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ORIGINAL ARTICLE

Non cross-linked equine collagen (Salvecoll-E gel) for treatment of complex ano-rectal fistula

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Summary *Background:* Fistula-in-ano is one of the most commonly presenting anorectal diseases. Sphincter sparing treatment options should be considered in patients with complex fistulas. Salvecoll-E gel is a native collagen deantigenated and purified, non-cross-linked equine dermal extract, with an amino acid composition identical to human collagen.
Methods: The multicentric trial study was a prospective, single-arm observational clinical study with the objective to assess the efficacy of Salvecoll-E gel for anal fistula repair in 70 patients. All patients had undergone preliminary surgical treatment consisting of positioning of a draining loosing seton that was maintained for a period of 4–6 weeks. After seton removal, a gentle debridement and washing of the fistula track was performed. The scar tissue was removed from the internal orifice. Internal opening was covered by a side-to side mucosal suture. Salvecoll-E was injected through the external opening into the fistula track, the external opening it has been opened.
Results: Twelve months after surgery, 55 patients demonstrated a clinically healed fistula (78,5%), 15 patients have a recurrence (21,5%). Most of the recurrences were observed in the first 6 months of treatment (13/15, 86.6%). We don't observe any worsening in CCF score. The results obtained at 1 year certainly seem satisfactory and in line with the best results published in literature using mini-invasive techniques.
Conclusion: Salvecoll-E gel is a promising non-invasive technique for conservative treatment of anal fistulas, it's well tolerated by the patients and, in case of recurrence, reinjection or all other known techniques are feasible.

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1. Introduction

Fistula-in-ano is one of the most commonly presenting anorectal diseases with an incidence of 8.6—10 per 100 000 people per year that varies among different countries of the European Union (EU).[1,2] Historical medical literature has referenced the considerable challenges in the management of fistulae since 400 BC, when Hippocrates described a fistulotomy and the use of a seton made of horsehair.[3] Surgery remains the definitive therapeutic approach; however, it can be a challenge for surgeons. The ideal surgical treatment for anal fistula should eradicate sepsis and promote healing of the tract, whilst preserving the sphincters and the mechanism of continence. A fistula may present de novo, but in about 30—50% of patients, it follows a previous anorectal abscess, which can cause the formation of a primary track and a secondary track in about 25% of patients presenting with anal fistula. Parks' classification identified four different types of anal fistula based on the relationship between the primary track and the sphincter.[4,5] A fistula can also be categorized as simple or complex: complex fistulas include high transsphincteric, suprasphincteric, extrasphincteric, recurrent and horseshoe fistulas, multiple tracks, anteriorly lying tracks in female patients, and those associated with inflammatory bowel disease, radiation, preexisting incontinence, or chronic diarrhea.[6] In some complex cases, a staged surgical procedure will be required. For the simple and most distal fistulae, conventional surgical treatment such as lay-open of the fistula tract as a complete transection of the tissue between the fistula tract and anoderm is very effective with a success rate of up to 100%.[7] Although reported incontinence rates following fistula surgery is very variable and is influenced by many factors, incontinence rate after laying open of intersphincteric and distal fistulae seems to be under 10%[8] but can reach 45% when attempted in patients with complex fistulas.[9] Therefore, sphincter sparing treatment options should be considered in patients with complex fistulas: those that involve a significant amount of sphincter or pelvic floor muscle (high transsphincteric or suprasphincteric fistulas). Despite a growing number of sphincter-sparing repair techniques, complex anal fistulas continue to be a problem for patients and surgeons alike.[10] It is quite common for patients with complex anal fistulas to require several procedures over months or years. Salvecoll-E® gel is a native collagen deantigenated and purified, non-cross-linked equine dermal extract, with an amino acid composition identical to human collagen. When Salvecoll-E® gel is injected into the dermis or other damaged tissues, fibroblasts and other non-resident cells begin to migrate from the surrounding tissues and invade the collagen gel. Additionally, the injection has the immediate effect of mechanically filling the defects, then a transition matrix is formed at the site of the Salvecoll® gel injection (aseptic inflammation), which stimulates the immune system and activation of granulocytes, macrophages and fibroblasts, accompanied by enhanced transport of growth factors released from cells, which in turn leads to increased migration and proliferation of fibroblasts and epithelial cells. The purpose of the collagen gel is to provide a matrix for the cells, allowing them to form new tissue. The fibroblasts produce new collagen fibers at the site of the gel injection and the gel itself is gradually degraded by collagenase enzymes produced by fibroblasts, and replaced by autologous human collagen, synthesized de novo.

