NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of collagen paste for closing an anal fistula

An anal fistula is a narrow tunnel that forms between the end of the bowel and the skin near the anus. It may cause pain or discomfort and leak blood or pus. In this procedure, collagen paste is injected into the fistula. The paste fills the fistula, sealing it. The aim is to encourage healing.

Contents

Introduction

The National Institute for Health and Care Excellence (NICE) prepared this interventional procedure overview to help members of the interventional procedures advisory committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the

medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in September 2018.

Procedure name

- Collagen paste for closing an anal fistula

Specialist societies

- Association of Coloproctology of Great Britain and Ireland
- British Society of Gastroenterology
- Royal Society of Medicine Coloproctology Section
- Royal College of Surgeons of England
- Royal College of Surgeons of Edinburgh
- Royal College of Physicians and Surgeons of Glasgow.

Description of the procedure

Indications and current treatment

Anal fistula is an abnormal tract between the anal canal and the skin around the anus. It usually results from previous anal abscesses (cryptoglandular) and can be associated with other conditions such as inflammatory bowel disease and cancer. It may cause symptoms such as pain or discomfort in the anal area, and leakage of blood or pus.

Anal fistulas can be classified according to their relationship with the external sphincter. Intersphincteric fistulas are the most common type and cross only the internal sphincter. Trans-sphincteric fistulas pass through the internal and external sphincter.

Treatment of anal fistulas usually involves surgery. The type of surgery depends on the location and complexity of the fistula. For intersphincteric and low trans-sphincteric anal fistulas, the most procedure is a fistulotomy or laying open of the fistula track. For deeper fistulas that involve more muscle, and for recurrent fistulas, a seton (a piece of suture material or rubber sling) may be used, either alone or with fistulotomy. Setons can be loose (designed to drain the sepsis but

not for cure) or snug or tight (designed to cut through the muscles in a slow controlled fashion). Fistulas that cross the external sphincter at a high level are sometimes treated with a mucosal advancement flap or other procedures to close the internal opening. Another option for treating an anal fistula is to fill the track with either a plug or glue.

What the procedure involves

The use of collagen paste for closing an anal fistula is usually done with the patient under general anaesthesia and in the lithotomy position. The fistula tract is de-epithelised and granulation tissue is removed, before being cleaned with dilute hydrogen peroxide followed by saline. A guiding catheter is connected to a syringe containing the paste and the other end is inserted into the external opening of the fistula. The paste is injected into the fistula until it is visible at the internal opening, and then the guiding catheter is slowly withdrawn. The internal opening of the fistula is closed using resorbable stitches. The external opening is partially closed, using resorbable stitches if needed, to allow any inflammatory fluid to drain out without allowing the collagen paste to escape.

The paste fills the exact shape of the tract, which is intended to reduce the risk of it being expelled from the body when defaecating.

It is a less invasive procedure than traditional surgery and the aim is to allow the fistula to heal whilst preserving sphincter function.

Efficacy summary

Fistula healing

In 2 case series of 100 and 31 patients with anal fistula, 53.5% (53/99) and 77.4% (24/31) of fistulas respectively were healed at 12 month follow-up.[1,4] In a case series of 21 patients with complex anal fistula who had fistulectomy with insertion of a draining seton 6 to 8 weeks before the collagen paste procedure, the success rate was 47.6% (10/21) at 12 month follow-up.[2] In a case series of 24 patients with complex anal fistula who had a non-cutting seton placed for at least 8 weeks followed by an advancement flap repair and collagen paste injection, the overall success rate was 75% (18/24) at a mean follow-up of 14 months. The healing rate for cryptoglandular fistulas was 82.3% (14/17) and the healing rate for inflammatory bowel related fistulas was 57.1% (4/7).[3]

Recurrence rate

In the 2 case series of 100 and 31 patients, the rates of recurrence at 12 month follow-up were 29.0% (29/100) and 22.6% (7/31) respectively.[1,4] In the case series of 21 patients, recurrence at 12 month follow-up in patients with closure at

