

Permacol™ Collagen Paste Injection in Anal Fistula Treatment: A Retrospective Study with One-Year Follow-Up

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ABSTRACT

Introduction: This study aimed to evaluate the applicability, safety, results, and functional performance of Permacol™ collagen paste injection in patients with an anal fistula.

Methods: Thirty-one patients with anal fistula underwent Permacol™ collagen paste injection between February 2015 and February 2017. The patients were followed up for a total of 12 months with recovery conditions monitored at intervals of 3, 6, and 12 months. Preoperative insertion of seton was performed in 15 patients for a period of 6–8 weeks and 2 patients for a period of 12 weeks.

Results: A trans-sphincteric anal fistula was present in 20 patients and an intersphincteric fistula was present in 11 patients. There was a recurrence in 7 patients (22.5%): 1 patient (3.2%) after 1-month follow-up, 3 patients (9.7%) after 3-month follow-up, 2 patients (6.5%) after 6-month follow-up, and 1 patient

(3.2%) after 12-month follow-up. A complete recovery was observed in 24 (77.5%) patients after a 12-month follow-up. The mean Fecal Incontinence Severity Index score was 0.29 ± 0.64 preoperatively and 0.55 ± 1.03 after 12 months.

Conclusion: In this study, we show that treatment of patients with an anal fistula by injection of Permacol™ is a safe and successful method that does not compromise continence.

Keywords: Anal fistula; Biomaterials; Incontinence; Permacol; Recurrence

INTRODUCTION

Optimal surgical treatment of an anal fistula must provide both recoveries of the fistula tract and anal continence. The risk of anal incontinence is high in the surgical treatment of complex and high trans-sphincteric fistulas. Although the treatment of short intersphincteric fistulas is fairly simple, there is still a risk of fecal incontinence and risk of wound infection [1]. In minimally invasive, sphincter-protective treatments, the occurrence of postoperative fecal incontinence is rare, but the success rate is low [2–5]. Many authors used biomaterials such as fibrin glue, fistula plugs, and stem cells to improve fistula healing and to reduce negative functional results. However, the reported success rates have varied considerably. The success

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rate of previous studies using fibrin glue has ranged from 64% to 85% [6–8]. However, subsequent studies have shown that the success rates were below 33% [9–11]. Similarly, the initial success rate of adipose-derived stem cells (eADSC) was reported to be as high as 71% [12], but at the 1-year and 3-year follow-up, the success rate was found to be 62% and 33%, respectively [13].

Recently, injection of collagen matrix as a new biomaterial for the treatment of anal fistulas has been on the agenda [14, 15]. Permacol™ collagen paste (Medtronic, MA, USA) is an acellular sterile suspension of cross-linked collagen from the porcine dermis. It has been shown to support cellular infiltration, facilitate angiogenesis and neovascularization from surrounding tissues, and promote fistula closure in the anal sphincter without complication. In its paste form, Permacol™ is malleable and can take on the shape of the fistula tract [15].

This study aimed to examine the side effects as well as fistula healing and fecal incontinence following Permacol™ collagen paste injection throughout a 1-year period.

METHODS

Thirty-one subjects with an anal fistula underwent Permacol™ injection in accordance with the guideline from the American Society of Colon and Rectal Surgeons [16]. Written approval was obtained from Cukurova University Faculty of Medicine Clinical Ethical Board. Before surgery, all patients received a full clinical examination that included imaging with magnetic resonance imaging (MRI). Patients with a fistula of cryptoglandular origin and primary or recurrent trans-sphincteric or intersphincteric fistula tract were included in the study. There were no patients with Crohn's disease and no fistulas caused by previous radiotherapy. The patients had not had a physiologic anorectal evaluation prior to surgery. All patients were given an enema on the eve of the surgery date. Before and after surgery, continence was assessed and determined using the Fecal Incontinence Severity Index (FISI) score [17]. Spinal or general anesthesia was

given to patients for the operation, which was performed in the lithotomy position. Silicon seton drainage was performed in 15 patients for a period of 6–8 weeks and 2 patients for a period of 12 weeks. By applying seton, edema and inflammation of the fistula tract were treated and it became a controlled fistula. Applying loose seton was not the primary operation type in our clinic. After inflammation and edema had ceased, we used Permacol™ as the primary operation for this disease.

A single injection of cefazolin (2 g) was given as prophylaxis. Openings of the internal and external fistula were determined. Permacol™ was injected according to the manufacturer's recommendations. Briefly, the seton was removed, and the fistula tract was subjected to gentle debridement and de-epithelialization using a wire brush. Then, the collagen suspension was injected into the fistula tract through a flexible 12-gauge cannula sheath using a 3-mL syringe until the paste was visualized at both openings. Internally, the opening was sutured (using a "Z" vicryl 0 suture) on the smooth muscle and overlaid with mucosal suture. The external opening was closed using an absorbable suture, and a sterile bandage was applied to the wound. Patients were followed up each day for 10 days and then at 1, 3, 6, and 12 months post-surgery. Pain after the procedure was calculated using the visual analog scale (VAS), where 1 was least and 10 was most. Surgical complications were evaluated and success was defined as wound closure, an absence of any anal symptom, and no signs of drainage from fistula on anal examination, but MRI was not performed to measure healing.

