

Title:

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FILAC® PROCEDURE FOR HIGHLY SELECTED ANAL FISTULA PATIENTS: INDICATIONS, SAFETY AND EFFICACY FROM AN OBSERVATIONAL STUDY AT A TERTIARY REFERRAL CENTER.

Study population	Methods	Outcomes
<p>n=36</p> <ul style="list-style-type: none"> Anatomically COMPLEX AF: <ul style="list-style-type: none"> High transphincteric Supra/extrasphincteric Patients with AF at HIGH RISK of fecal incontinence: <ul style="list-style-type: none"> Anterior anal fistula Some degree of associated fecal incontinence Previous anal surgeries CD patients without signs of rectal activity disease (n=13, 36%) Wide internal opening Perianal cavities 	<p>Step 1: Perianal sepsis control</p> <ul style="list-style-type: none"> Surgical drainage Loose SETON placement <hr/> <p>* CD: Without rectal activity disease</p> <p><i>At least 3 doses of biological treatment</i></p> <hr/> <p>Step 2: FiLaC® procedure</p> <ul style="list-style-type: none"> Irrigation of the fistula tract with saline solution <p>Ambulatory procedure</p>	<p>♂ 55,6% (n=20)</p> <p>Mean age: 48 ± 13.9 years</p> <p>Median follow-up: 12 m (IQR 7-29)</p> <p>Higher in CD patients ↓</p> <p>76.9% vs. 43.5% (p=0.048)</p>

*AF: Anal fistula

*CD: Crohn Disease

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FiLaC® procedure for highly selected anal fistula patients: indications, safety and efficacy from an observational study at a tertiary referral center

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Ethical considerations: all the procedures performed were adjusted to the ethics rules of the institutional and/or national research committee and to the Declaration of Helsinki of 1964 and its later modifications or similar ethics rules. The study was approved by the Clinical Research of Ethics Committee (CREC) of Hospital Universitario La Princesa (register number 4734) on June 2022.

Conflict of interest: the authors declare no conflict of interest.

ABSTRACT

Background: the ideal clinical profile of patients or fistula features for fistula laser closure (FiLaC®) technique remain to be established. The aim of this study was to analyze clinical outcomes and the safety profile of FiLaC® in search for an ideal setting for this technique.

Methods: a retrospective observational study was performed from a prospective database including all consecutive patients who underwent surgery for anal fistula (AF) with FiLaC® in the coloproctology unit of a tertiary referral center, between October 2015 and December 2021. The FiLaC® procedure was offered to AF patients who were considered to be at risk of fecal incontinence. Fistulas were described according to Parks' classification and categorized as complex or simple according to the American Gastroenterological Association (AGA) guidelines. Healing was defined by the closure of the internal and external openings for at least six months. Predictive factors of AF healing were investigated.

Results: a total of 36 patients were included, with a mean age of 48 ± 13.9 years. Twenty patients (55.6 %) were male and 13 patients (36 %) had Crohn's disease (CD). Fourteen patients (38.8 %) had a complex fistula. The primary and secondary healing rates were 55.6 % and 91.7 %, respectively, during a median follow-up time of 12 months (IQR 7-29). No fecal continence impairment was registered in any case. The proportion of patients with primary healing was significantly higher in CD patients (76.9 % vs 43.5 %, $p = 0.048$).

Conclusions: FiLaC® is a sphincter-preserving procedure with an excellent safety profile and reasonable success rate despite of the strict patient selection. This technique may be attractive for patients with CD due to its higher primary healing rate.

Keywords: Anal fistula. FiLaC®. Crohn's disease. Laser.

INTRODUCTION

Perianal fistula is a common anorectal disease that can be associated with significant morbidity and impaired health-related quality of life (1). Most fistula might be

explained by the cryptoglandular theory (2) or as secondary to inflammatory bowel disease, mostly Crohn's disease (CD).