3 or 6 months was 28.6% (4/14).[2] In the case series of 24 patients with a mean follow-up of 14 months, recurrence was 25% (6/24).[3]

Reoperation

In the case series of 21 patients, 28.6% (6/21) of patients had another operation within 6 months of the collagen paste procedure.[2] In the case series of 24 patients, all 6 (25%) patients with a failed procedure had a new seton inserted and drainage; 2 patients had an advancement flap and faecal diversion and 1 patient had a repeat advancement flap.[3] In the case series of 31 patients, all 7 (22.6%) patients with fistula recurrence had reoperations: 1 patient had abscess drainage, 5 patients had ligation of intersphincteric fistula tract and 1 patient had fistulotomy.[4]

Patient satisfaction

In the case series of 100 patients, 73% (62/85) of patients were satisfied or very satisfied with the procedure.[1]

Quality of life

In the case series of 100 patients, statistically significantly fewer patients reported problems engaging in usual activities, or had problems with anxiety and depression at the 6 month follow-up compared with before the procedure.[1]

Pain relief

In the case series of 100 patients, pain was reduced at all follow-up periods, compared with baseline ($p<0.001$). At baseline, 29.6% (29/99) of patients were pain free compared with 45.9% (45/99) at 1 month follow-up. At 12 months, 88% (66/75) of patients had only mild pain or no pain at all.[1]

Faecal continence status

In the case series of 21 patients, the mean Fecal Incontinence Severity Index score before surgery was 0.33 compared with 0.61 at 12 month follow-up ($p=0.27$). No patients reported a worsening in their continence status.[2] In the case series of 31 patients, the mean Fecal Incontinence Severity Index score before surgery was 0.29 compared with 0.55 at 12 month follow-up (p value not stated). No patients reported a worsening in their continence status.[4]

Safety summary

Anal abscess

Anal abscess was reported in 4.0% (4/100) of patients in a case series of 100 patients; 2 of these were considered to be serious adverse events.[1] Abscess at the fistula tract injection site was reported in 1 patient in a case series of 24 patients with complex anal fistula who had a non-cutting seton placed for at least 8 weeks followed by an advancement flap repair with collagen paste injection.[3]

Infection

Anal fistula infection, wound infection at the external fistula opening, or anal infection was reported in 9.0% (9/100) of patients in the case series of 100 patients.[1] Urinary tract infection was reported in 1 patient in the case series of 24 patients.[3]

New anal fistula

New anal fistula was reported in 2.0% (2/100) of patients in the case series of 100 patients; 1 of these was considered to be a serious adverse event.[1]

Anal fissure

Anal fissure was reported in 1 patient in the case series of 100 patients.[1]

Pain

Procedural pain was reported in 3.0% (3/100) of patients in the case series of 100 patients; 1 of these were considered to be a serious adverse event.[1] Complex regional pain syndrome was reported in 1 patient in the same study.[1] Severe pain during the first week after surgery was reported in 21% (5/24) of patients in the case series of 24 patients, but these patients had an advancement flap repair done at the same time as the collagen paste injection.[3]

Proctalgia

Proctalgia was reported in 7.0% (7/100) of patients in the case series of 100 patients.[1]

Haemorrhage or haematoma

Haemorrhage was reported in 1 patient in the case series of 100 patients.[1] Bleeding and haematoma were each reported in 1 patient in the case series of 24 patients.[3]

Tachycardia

Tachycardia was reported in 1 patient in the case series of 100 patients.[1]

Other

Eczema and hypertrophic scar were each reported in 1 patient in the case series of 100 patients.[1] Haemorrhoidal thrombosis was reported in 1 patient in the case series of 24 patients.[3]

Anecdotal and theoretical adverse events

In addition to safety outcomes reported in the literature, specialist advisers are asked about anecdotal adverse events (events which they have heard about) and about theoretical adverse events (events which they think might possibly occur, even if they have never happened). For this procedure, specialist advisers did not describe any additional anecdotal or theoretical adverse events.