Statistical Analysis

Statistical analysis was performed using SPSS software v16.0 (SPSS Inc., Chicago, IL, USA). All numerical data were defined as the median value (minimum–maximum). A Mann–Whitney *U* test was used for the data not normally distributed to compare groups. Categorical variables were analyzed by using the chi-square test or Fisher Exc. between groups. Pre–post measures data were analyzed using a McNemar

test. A p value of less than 0.05 was considered statistically significant.

RESULTS

Thirty-one patients with an anal fistula were recruited and enrolled for this study from February 2015 to February 2017 and were followed up (median 13 ± 1.6 months). There were 17 (54.8%) male and 14 (45.2%) female subjects recruited, and the ratio was 1.2:1 (male/female) and the median age patient age was 45.4 ± 11 years (range 25–68). The fistula tracts were 3–5 cm in length. Seventeen subjects (54.8%) previously underwent a loose seton insertion (15 patients for 6–8 weeks; 2 patients for 12 weeks). Twenty patients had a trans-sphincteric anal fistula and 11 patients (35.5%) had an intersphincteric fistula (64.5%) according to Parks' classification. In addition, four patients (12.9%) had a fistula with multiple tracts. Six fistulas were caused by previous surgery (recurrent fistula). The previous fistula operations in these patients were fistulotomy in five patients and ligation of intersphincteric fistula tract (LIFT) operation in one other patient (Table 1).

A single injection (less than 3 mL) of Permacol™ was adequate to block and fill the fistula tract completely in 30 out of 31 subjects.

The average (mean \pm SD) preoperative FISI score was 0.29 ± 0.64 . The median operation time for the Permacol™ injection was 24.9 ± 5.1 min (range 18–35 min). There were no intraoperative complications to report, and the pain was not severe. Following the first week post-surgery, the average VAS score was 0.70 ± 0.50 (Table 2). Most patients (77.4%) were released as outpatients the same day, while 5 (16.1%) stayed one night and 2 (6.5%) were kept longer.

There was a postoperative recurrence in 1 patient (3.2%) at the 1st month. The cause of recurrence in this patient was an abscess. There was recurrence in 3 patients (9.7%) at postoperative 3rd month due to leakage from the external orifice. And there was a recurrence in 2 patients (6.5%) at a postoperative 6th month and in 1 patient (3.2%) at postoperative 12th

month (Fig. 1). The fistula healing rate was 87.0%, 80.6%, and 77.4% in postoperative 3rd, 6th, and 12th month, respectively.

Seven patients who developed fistula recurrence were reoperated on. Abscess drainage was done in one patient. In five patients LIFT was performed, and one patient underwent fistulotomy.

There was no significant relationship between recurrence and preoperative seton placement or fistula length. Furthermore, there was no significant relationship between recurrence and the fistula type (trans-sphincteric or intersphincteric), fistula number (single or multiple), or previous recurrent fistula ($p = 1.00$).

At 12 months, the FISI score was 0.55 ± 1.03 without any significant difference from the preoperative value. No patients reported a worsening in their continence status.

The cost of each Permacol™ paste (3 mL) injection was \$500 in our country.

DISCUSSION

The overall goals for treatment of anal fistula are complete fistula tract healing and recovery as well as normal continence. A 100% success rate for a fistulotomy has been reported. However, this procedure impedes continence in 20–82% of cases [18, 19]. There are some studies reporting that cutting seton causes fecal incontinence in a significant percentage of patients, although it provides a high degree of healing [20]. As a result, biomaterials have been recommended to reduce incontinence rates while improving healing of the fistula [6–8, 12]. However, these biomaterials have given unpredictable results (success rates range from 16% to 85%) [13, 21, 22]. In many cases, the initial findings have not been reproducible, resulting in outcomes that are confusing.

Permacol™ paste has been reported to slow bacterial enzymatic degradation when contaminated and has also been shown to promote tissue regeneration and cell migration into the fistula tract [23]. Furthermore, the collagen suspension has been documented to take on the shape of the fistula tract as well as fill secondary

Table 1 Patients demographics

	<i>n</i>	%
Gender		
Male	17	54.8
Female	14	45.2
Fistula type according to Parks' classification		
Intersphincteric	11	35.5
Trans-sphincteric	20	64.5
Recurrent fistula		
Previous LIFT operation	1	3.2
Previous fistulotomy	5	16.1
Level of internal opening		
Above dentate line	5	16.1
At dentate line	26	83.9
Length of fistula tract (cm)		
3	9	29.0
4	14	45.2
5	8	25.8
Prior treatment of fistula with loose seton (weeks)		
6–8	15	48.4
12	2	6.5
Units of paste required per patient		
1	30	96.8
2	1	3.2
Number of fistula openings (external orifice)		
Single	27	87.1
Multiple	4	12.9
Age	Median (min–max)	Mean ± SD
	46 (25–68)	45.4 ± 11.0