The surgical treatment of AF remains challenging due to the difficulty of achieving definitive healing of the fistula while preventing fecal incontinence (3). To overcome this problem. Many sphincter-preserving surgical techniques have evolved in the last decade (4-7). However, most of them lack long-term results and universally accepted indications due to their novelty. In fact, previous literature only reports outcomes from single center studies based on patients' and surgeons' preferences.

Fistula-tract Laser Closure (FiLaC®) is one of these novel techniques initially described by Wilhelm et al. in 2011 (8). It consists of the obliteration of the fistula tract by destruction the epithelium along this tract with a radial application of thermal energy. This procedure results in better accuracy and minimal trauma to the sphincter muscle and the perianal skin (9). Based on these two outcomes, some authors have advocated for its use in perianal CD patients, as they need repetitive repair surgeries resulting in a high risk of sphincter injury with wound healing difficulty (10). However, there has been a worrisome variability in its indication that might have led to suboptimal healing rates in some groups of patients (11).

To date, there are no appropriate and universally accepted indications for this technique. In this context, the aim of this study was to evaluate the effectiveness and safety of FiLaC® for the treatment of AF, especially focusing on anatomic features of the AF and patients characteristics as possible factors associated with surgery success.

MATERIAL AND METHODS

Study designs and patients

In this retrospective study, data were retrieved from a prospectively maintained database incorporating a group of adult patients presenting with AF, both cryptoglandular or CD origin, who were treated with the FiLaC® procedure. Data were collected from patients registered between October 2015 and December 2021. Ano-vaginal, anastomotic or cancer-related fistulas were excluded. This study was approved by the local ethical committee and all patients signed the informed consent before the surgical procedure.

Definitions

- Fistula type was described according to Parks' classification (2) into four groups: intersphincteric, transphincteric, suprasphincteric and extrasphincteric, according to their relationship to the anal sphincters. In addition, fistulas were categorized as complex or simple in nature according to the American Gastroenterological Association (AGA) guidelines (12), defining complex fistulas as high intersphincteric, high transphincteric, extrasphincteric or suprasphincteric ones and those with multiple external openings. Complex fistulas in CD can be related to anorectal strictures or endoscopic signs of rectal disease activity.
- Healing: closure of the internal and external openings, together with the absence of leakage beyond six months. Primary healing: after the first attempt with FiLaC®. Secondary healing: a repeat surgical therapy after initial laser treatment failure.
- Persisting AF: perianal discharge is always present after treatment for AF.
- Recurrence: drainage return after the disappearance of perianal discharge for a period of at least six months.
- Treatment failure was defined as non-healing or recurrence of the fistula after the FiLaC® procedure.

Patient selection

Preoperative evaluation included past and recent medical history, anal inspection, digital rectal examination and anoscopy. In our institution, and according to guidelines (13), the FiLaC® procedure is offered to patients with anatomically complex AF (high transphincteric, supra/extrasphincteric) and to patients with anatomically simple AF (low transphincteric, intersphincteric or superficial) who were considered to be at high risk of fecal incontinence if a fistulotomy was performed. This includes females with anterior fistula, some degree of associated fecal incontinence, previous anal surgeries or CD

patients without clinical or endoscopic signs of rectal disease activity.

The presence of a wide internal opening indicating a wide tract, and the presence of perianal cavities or abscesses were considered as contraindications for FiLaC®. Based on these criteria and the patients' history and physical examination, endoanal ultrasound (EAU) and/or magnetic resonance imaging (MRI) are usually performed in cases that are considered as candidates for this technique, but not systematically as guidelines recommend (13). All CD patients underwent a clinical examination and proctoscopy by an inflammatory bowel disease gastroenterologist before fistula surgery. CD patients underwent surgery with curative intention when proctitis was preoperatively dismissed. Specific previous biological treatment in these cases was registered.

Surgical technique

In our unit, the FiLaC® procedure was attempted once every perianal sepsis had been previously controlled through surgical drainage and the placement of loose setons in each identified fistula tract. In cases of cryptoglandular origin, the FiLaC® procedure was performed after at least two-months with the loose seton in site. This time-period is considered to be sufficient to see a decline in fistula swelling as well as the epithelization of the fistula tract. CD patients underwent surgery for AF with the FiLaC® procedure in the following cases: seton placement and biologic treatment for at least three doses.