The evidence assessed

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to collagen paste for closing an anal fistula. The following databases were searched, covering the period from their start to 24 July 2018: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see the literature search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with anal fistula.
Intervention/test	Collagen paste.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the IP overview

This IP overview is based on 176 patients from 4 case series.[1–4]

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) are listed in the appendix.

Table 2 Summary of key efficacy and safety findings on collagen paste for closing an anal fistula

Study 1 Giordano P (2018)

Details

Study type	**Case series (prospective)**
Country	Denmark, Italy, UK (10 sites)
Recruitment period	2012 to 2014
Study population and number	**n=100** Patients with cryptoglandular anal fistula (27 intersphincteric, 73 trans-sphincteric)
Age and sex	Median age 47.5 years (range 20 to 78); 70% (70/100) male
Patient selection criteria	Patients with a solitary, primary or recurrent, trans-sphincteric or intersphincteric fistula tract of cyptoglandular origin. All patients had an MRI of the perineum.
Technique	Permacol collagen paste (Medtronic; US) was used. No other fistula surgery was done at the same time, other than placement of a draining or loose seton if appropriate. Bowel preparation was at the discretion of the surgeon.
Follow-up	**Median 50 weeks (range 1.6 to 74.4)**
Conflict of interest/source of funding	Study was sponsored and funded by Medtronic. All authors received research support from Medtronic to conduct the study. In addition, 1 author received personal fees from Covidien (now a subsidiary of Medtronic) and 1 author received honorarium as a speaker for Medtronic.

Analysis

Follow-up issues: Patients were reviewed at 1, 3, 6 and 12 months after the procedure. 75% (75/100) of patients completed follow-up to 12 months. In 24 patients who exited the study early, the fistula failed to heal at the final assessment (n=18) or the fistula recurred after an initial apparent healing (n=7). One patient was lost to follow-up after the 3 month visit and at that time the fistula had not healed.

Study design issues: Multi-centre, prospective, observational study. The primary endpoint was the rate of fistula healing at 6 month follow-up, defined as the absence of any anal symptom or discharge from the treated fistula. If a patient exited the study after the 3-month follow-up visit with a non-healed fistula, that patient's fistula was considered to be unhealed at the 6-month and 12-month assessments. Secondary outcome measures were safety, pain, faecal continence, patient satisfaction, and quality of life.

Pain was assessed using a 10-point visual analogue scale. Faecal continence was assessed using the Cleveland Clinical Florida Faecal Incontinence (CCF-FI) questionnaire. At each follow up, patient satisfaction was measured by questionnaire and graded as "very satisfied," "satisfied," "dissatisfied," or "very dissatisfied". The EQ-5D Quality of Life (QOL) score was assessed at baseline, 3, 6, and 12 months.

The sample size was based on an expected healing rate of 60%, with an assumed drop-out rate of 7% at 6 months. The final sample size was determined to be 100 for the evaluable population, and the final analysis included all 100 patients treated.

Study population issues: Most (86%) patients had previously had a loose seton inserted (median placement 99 days). 39% (39/100) of patients had a recurrent fistula.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **100**

Rate of fistula healing

	1 month	3 months	6 months	12 months
Clinical assessment done, n	99	89	81	75
Missing, n	1	6	3	1
Exited from study, n	0	5	16	24
Clinically healed fistula, n/N (%) 95% CI	47/99 (47.5) 37.3% to 57.8%	50/94 (53.2) 42.6% to 63.6%	55/97 (56.7) 46.3% to 66.7%	53/99 (53.5) 43.2% to 63.6%

Fistula healing at 12 months, by subgroup (n=99)

	Fistula healing at 12 months	p value
Paste extrusion or leakage		
Yes (n=27)	25.9% (n=7)	
No (n=72)	63.9% (n=46)	<0.001
Fistula tract length		
≤4 cm (n=84)	60.7% (n=51)	
>4 cm (n=15)	13.3% (n=2)	<0.001
Fistula Parks classification		
Intersphincteric (n=27)	70.4% (n=19)	
Trans-sphincteric (n=72)	47.2% (n=34)	0.04

Fistula recurrence at 12 months = 29% (29/100)

Patient satisfaction

73% (62/85) of patients were satisfied or very satisfied with the procedure.