The use of Salvecoll-E® gel in the filling of anorectal fistula tract is a new sphincter-preserving method for fistula repair. The multicentric trial study was a prospective, observational clinical study with the objective to assess the efficacy of Salvecoll-E® gel for anal fistula repair.

Primary endpoint of the study is to assess the healing rate of fistulas at 12 months after implantation of Salvecoll-E® gel. The healing of the fistula is defined as no secretions and complete closure of the external orifice.

Secondary end-point is to assess changes in the anal continence in the immediate post-operative period and 12 months after the procedure.

2. Materials and methods

This study is a prospective, multicenter, single-arm observational study on the use of Salvecoll-E® gel 150 mg/ml in the treatment of complex anal fistulae in 70 patients. 9 Italian centers participated. This study received approval from both local and regional Ethics Committees and was conducted according to Good Clinical Practice (GCP) guidelines and with adherence to all European and national regulations.

Between May 2016 and May 2017, 70 consecutive patients underwent Salvecoll-E® gel injection for complex anal fistula, defined according to American Society of Colon and Rectal Surgeons guidelines.[11] The inclusion criteria are summarized in Table 1. All patients underwent clinical examination and pelvic magnetic resonance imaging before surgery. Continence was evaluated before and after surgery, using the validated Wexner/Cleveland Clinic Florida Fecal Incontinence Score (CCF_FIS). All patients took an enema the evening before surgery. All operations were performed under spinal or general anesthesia with patients in the lithotomy position. All patients had undergone preliminary surgical treatment consisting of positioning of a draining loosing silk 0 seton that was maintained for a period of 4—6 weeks to allow adequate drainage of the septic material and definition of the fistula tract. Prophylaxis consisted of a single preoperative administration of cefazolin 1 g and metronidazole 500 mg. After seton removal, a gentle debridement and washing of the fistula track was performed. The scar tissue was removed both from the internal and external orifice in order to obtain a minimal bleeding which allows a better collagen rooting. The closure of the internal opening was performed with a ''Z'' vicryl 0 suture on the smooth muscle covered by a side-to side mucosal suture. After pre-heating of the syringe to body temperature, non cross-linked equine collagen gel (Salvecoll-E®) was injected through the external opening into the fistula track, the external opening it has been opened. The gel was injected until the tract was completely filled. Postoperative pain was measured with a visual analog scale [VAS range 1 (least)—10 (most)]. Patients were evaluated at 7 days and at 1, 3, 6 and 12 months after surgery. Success of the treatment was defined as the closure of the external opening and the absence of drainage from the fistula, confirmed on clinical evaluation that

Table 1 Inclusion criteria.

Inclusion criteria	Exclusion criteria
• Age> 18 years	• Chronic inflammatory diseases of the intestine
• Anal fistulas of glandular cryptic origin	• Abscesses and acute anal sepsis in progress.
• Complex fistulas.	• Immunosuppressive therapy.
	• Rectovaginal fistulas.
	• Infectious diseases, HIV, tuberculosis, suppurative hydrosadenitis, pilonidal sinus disease.
	• Radiation treatment of the pelvic region;
	• Anal and/or rectal carcinoma.
	• Previous fecal incontinence with a score> 2 according to the Wexner Continence Grading Scale (WCGS)
	• Anorectal diseases of infectious, actinic, endocrine or drug origin
	• Renal, hepatic, haematological, cardiovascular, pulmonary, neurological, psychiatric, immunological, gastrointestinal or endocrine diseases, if they are clinically significant
	• Women with an established or planned or lactating pregnancy
	• Malignant neoplasia of any kind, or with a history of previous malignancy
	• Abuse of alcohol, drugs or psychotropic drugs that can change the state of vigilance and physical perception.
	• Presence of a dementia of any type or other possible causes of progressive deterioration of the ability to understand and want or a psycho-physical disability that reduces the ability to take the prescribed therapy as planned
	• Not adequate reliability or presence of conditions that can determine a patient's non-compliance/compliance with the protocol
	• Previous participation in this study

suggested the fistula track was closed. Surgical complications, including continence disorders, were also evaluated with Wexner continence score.