The first step was seton removal and irrigation of the fistula tract with a saline solution. Physical abrasion was avoided since bleeding could interfere with the healing process. A ceramic diode laser platform (12 watts, 1,470-nm wavelength) was used for the FiLaC® procedure. The laser fiber was introduced into the fistula tract through the external anal orifice using the Seldinger maneuver until the internal orifice was reached. The laser fiber was activated while it was withdrawn at a constant speed of 1 mm/s. Closure of the internal orifice was performed on demand, depending on its size, especially those internal openings that exceed the size of the seton, when a direct absorbable suture was placed with a Z-stitch.

Outcome measures

The main outcome measure was primary healing and secondary healing, as well as complications secondary to the procedure, such as pain, perianal abscess formation, readmission to hospital or *de novo* fecal incontinence.

Statistical analysis

Quantitative variables were expressed as mean and standard deviations (SD) in cases of normal distribution, or median and interquartile range (IQR) for those with non-normal distribution. Qualitative variables are presented with their frequency. Differences between demographic and clinicopathological variables between patients with and without fistula healing were analyzed using the Chi-squared or Fisher's test for categorical variables and the Mann-Whitney-Wilcoxon test for continuous variables.

RESULTS

During the study period, a total of 307 patients underwent surgery for anal fistula. From them, 36 (11.7 %) had been operated using FiLaC® (October 2015-December 2021). Their overall mean (SD) age was 48 (13.9) years; 20 (55.6 %) patients were male. Regarding AF etiology, 23 patients had AF with cryptoglandular origin (64 %) and in the other 13 patients AF was secondary to CD (36 %).

The most common fistula type was transphincteric in 25 (70 %) patients, followed by intersphincteric in eight (22 %) patients and supra/extrasphincteric in three (8 %) patients. According to AGA classification, 14 (38.8 %) patients had a complex fistula, including seven patients with two or more fistula tracts. Other patient demographics and fistula characteristics are shown in table 1. Disease extension, behavior and treatment in CD patients are shown in table 2.

A seton was placed in every patient at the first stage of the operation. The median duration of a drainage seton in place prior to the definitive FiLaC® attempt for fistula treatment was 32 (IQR 27-56) weeks. Suturing of the internal opening as an additional

surgical maneuver was performed in 12 (33 %) patients. There were no intraoperative complications, unplanned admissions after the procedure, or 30-day readmissions caused by pain or bleeding.

A total of 20 (55.6 %) patients achieved primary healing after primary FiLaC® with a median follow-up of 12 (IQR 7-29) months. The secondary success rate after initial laser treatment failure was 91.7 %. Table 3 shows the results of a univariate analysis to determine which factors correlated with primary and secondary healing. AF etiology was associated with clinical outcome, CD patients being more likely to achieve a primary healing in comparison to those with cryptoglandular origin (76.9 % vs 43.5 %, $p = 0.048$), with no difference in secondary healing (92.3 % vs 91.3 %, $p = 0.91$). The variables statistically associated to secondary healing were simple fistula (100 % vs 0 %, $p = 0.023$) and the absence of secondary tract (96.6 % vs 3.4 %, $p = 0.031$).

FiLaC® failed in 16 patients (44.4 %), 13 (81 %) had persistence of the AF, while three (19 %) had recurrence. Conversion from a complex to a simple fistula was observed in three of the six failed complex cases. Fistulotomy was the most frequent surgical technique used after an initial failed FiLaC® procedure ($n = 11$).

The specific analysis in CD showed that this procedure was more effective in CD patients with a simple tract (100 % primary healing rate) than in those with secondary tracts (40 % primary healing rate). No *de novo* fecal incontinence was documented in any of the patients included in the present study.