Median interval to return to work and resume usual daily activity = 7 days (range 1 to 35)

Multivariate Cox regression analysis of potential risk factors

Variable	p value	Hazard ratio (95% CI)
Paste expulsion/leakage	0.002	3.13 (1.57 to 6.84)
Recurrent fistula	0.406	1.22 (0.77 to 1.96)
Fistula type (ref: trans-sphincteric)	0.990	1.00 (0.53 to 1.94)
Occurrence of anal abscess	0.05	4.24 (1.26 to 26.5)
Length of fistula tract	0.03	0.74 (0.56 to 0.96)
Age	0.004	1.03 (1.01 to 1.06)
Time between placement and removal of seton	0.04	0.999 (0.998 to 1.000)

Diabetes, smoking history, gender, and BMI were not statistically significant risk factors.

Pain

Mean patient pain was reduced at all follow-up periods, compared with baseline (p<0.001). At baseline, 29.6% (29/99) of patients were pain free compared with 45.9% (45/99) at 1 month follow-up. At 12 months, 88% (66/75) of patients had only mild pain or no pain at all.

Quality of life

Relative to baseline, statistically significantly fewer patients reported problems engaging in usual activities, or had problems with anxiety and depression at the 6 month follow-up.

Safety

Patients with at least 1 adverse event=29% (29/100)
Patients with at least 1 serious adverse event=4% (4/100)
Patients with at least 1 device-related adverse event=16% (16/100)
Patients with at least 1 procedure-related adverse event=16% (16/100)

Device and procedure related adverse events (n=100)

Event	n (%)
Anal abscess	4 (4.0)
Anal fissure	1 (1.0)
New anal fistula	2 (2.0)
Anal fistula infection, wound infection at the external fistula opening, or anal infection	9 (9.0)
Complex regional pain syndrome	1 (1.0)
Eczema	1 (1.0)
Haemorrhage	1 (1.0)
Hypertrophic scar	1 (1.0)
Procedural pain	3 (3.0)
Proctalgia	7 (7.0)
Tachycardia	1 (1.0)

Serious adverse events

Event	n (%)
Anal fistula	1 (1.0)
Anal abscess	2 (2.0)
Procedural pain	1 (1.0)
Complex regional pain syndrome	1 (1.0)
Pregnancy (‘considered as serious adverse event because of regulation’)	1 (1.0)

Abbreviations used: CI, confidence interval

Study 2 Fabiani B (2017)

Details

Study type	**Case series (prospective)**
Country	Italy
Recruitment period	2013 to 2014
Study population and number	**n=21** Patients with complex anal fistula (18 high trans-sphincteric, 3 anterior trans-sphincteric)
Age and sex	Median age 48 years (range 22 to 72); 62% (13/21) male
Patient selection criteria	Patients with complex anal fistula, defined according to American Society of Colon and Rectal surgeons guideline. All patients had clinical examination, endoscopic ultrasound or MRI before surgery.
Technique	All patients had fistulectomy with insertion of a draining seton 6 to 8 weeks before the collagen paste procedure. When the tract was too long and an external orifice was present far from the anus, fistulectomy was done, which extended up to the external part of the external sphincter. Drainage was done when an external orifice was absent. A draining seton was always placed. The collagen paste procedure was done under spinal or general anaesthesia. All patients had an enema the evening before surgery. After seton removal, the fistula track was debrided. Scar tissue was removed from the internal orifice and the internal opening was closed with a suture. Collagen paste (Permacol) was then injected through the external opening into the fistula track, and the external opening was sutured closed.
Follow-up	**12 months**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: Patients were evaluated at 7 days and at 1, 3, 6 and 12 months after surgery. No losses to follow-up were described.

Study design issues: Prospective case series with consecutive patients. Success was defined as the closure of the external opening and the absence of drainage from the fistula, confirmed on clinical evaluation. Postoperative pain was measured with a visual analogue scale from 1 (least) to 10 (most).