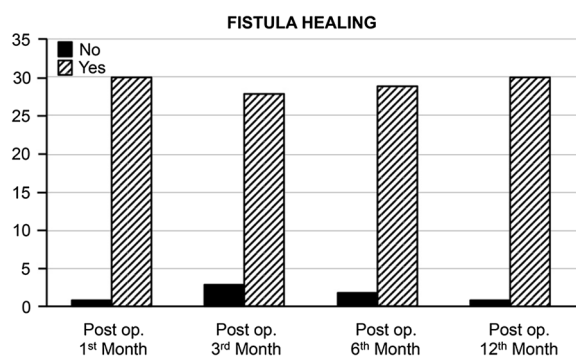
tracts, which reduces early extrusion and recurrence.

Interestingly, PermacolTM paste has only been used in a couple of previous reports. In recently published preliminary and final results

of a prospective multicentre study (the MASERATI100), the efficacy of PermacolTM paste at long-term follow-up was reported with a fistula healing rate of 54% and 53.5%, respectively, at 12 months after surgery [15, 24].

Table 2 Patients VAS score, FISI score, and operation time

	Mean \pm SD
Postoperative VAS pain score	0.70 \pm 0.50
Preoperative FISI score	0.29 \pm 0.64
Postoperative FISI score	
10th day	0.55 \pm 0.96
12th month	0.55 \pm 1.03
Duration of surgery (min)	24.9 \pm 5.1

**Fig. 1** Fistula healing

The authors suggested various causes of failure, including residual undetected sepsis and abscess formation, including implant extrusion [24]. In the MASERATI100 final results study, fistula healing was found to be significantly related to trans-sphincteric fistula and fistula length of 4 cm or less. In addition, the presence of a previous recurrent anal abscess, four times or more, was found to affect fistula healing [15] negatively. In our study, no significant relationship between fistula healing rate and the fistula length or the type of the fistula tract (trans-sphincteric/intersphincteric) was reported. Fabiani et al. detected a healing rate of 47.6% in complex fistula in 18 patients during 12-month follow-up [14].

Speculation about fistulectomy and seton draining has suggested that these methods are not needed for a regular and chronic fistula tract. However, further studies are necessary to prove that this is the case. We preferred to use

PermacolTM paste in patients who had previously undergone cutting seton to avoid the risk of fecal incontinence.

Stamos et al. [25] had documented that the healing rate (73%) was higher in patients with plug implantation when the seton was not used compared to patients given a seton (43%). There was no significant relationship between preoperative seton placement and recurrence either in our study.

The use of any implant material for fistula surgery must impact healing and recovery in a positive manner. For example, fibrin glue, as a result of its fluid consistency, hampers fixation of the glue within the track, which reduces the seal. Surgisis biomaterial (Cook Biotech) has a non-cross-linked matrix that may lead to premature degradation in complex environments [26]. In contrast, PermacolTM is cross-linked and may increase the promotion of vascular and tissue growth [26–28]. It has greater flexibility than a solid implant, which minimizes the risk of extrusion and conforms to the specific shape of the fistula cavity.

MRI was not used to assess healing because it was not carried out routinely for this condition in our clinic. There is no study of how to look at a fistula healed on MRI following collagen paste injection [15]. Ellis et al. [29] conducted a study in 63 patients whose complex anal fistula was treated with bioprosthetic plugs. At 1-year follow-up patients with clinically healing fistula were offered MRI. Eight patients underwent MRI voluntarily. There was evidence of residual fluid and fistula tract in 2 out of 8 patients. However at 14 and 17 months follow-up, no clinical recurrence was detected in these patients. Panés et al. [30] achieved 56.3% combined remission and 59.2% clinical remission at 52 weeks follow-up using stem cell therapy (Cx601) in patients with Crohn's disease and complex perianal fistulae. Recurrence was defined as fluid leakage from the external orifice on clinical examination or perianal collection greater than 2 cm on MRI.

In our study, the overall success rate was 77.4% at 12 months. In addition, we report no significant difference in FISI scores pre- and post-surgery. This suggests that PermacolTM injection reduces the complications associated

with fistula healing and recovery. However, in our study, all fistulas were non-complicated. Our results cannot be extrapolated to groups of patients with the more complicated disease.

Limitations of our work were the retrospective nature of the study, the small number of patients, and the follow-up period of only 1 year.

CONCLUSION

Permacol™ paste injection should be preferred because it is easy to use, it is well tolerated by patients, the pain score is low, the success rate is high, and it has no adverse effect on incontinence.

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Compliance with Ethics Guidelines. Written approval was obtained from Cukurova University Faculty of Medicine Clinical Ethical Board. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Data Availability. All data generated or analyzed during this study are included in this article as supplementary information files.

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