DISCUSSION

Our results have confirmed that FiLaC® has a reasonable efficacy for the treatment of AF with an excellent security profile. In this study, the mean rate of primary success was 55.6 % and the mean rate of secondary healing was 91.7 % over a median follow-up of 12 months. Interestingly, CD patients appeared to have a significantly better prospect of fistula healing with the use of this technique, especially those with a single fistula tract.

FiLaC® is mainly indicated in patients in whom fistulotomy procedures have a high risk of impaired anal continence. This fear of anal incontinence has led to an explosive increase of surgical techniques for the treatment of AF called “sphincter-preserving

procedures" (4,6,7) including FiLaC® (8). The initial enthusiasm associated with this security profile was followed by a wide range of surgical indications with disappointing results. Terzi et al. analyzed the results of a cohort of 103 patients and reported a success rate of 40 % (14); this rate was even lower in the study by Lauretta et al. (33.3 %) in 30 patients (15). However, the healing rates in the most recently published studies were slightly higher (74.7 % or 62 %), probably due to a better knowledge of technical issues of the procedure and indications (16,17).

According to the available literature, the failure rate could be attributed to several factors. On one hand, the main factors are secondary tracts and large caliber of the fistula lumen, which may hinder the sealing effect of the laser fiber due to failure to adhere to the lining epithelium of the tract (18). In this regard, this kind of patients were excluded from our cohort. Another controversial point is closure of the internal opening, which Wilhelm considered to be a principal factor for an unsuccessful technique (8). However, no significant difference was found in our study between procedures, with or without closure of the internal opening (66.7 % vs 50 %, $p = 0.34$, respectively). At this point, it is also very important to use strict inclusion and exclusion criteria, such as those used in our study, both related to the risk of incontinence because of the patient and fistula characteristics.

The seton drainage is a crucial part of the procedure, enabling continuous drainage of the fistula tract to reduce local infection. Furthermore, the laser fiber is easier to insert in those patients who already have an indwelling seton that can be used to railroad the laser probe across the fistula and to assist maturation of the principal tract by inducing a more homogeneous fibrotic reshaping of the fistula lumen (11). Such an effect permits a more uniform shrinkage distribution along the fistula tract when the laser is employed in the second stage of the procedure. The use of a seton and conversion of a "one-stage" to a "two-stage" procedure benefits from preliminary drainage of abscesses and should facilitate the closure of small secondary tracts, thereby improving the likelihood of fistula's cure, as Giamundo et al. (18) showed. Patients in the present study carried a seton for a median period of 32 (IQR 27-56) weeks.

Interestingly, in most of the series, failure of the procedure seemed to be related to the persistence rather than recurrence of the fistula (11,18). This was confirmed in our

results, as amongst 16 patients who experienced failure, 81 % did not have primary healing, while only 19 % had recurrence. In addition, a downgrading in fistula height has been reported (9,18), possibly due to the progression of the shrinking effect toward the most distal part of the sphincter complex. In three of the six failed cases with complex fistula, recurrence became more superficial, allowing fistulotomy to be successfully performed with no further impairment of sphincter function. In this regard, although “secondary” cure rates are high with some of these treatments (9,16), we cannot consider this as a desirable goal since most patients, especially CD patients, have already undergone a number of major surgeries. These reinterventions have a personal and occupational impact that must be taken into account. Therefore, we must look for the surgical technique that offers the best chance for cure, without continence sequelae and with the fewest number of procedures. All surgical procedures were taken into account for the reintervention, evaluating the risk of fecal incontinence and the anatomy of the fistula after the laser procedure, and finally, fistulotomy was chosen in most cases. In our unit, FiLaC® does not seem to contribute to a worse future outcome in cases of recurrence and the need for AF reintervention, as secondary healing rate in this case was high (91.7 %).