Study population issues: One patient had Crohn's disease, 3 (14%) patients had a recurrent fistula and 7 (33%) patients had a fistula with multiple tracks. Median fistula tract length was 31 mm (range 9 to 77 mm)

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **21** **Median hospital stay=1 day (range 1 to 2 days)** **Overall mean pain score during the first week after surgery=0.62±0.97** **Success rate=47.6% (10/21)** At 3 month follow-up, 1 patient had an abscess that was drained and 28.6% (6/21) of patients had an external opening with secretions still present. One of these patients had a premature opening (within 30 days of the procedure) of the external orifice with a partial leakage of the collagen paste. **Reoperation within 6 months=28.6% (6/21)** **Recurrence at 12 month follow-up (in patients with closure at 3 or 6 months)=28.6% (4/14)** **Fecal Incontinence Severity Index** • Before surgery=0.33±.57 • 12 month follow-up=0.61±1.02 (p=0.27) No patients reported a worsening in their continence status. The patient with Crohn's disease had successful closure at 12 months. The authors stated that there was no correlation between fistula tract length and fistula healing.	There were no intraoperative complications. No patient had severe pain (visual analogue score >7) during the first week after surgery.

Study 3 Sileri P (2012)

Details

Study type	**Case series (prospective)**
Country	Italy
Recruitment period	2009 to 2012
Study population and number	**n=24** Patients with complex anal fistula (17 high trans-sphincteric, 6 rectovaginal or anovulvular, 1 horseshoe)
Age and sex	Median age 56 years (range 22 to 75); sex not reported
Patient selection criteria	Age between 18 and 75 years; presence of a complex anal fistula, defined as Crohn's, rectovaginal, or high trans-sphincteric. All patients had outpatient clinic evaluation and preoperative MRI or endoscopic ultrasound. Patients with a Faecal Incontinence Severity Index score >6 had anal manometry evaluation before surgery.
Technique	All procedures were done in 2 stages. The first stage involved placing a non-cutting seton under general anaesthesia. This was kept in place for at least 8 weeks. Stage 2 was also done under general anaesthesia. An advancement flap repair was done to cover the internal source of the fistula, and then collagen paste (Permacol, Covidien) was injected through the external orifice to fill the entire tract. The external orifice was sutured closed. The suture was removed at the first outpatient visit. After November 2011, the collagen preparation was concentrated using centrifugation and filters before use, to make it more paste-like and less liquid.
Follow-up	**Mean 14 months (range 3 to 36 months)**
Conflict of interest/source of funding	The first author has received honoraria for lecturing on porcine collagen from Covidien.

Analysis

Follow-up issues: There were no losses to follow-up. Patients were seen at 1, 2 and 4 weeks after surgery and then routinely every 4 months.

Study design issues: Prospective case series with consecutive patients. The primary endpoint was fistula closure rate. Success was defined as closure of all external openings, absence of drainage or persisting fistula tract, without further intervention as well as no abscess formation. Secondary endpoints were postoperative pain, measured with a visual analogue scale (>7 was considered to be severe) and surgical complications, including continence changes.

Study population issues: 33.3% (8/24) of patients had recurrent fistula and 15 (62.5%) had multiple tracts. The fistula was related to inflammatory bowel disease in 7 patients (29.2%); 4 of these patients started anti-TNF treatment after surgery. Two patients had incontinence (Faecal Incontinence Severity Index score>6) before the procedure.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **24** Early extrusion of the infill material (within 30 days) = 25% (6/24) (none of these were after the modification to a more viscous preparation; 4 were within the first week after surgery). **Early failure=8.3% (2/24)** (both were secondary to flap displacement; 1 was in a patient with Crohn's disease, who had a severe recurrence with frequent bowel motions [>10/day] and the other was in a patient with a horseshoe abscess of cryptoglandular origin.) **Recurrence=25% (6/24)** (including the 2 early failures) **Overall success rate=75% (18/24)** **Healing rate for cryptoglandular fistulas=82.3% (14/17)** **Healing rate for inflammatory bowel disease related fistulas=57.1% (4/7)** Failures presented as flap detachment, persisting fistula tract drainage, and 'ex-novo' or recurrent abscess/fistula tracts after initial apparent healing. All patients with a failed procedure were treated with a new seton insertion and drainage. Two patients had an advancement flap and faecal diversion, and 1 patient had a repeat advancement flap.	After the first stage surgery (seton insertion), 1 patient needed a second exploration under anaesthesia for a persisting fistula that was possibly missed at the first surgery. **Surgical complications (excluding the failures within 30 days) = 21% (5/24)** • Haematoma, n=1 • Urinary tract infection, n=1 • Bleeding, n=1 • Haemorrhoidal thrombosis, n=1 • Abscess at the fistula tract injection site, n=1 Overall mean visual analogue scale score for pain during the first week after flap and injection surgery = 4±2 21% (5/24) of patients had severe pain (score >7) during the first week (3 were patients with Crohn's disease).