3. Results

No patient was lost to follow-up before the 12-month visit. Patient demographics and fistula characteristics are shown in Table 2. All the patients had previous insertion of a loose seton, which had been in place for a median of 36 days. Granulation tissue was removed in all patients before the gel injection. A single unit of the gel (1,5 ml of Salvecoll-E®) was sufficient to fill the fistula tract completely in all patients. The surgical procedure lasted a median of 24.0 (10—45) min and all the patients were discharged on 24 h. The median interval from the procedure to return to work and normal daily activity was 6 (1—10) days. Six months after surgery we found a clinically healed fistula in 62% of cases, while twelve months after surgery 55 patients demonstrated a clinically healed fistula (78,5%) and 15 patients have a recurrence (21,5%). We have observed that most of the recurrences were observed in the first 6 months of treatment 13/15 (86,6%). In the recurrence group 9 fistula were median transphincteric and 6 were high transphincteric, with a median age of 42 years (Table 3). We don't have any worsening in CCF-FIS after the procedure with 0 results before and 12 months after the procedure; patients were also asked about their overall satisfaction with the procedure, with ratings from very satisfied to very dissatisfied. At the final visit, 51/70 (72,8%) patients were either satisfied or very satisfied with their operation. During the trial we have not observed any adverse reaction related to the injection of Salvecoll-E® gel.

4. Discussion

Initial results of the use of biological materials in the treatment of anal fistula have been reported to be very encouraging initially but have often been disappointing with more widespread use of the technique and longer follow-up. The range of reported success has also been great with an overall mean clinical success of 16—85%.[12,13]

The device that is more similar to the Salvecoll-E® gel for the treatment of complex perineal fistulas is the Permacol® paste, also derived from collagen but which, unlike the Salvecoll-E®, present a cross-linked structure. The results published in the literature using this device report a 50% success rate at 24 months.[13—15]

Table 2 Patient demographics and fistula characteristics.

Mean age (years)	45,6 (25—78)
Sex	
- female	18 (26%)
- male	52 (74%)
Mean Body Mass Index (kg/m^2)	27 (24—38)
Mean ASA grade	2
Type of fistula	
- Low transphincteric	17 (24,3%)
- Median transphincteric	35 (50%)
- High transphincteric	18 (25,7%)
Prior treatment with loosing seton	70/70 (100%)
Mean time between placement and removal of seton (days)	36 (28—43)
Mean hospital stay (days)	1

Table 3 Recurrences.

Recurrence's characteristics	
Mean age (years)	42
Patients with recurrence (n°)	15 (21,4%)
Period of recurrence (n° of patients)	
- <6 months	13 (86,6%)
- >6 months	2 (13,3%)
Type of fistula	
- Low transphinteric	0 (0%)
- Median transphinteric	9 (60%)
- High transphinteric	6 (40%)

Preclinical and clinical data indicate that cross-linking methods employed may have adverse effects on host response.[16] It has been known for a long time that the collagen inserted inside a cavity forms a sort of scaffolding that stimulates the cellular proliferation (Vroman's effect).[17]

Probably, in the context of a naturally high bacterial environment like that of a fistula it is more advantageous to use a structure that is more easily degradable to prevent the formation of foreign body granulomas that could cause more rejection and therefore the failure of the procedure.

It is based on this assumption that we have decided to use a material that is not cross-linked and therefore more easily degradable.

The results we obtained at 1 year certainly seem satisfactory and in line with the best results published in literature using mini-invasive techniques.[14,15]

Another strength of this technique is the possibility of reinjection of Salvecoll-E® or feasibility of all other known techniques in case of recurrence.

In order to validate these results, other works are certainly needed to increase the number of patients and, probably, a longer follow-up.

In fact, we have seen how many methods at the beginning of the very promising experience have proved to be less effective with the passage of time.

It is certain that there should be a push to the study of minimally invasive methods for the treatment of a disease with a large incidence in the population and whose treatment is often very complex, this also with a view to preserving at best the sphincter anatomy.

Unfortunately, to date, it's technically difficult from the available literature, to determine any comparison between strategies, as patient demographics and disease vary considerably.

Another important element is the fact that these methods can also be used in day-surgery, given their low invasiveness, with economics advantages.[18]

Conflict of interest

All the authors declare don't have any conflict of interest.

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