The treatment of AF in patients with CD requires a combination of medical and surgical treatments according to current guidelines (19) and should be approached with knowledge of disease activity in the rectum, the location and type of fistulas present, and the severity of the patient’s symptoms. Particularly in these scenarios, prior to any surgical technique, local sepsis should be controlled with a seton drainage. CD patients who have simple fistulas may be treated by laying open the fistula tract through one or two stage fistulotomy with high healing rates (12). Nevertheless, it is well known that the treatment of AF in these patients is especially challenging, even the simple ones, and it requires a more conservative surgical approach to reduce the risk of incontinence. In our cohort, we have observed better results with FiLaC® in CD patients (76.9 %), especially those with simple tract (100 %). This is in accordance with the study by Wilhelm et al. (9) in 117 patients treated with laser, in which the healing rate was 69.5 % in the 13 patients with CD, and 63.5 % in those with cryptoglandular fistulas.

Drainage and caliber of the fistula lumen should be taken into account in these CD patients. In a recent review and meta-analysis of CD patients, Cao et al. (20) reported a similar success rate (68 %). However, despite the fact that six European studies were included, only 50 perianal fistulizing CD patients could be reviewed. Therefore, this evidence should be viewed with caution because of the small number of patients reported. Multicenter studies are needed to evaluate more homogenous groups of patients, especially those at higher risk of incontinence, such as CD patients. Furthermore, comparative studies with other new sphincter-saving procedures, such as darvadstrocel (21) or platelet-rich plasma (22), would be helpful to determine the best option for these patients.

The present study has limitations: first, it is based on a retrospective analysis; and second, the absence of comparative analysis and a relatively small number of patients. The small size of the sample is explained because the FiLaC® is not a technique indicated for all patients, and is more a resource in selected cases, even in larger multicentric studies it only represents about 5.5 % of all procedures (23).

Nevertheless, our study has some important strengths. First, we carried out a one-year follow-up of a group of patients selected for this surgical technique, which included not only patient characteristics, but also anatomical features of the AF (patients with wide tract or the presence of perianal cavities or abscesses were excluded). Furthermore, the findings of our study show that FiLaC® could be an important contribution to the surgical armamentarium for the treatment of AF in CD patients. These results are interesting as this technique requires a very short learning curve and short operating time, does not create open wounds, needs limited postoperative care and simplifies a second surgery if required.

In conclusion, FiLaC® is a surgical procedure with a reasonable healing rate depending on the indication, but with an excellent safety profile. This technique may be attractive in patients with CD due to their risk of future perianal interventions and the higher primary healing rate, mainly in those with single tract. Furthermore, FiLaC® use does not seem to contribute to a worse future outcome in cases of recurrence and the need for fistula reintervention.

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Table 1. Patient and fistula characteristics

Characteristics	Cryptoglandular patients <i>n</i> = 23	CD patients <i>n</i> = 13	Overall <i>n</i> = 36
Age (years, mean \pm SD)	49.26 \pm 11.8	46 \pm 17.5	48 \pm 13.9
Gender (male), <i>n</i> (%)	14 (60.9)	6 (46.2)	20 (55.6)
BMI, kg/m ² (mean \pm SD)	26.2 \pm 3.5	22.4 \pm 3.3	24.6 \pm 3.9
Diabetes <i>mellitus</i> , <i>n</i> (%)	2 (5.6)	0 (0)	2 (5.6)
Smoking, <i>n</i> (%)	7 (30.4)	3 (23.1)	10 (27.8)
Previous fistula surgery, <i>n</i> (%)	13 (56.2)	6 (46.1)	19 (52.7)
Type of fistula, <i>n</i> (%)			
Intersphinteric	5 (21.7)	3 (23.1)	8 (22.2)
Transphinteric	17 (73.9)	8 (61.5)	25 (69.4)
Low	2 (11.8)	1 (12.5)	3 (12)
High	15 (88.2)	7 (87.5)	22 (88)
Supra/extrasphinteric	1 (4.3)	2 (15.4)	3 (8.3)
AGA classification, <i>n</i> (%)			
Simple	15 (65.2)	6 (46.2)	21 (58.3)
Complex	7 (30.4)	7 (53.8)	14 (41.7)
Localization, <i>n</i> (%)			
Anterior	15 (65.2)	8 (61.5)	23 (63.9)
Posterior	7 (30.4)	4 (30.8)	11 (30.6)
Both	1 (4.3)	1 (7.7)	2 (5.5)
Secondary tracts, <i>n</i> (%)	2 (8.7)	5 (38.5)	7 (19.4)
Average duration of drainage by seton, weeks (median, IQR)	32 (28-36)	31 (22-96)	32 (27-56)

AGA: American Gastroenterological Association; BMI: body mass index; CD: Crohn's disease; IQR: interquartile range; SD: standard deviation.