Study 4 Bayrak M (2018)

Details

Study type	**Case series**
Country	Turkey
Recruitment period	2015 to 2017
Study population and number	**n=31** Patients with an anal fistula (20 trans-sphincteric, 11 intersphincteric)
Age and sex	Median 45 years (range 25 to 68); 55% (17/31) male
Patient selection criteria	Patients with a fistula of cryptoglandular origin and primary or recurrent trans-sphincteric or Intersphincteric fistula tract. Before surgery, all patients had a full clinical examination including an MRI scan.
Technique	All patients were given an enema the evening before surgery. A single injection of cefazolin was given as prophylaxis. Spinal or general anaesthesia was used. Silicon seton drainage was done in 17 patients for 6 to 12 weeks beforehand, to treat oedema and inflammation of the fistula tract. The seton was removed before collagen paste (Permacol, Medtronic, US) was injected into the fistula tract. The internal opening was sutured 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.
Follow-up	**Median 13 months**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: There were no losses to follow-up. Patients were followed up each day for 10 days and then at 1, 3, 6 and 12 months after surgery.

Study design issues: Retrospective case series. Success was defined as wound closure, an absence of any anal symptom and no signs of drainage from fistula on anal examination. MRI was not done to measure healing. Continence was assessed before and after surgery using the Fecal Incontinence Severity Index. Pain after the procedure was assessed using a visual analogue scale from 1 (least) to 10 (most).

Study population issues: All fistulas were described as ‘non-complicated’. There were no patients with Crohn’s disease and no fistulas caused by previous radiotherapy. Fistula tracts were 3 to 5 cm long. Four (13%) patients had a fistula with multiple tracts and 6 (19%) patients had recurrent fistulas (5 patients had a previous fistulotomy and 1 had ligation of intersphincteric fistula tract [LIFT]).

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **31** **Mean duration of surgery=24.9±5.1 minutes** 77.4% (24/31) of patients were discharged the same day, 16.1% (5/31) stayed in hospital for 1 night and 6.5% (2/31) stayed more than 1 night. **Fistula healing rate by follow-up period** • 3 months=87.0% (27/31) • 6 months=80.6% (25/31) • 12 months=77.4% (24/31) **Postoperative fistula recurrence by follow-up period** • 1 month=3.2% (1/31) (caused by an abscess) • 3 months=9.7% (3/31) (leakage from the external orifice) • 6 months=6.5% (2/31) • 12 months=3.2% (1/31) All 7 (22.6%) patients with fistula recurrence had reoperations: 1 patient had abscess drainage, 5 patients had ligation of intersphincteric fistula tract and 1 patient had fistulotomy. There was no statistically significant relationship between recurrence and preoperative seton placement, fistula length, fistula type, fistula number or previous recurrent fistula. **Mean Fecal Incontinence Severity Index score** • Before surgery=0.29±0.64 • 10 day follow-up=0.55±0.96 • 12 month follow-up=0.55±1.03 No patients reported a worsening in their continence status.	There were no intraoperative complications. The mean pain score (measured on a visual analogue scale) during the first week after surgery was 0.70±0.50.

