life scores as measured by the EuroQual-5D at baseline and the 3-, 6-, and 12-month follow-up assessments.

Table 3
Summary of adverse events by treatment group.

Treatment group			
Adverse Event, n (%)	Advancement flap (n = 39)	Fistula flug (n = 43)	p-value
Fistula tract reopened after documentation of closure	1 (2.6)	4 (9.3)	0.36
Induration, redness, or swelling affecting the external opening	2 (5.1)	2 (4.7)	1.0
Infection or abscess involving the fistula	3 (7.7)	3 (7.0)	1.0
Flap failed or plug fell out	2 (5.1)	0 (0.0)	0.22
Other[a]	2 (5.1)	1 (2.3)	0.60

[a] Light bleeding from external wound, bleeding from fistula, or new apparent fistula forming.

statistically significant differences between groups in the composite score for fecal incontinence or the subscales for gas, mucus, liquid stool, and solid stool as measured by the FISI.

While not statistically significant, median pain scores in the plug group were lower on the day of the procedure (21.0; range 0, 84) compared to the advancement flap group (25.5; 0, 95; P = 0.74). A similar trend was evident at discharge with median pain scores of 10.5 (0, 49) and 16.5 (0, 49) in the plug and advancement flap groups (P = 0.33), respectively, and 9.0 (0, 61) for the plug group versus 10.5 (0, 91) for the advancement flap group 2 weeks after surgery (P = 0.13).

3.4. Safety

Twenty-two adverse events (AEs) occurred in 15 patients. The frequency of AEs was similar between treatment groups at 7 (17.9%) and 8 (18.6%) patients in the advancement flap and the plug group, respectively (p = 0.51). Among the 12 AEs reported for the advancement flap group, 5 (41.7%) were considered definitely related, 1 (8.3%) was considered probably related, and 6 (50.0%) were considered unrelated to the procedure. Ten AEs were reported for the plug group, including no events that were definitely or probably related, 6 (60.0%) considered possibly related, and 4 (40.0%) AEs considered unrelated to the procedure. The most frequent AE in the advancement flap group was infection or abscess involving the fistula. Reopening of the fistula tract following confirmation of closure was the most common AE among patients treated with the plug (Table 3).

4. Discussion

Our results confirm the noninferiority of the plug when compared to the advancement flap. Both interventions achieved acceptably high rates of healing at 12 months, ranging from 67% to 76% in a difficult-to-treat patient population. There were no significant differences between the groups in fecal continence. The overall safety profile was similar between the two interventions. It is noteworthy that 50% of AEs in the advancement flap group were considered procedure-related while no AEs were related to the plug. There also was a trend for lower pain scores among patients in the plug group at the time of surgery and through 2 weeks postoperatively, as well as a general trend for improved overall quality of life in the plug group as measured by the EQ-5D.

The time required to implant the plug was, on average, 34% shorter than the time required for the advancement flap procedure. A shorter surgical duration offers several benefits including reduced risk to the patient, increased efficiencies in the use of hospital resources, and lower overall costs. While this study was not designed to evaluate economic factors, the less invasive nature of the plug procedure makes it possible that patients could undergo plug placement in an outpatient setting [27] or have shorter hospital stays as compared to the flap [22], resulting in lower healthcare costs. A separate comparison of the plug to the advancement flap that reported no statistically significant differences in healing rates between groups [28] revealed that the costs for patients treated with the plug were reduced by $1588 (P < 0.0001) and the hospital stay by 1.5 days (P = 0.0002) per healed fistula, suggesting that the plug may be a cost-effective intervention for complex anal fistulas with similar efficacy when compared to the advancement flap [28].

Earlier plug research showed both diabetes and smoking directly correlated with procedural success [29,30]. In the present study, age, sex, tobacco use, and fistula duration at the initial visit were not associated with significant differences in overall healing rates. However, significantly better closure rates for patients with a higher BMI, shorter fistula length, and fewer previous colorectal surgeries were observed. The lack of consistency in factors associated with successful fistula closure across studies and literature reflects gaps in the current understanding of anal fistula disease pathophysiology.

This study demonstrated similar closure rates and lower risk of procedure-related complications for the plug when compared to the advancement flap, confirming that the plug is an effective intervention for selected patients with complex anal fistula. Because SIS performs well in contaminated operative fields [17,31–33], it may be an ideal treatment option for cases with significant amounts of fecal soilage.

There is growing acknowledgement that the optimal intervention for patients with anal fistula must be tailored to the individual fistula [4]. Additional studies that include an adequate number of clinical sites, standardization of operative technique, and strategies to optimize patient recruitment and retention will refine these results by clarifying the characteristics of patients who are likely to achieve the greatest benefit from the plug compared to alternative interventions [4,22]. Standardized techniques for plug insertion also will enhance efforts to ensure the best outcomes for patients who are treated with the fistula plug [34]. While randomized controlled trials comparing surgical interventions can be difficult to design and implement [35], a model for the development and implementation of surgical innovations is available [36] and should be used to advance our understanding of the optimal treatment options based on clinical and demographic characteristics [2].

4.1. Limitations

There are several limitations of this study. While we demonstrated noninferiority of the plug compared to advancement flap surgical repair, we did not confirm higher healing rates for the plug as expected. A possible explanation for this finding is that two of the six sites enrolled the majority of subjects, which could have resulted in higher healing rates for the flap surgery. Our study was powered to detect a 25% difference in healing rates between the two interventions. However, delays in patient recruitment because patients were reluctant to be randomized to procedures that differed significantly in the level of invasiveness of the surgical approach, prevented accrual of the needed number of subjects. Several subjects in both groups failed to complete the 12-month follow-up evaluation.

There is the possibility that patients who agreed to study participation were not representative of the wider population of patients with anal fistula, thereby limiting the generalizability of our findings. The list of demographic, clinical, and fistula characteristics was not an exhaustive list of all factors that might affect healing. Of note, eligible patients were limited to those who had not undergone prior surgical intervention for fistula repair. We also included only patients with cryptoglandular disease. Additional studies are needed to examine the role of the fistula plug in treating patients with Crohn's disease or those with recurrent fistulas.

5. Conclusions

In our study, the plug was an equally effective treatment for complex anorectal fistula when compared to the advancement flap and offered the clinical advantages of significantly less surgical time and a favorable safety profile.

Ethical approval

This study was conducted following approval by the Ethics Committee of the University of Giessen. Reference number: 133/07.

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Author contribution

TS: Study Design, Data Collection, Data Analysis, Writing & Approving Manuscript.
AT: Study Design, Data Collection, Writing & Approving Manuscript.
RS: Study Design, Data Collection, Writing & Approving Manuscript.
JPH: Study Design, Data Analysis, Writing & Approving Manuscript.
US: Study Design, Data Collection, Writing & Approving Manuscript.
MR: Study Design, Data Collection, Writing & Approving Manuscript.
WP: Study Design, Data Collection, Writing & Approving Manuscript.
AF: Study Design, Data Collection, Writing & Approving Manuscript.

Conflict of interest statement

Cook Biotech Incorporated has provided honoraria to Dr. Schwandner and Dr. Roland Scherer. Jason P. Hodde is an employee of Cook Biotech Incorporated.

Guarantor

Jason Hodde.

Research Registration Number

Not applicable.

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