Table 2. Crohn's disease characteristics

	<i>n</i> = 13
<i>Montreal classification (location), n (%)</i>	
L1 - Terminal ileum	3 (23.1)
L2 - Colonic	2 (15.4)
L3 - Ileocolonic	8 (61.5)
<i>Montreal classification (behavior), n (%)</i>	
B1 - Non-stricturing, non-penetrating	10 (76.9)
B2 - Stricturing	3 (23.1)
B3 - Penetrating	0 (0.0)
<i>Crohn's disease treatment, n (%)</i>	
Biological treatment	13 (100)

CD: Crohn's disease.

Table 3. Univariate analysis of possible factors associated to primary and secondary success rates after FiLaC®

Patient characteristics	Primary healing		<i>p</i>	Secondary healing		<i>p</i>
	Yes	No		Yes	No	
Age (years, mean \pm SD)	48.5 \pm 16.1	48.1 \pm 11.2	0.93	47.6 \pm 13.6	56 \pm 117.4	
<i>Gender, n (%)</i>						
Male	10 (50.0)	10 (50.0)	0.45	18 (54.5)	2 (66.7)	0.68
Female	10 (62.5)	6 (37.5)		15 (45.5)	1 (33.3)	
<i>Diabetes mellitus, n (%)</i>						
Yes	1 (50.0)	1 (50.0)	0.87	2 (100)	0 (0.0)	0.66
No	19 (55.9)	15 (44.1)		31 (91.2)	3 (8.8)	
<i>Smoking, n (%)</i>						
Yes	4 (40.0)	6 (60.0)	0.24	9 (90.0)	1 (10.0)	0.82
No	16 (61.5)	10 (38.5)		24 (92.3)	2 (7.7)	
<i>Etiology, n (%)</i>						
Cryptoglandular	10 (43.5)	3 (56.5)	0.048	21 (91.3)	2 (8.7)	0.91
Crohn	10 (76.9)	13 (23.1)		12 (92.3)	1 (7.7)	
<i>Type of fistula, n (%)</i>						
Intersphinteric	4 (50.0)	4 (50.0)	0.63	8 (100)	0 (0.0)	0.20
Transphinteric	15 (60.0)	10 (40.0)		23 (92.0)	2 (8.0)	
Supra/extrasphinteric	1 (33.3)	2 (66.7)		2 (66.7)	1 (33.3)	
<i>AGA classification, n (%)</i>						
Simple	12 (54.5)	10 (45.5)	0.87	22 (100)	0 (0.0)	0.023
Complex	8 (57.1)	6 (42.9)		11 (78.6)	3 (21.4)	
<i>Localization, n (%)</i>						
Anterior	13 (56.5)	10 (43.5)	0.46	21 (91.3)	2 (8.7)	0.95
Posterior	7 (63.6)	4 (36.4)		10 (90.9)	1 (9.1)	
Both	0 (0.0)	2 (100.0)		2 (100)	0 (0.0)	
<i>Secondary tracts, n (%)</i>						
Yes	3 (42.9)	4 (57.1)	0.45	5 (71.4)	2 (28.6)	0.031

No	17 (58.6)	12 (41.4)		28 (96.6)	1 (3.4)	
<i>OFI closure, n (%)</i>						
Yes	8 (66.7)	4 (33.3)	0.34	12 (100)	0 (0.0)	0.21
No	12 (50.0)	12 (50.0)		21 (87.5)	3 (12.5)	

AGA: American Gastroenterological Association; SD: standard deviation; OFI: internal opening of anal fistula.