Validity and generalisability of the studies

- No randomised controlled trials were identified.
- The evidence includes some data from the UK.
- In 1 of the studies, patients had a non-cutting seton inserted for 8 weeks before the procedure, and an advancement flap repair was done at the same time as the collagen paste injection.[3] In another of the studies, all patients had fistulectomy with insertion of a draining seton 6 to 8 weeks before the collagen paste procedure.[2]
- In 1 of the studies, the collagen preparation was made more viscous after extrusion was reported in some patients within 30 days of the procedure. No early extrusions were reported after this modification.[3]
- Two of the studies only included patients with complex anal fistula. [2,3]
- There is a lack of long-term follow-up data.

Existing assessments of this procedure

There were no published assessments from other organisations identified at the time of the literature search.

Related NICE guidance

Below is a list of NICE guidance related to this procedure.

Interventional procedures

- Closure of anal fistula using a suturable bioprosthetic plug. NICE interventional procedures guidance 410 (2011). Available from http://www.nice.org.uk/guidance/IPG410

Additional information considered by IPAC

Specialist advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by Specialist Advisers, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate. Two Specialist Adviser Questionnaires for Collagen paste for closing an anal fistula were submitted and can be found on the NICE website.

Patient commentators' opinions

NICE's Public Involvement Programme will send questionnaires to NHS trusts for distribution to patients who had the procedure (or their carers). When NICE has received the completed questionnaires, these will be discussed by the committee.

Company engagement

A structured information request was sent to 1 company who manufactures a potentially relevant device for use in this procedure. NICE received 1 completed submission. This was considered by the IP team and any relevant points have been taken into consideration when preparing this overview.

Issues for consideration by IPAC

None other than those described above.

References

1. Giordano P, Sileri P, Buntzen S, et al. (2018) Final results of a European, multicentre, prospective, observational study of Permacol™ collagen paste injection for the treatment of anal fistula Colorectal Disease 20: 243–51
2. Fabiani B, Menconi C, Martellucci J, et al. (2017) Permacol™ collagen paste injection for the treatment of complex anal fistula: 1-year follow-up Techniques in coloproctology 21: 211–15
3. Sileri P, Boehm G, Franceschilli L, et al. (2012) Collagen matrix injection combined with flap repair for complex anal fistula. Colorectal Disease 14 (Suppl.3): 24–8
4. Bayrak M and Altintas Y (2018) Permacol™ Collagen Paste Injection in Anal Fistula Treatment: A Retrospective Study with One-Year Follow-Up Advances in Therapy: 1–7

Literature search strategy

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	24/07/18	Issue 7 of 12, July 2018
HTA database (Cochrane Library)	24/07/18	Issue 4 of 4, October 2016
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	24/07/18	Issue 6 of 12, June 2018
MEDLINE (Ovid)	24/07/18	1946 to July 23, 2018
MEDLINE In-Process (Ovid) & MEDLINE ePubs ahead of print (Ovid)	24/07/18	July 23, 2018
EMBASE (Ovid)	24/07/18	1974 to 2018 Week 30
BLIC	25/07/18	n/a

Trial sources searched 23rd April 2018

- Clinicaltrials.gov
- ISRCTN
- WHO International Clinical Trials Registry

Websites searched 23rd April 2018

- National Institute for Health and Care Excellence (NICE)
- NHS England
- Food and Drug Administration (FDA) - MAUDE database
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- EuroScan
- General internet search

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

1 Rectal Fistula/ or Anal Canal/
2 ((Anal or anus or rectal or rectum or transphincteric or intersphincteric or ano-rectal or anorectal or plural or peri-anal or perianal or multiple or recurr* or high or horse shoe) adj4 fistula*).tw.
3 (fistula-in-ano or fistula in ano).tw.
4 Fistulotom*.tw.
5 or/1-4
6 Ointments/

7	COLLAGEN/
8	Tissue Adhesives/
9	((Collag* or tissue* or porcine* or pliable*) adj4 (paste* or seal* or Adhesiv* or plug* or glue* or inject* or collag* or ointment*)).tw.
10	or/6-9
11	5 and 10
12	Animals/ not Humans/
13	11 not 12

Appendix

There were no additional papers identified.