Randomized clinical trial

Randomized clinical trial of local gentamicin–collagen treatment in advancement flap repair for anal fistula

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Background: **Endoanal advancement flap repair is widely used in sphincter-preserving surgery for anal fistula, but the high recurrence rate is a major problem. A possible cause of non-healing is local infection of the flap. The aim of this study was to evaluate whether local antibiotic treatment with gentamicin–collagen improves healing after endoanal advancement flap repair for anal fistula.**
Methods: **Eighty-three patients (52 men and 31 women; mean age 47 (range 17–71) years) who had endoanal advancement flap repair for anal fistula between September 1998 and January 2004 were randomized to surgery with (42 patients) or without (41 patients) application of gentamicin–collagen beneath the flap. Patients were evaluated at 1–3 and 12 months after surgery for healing and/or recurrence.**
Results: **The overall healing rate with no recurrence at 1 year after surgery was 57 per cent (47 of 83). Twenty-six of 42 patients randomized to gentamicin–collagen healed primarily compared with 21 of 41 patients randomized to surgery only. There were no overall differences in healing rate according to sex, previous fistula surgery, complexity of fistula, smoking habit or body mass index.**
Conclusion: **Endoanal advancement flap repair for anal fistula has a fairly high primary recurrence rate. Healing was not significantly improved by local application of gentamicin–collagen.**

Presented to a meeting of the Swedish Society of Surgery, August 2005, Gävle, Sweden

Paper accepted 20 February 2006
Published online 4 September 2006 in Wiley InterScience (www.bjs.co.uk). **DOI:** 10.1002/bjs.5398

Introduction

The aim of anal fistula surgery is to eradicate perianal sepsis and achieve healing of the fistula while preserving anal continence. To minimize sphincter damage, the use of fistulotomy is now often restricted to subcutaneous and other very low fistulas. Various techniques of fistulectomy and closure of the internal opening have been developed, including endoanal advancement flap repair[1–3], anocutaneous advancement or island flap repair[4–6] and direct closure without a flap[7,8].

Endoanal advancement flap repair has increasingly become the method of choice for trans-sphincteric or higher fistulas, but recurrence rates tend to be higher than those after fistulotomy or cutting seton treatment. The recurrence rate was 36–40 per cent in two recent large studies[9,10] and 45 per cent in the authors' experience[11]. Possible reasons for non-healing or recurrence after an advancement flap procedure could be tension of the flap with impaired blood flow, unrecognized extensions with insufficient drainage and local infection beneath the flap. The latter might be influenced by antibiotic treatment. Local application of gentamicin–collagen has been used both to prevent and treat surgical wound infection[12–14]. This treatment has been demonstrated to improve perineal wound healing after abdominoperineal excision of rectal cancer[15] and to reduce postoperative complications after rectal cancer surgery[16]. The primary aim of the present study was to evaluate whether local antibiotic treatment with gentamicin–collagen improves healing after endoanal advancement flap repair for anal fistula. A secondary aim was to analyse the relationship between patient characteristics and healing.

Patients and methods

Between September 1998 and January 2004, 87 patients (54 men and 33 women) scheduled for surgery with

endoanal advancement flap repair for anal fistula at the University Hospital, Uppsala, were randomized to surgery with or without local gentamicin–collagen treatment. Eligible patients had intersphincteric or higher anal fistula; division of sphincter muscle was considered unsuitable and an advancement flap procedure was planned. Patients with Crohn's disease or ongoing preoperative antibiotic treatment or fistula(s) with more than one internal opening were excluded. All included patients were informed about the study aim and protocol, and gave their informed consent. The study was approved by the Medical Research Ethics Committee of Uppsala University.

Patients were randomized from numbered, sealed envelopes in blocks of four. Envelopes were prepared by a research secretary and the size of the blocks was unknown to patients and to surgeons enrolling them during the study. Patients, and surgeons performing the surgery and/or follow-up, were not blinded to the randomization result.

Sixty-three (72 per cent) of 87 patients came from the primary catchment area of the hospital and the remaining 24 (28 per cent) were referred from surgeons in other hospitals in the Uppsala healthcare region. All patients had been investigated previously by clinical examination, proctoscopy and endoanal ultrasonography. Colonoscopy or barium enema was also performed when appropriate.

Two patients were randomized in error and two were lost to late follow-up, leaving 83 patients for evaluation. Their mean age was 47 (median 49, range 17–71) years. Forty-two patients had previously undergone fistula surgery with curative intent; the remaining 41 had only had incision of an abscess and/or draining seton, or no surgery at all. The fistula was trans-sphincteric in 66 patients, intersphincteric in 14, suprasphincteric in two and anovaginal in one patient. The primary tract or internal opening was situated dorsally in 46 patients, ventrally in 33 and in four patients at 3 or 9 o'clock. Nineteen fistulas were complex, that is suprasphincteric or anovaginal, or with horseshoe or other extensions.

Gentamicin–collagen

The gentamicin–collagen sponge (Collatamp® G; Schering-Plough, Stockholm, Sweden) used in this study consists of a matrix of purified bovine collagen type I impregnated with 2·0 mg/cm^2 gentamicin sulphate. The drug is released by a combination of diffusion and enzymatic breakdown of the collagen matrix, giving a high local concentration for at least 72 h[12]. According to the manufacturer, the collagen matrix itself is fully resorbed within 1–7 weeks depending on location (well vascularized tissues *versus* bone cavities).

Surgical procedure

Before surgery all patients had routine bowel preparation and most had standard antibiotic prophylaxis (*Table 1*). Surgery was performed under general or regional anaesthesia, with the patient in the lithotomy or prone jack-knife position depending on the location of the internal opening. After determining the anatomy of the fistulous tract, the external opening was excised and the tract cored out into or through the sphincters. Any remaining short tract was curetted. The primary tract was treated by excision in 38 patients, with a combination of excision and curettage in 37, and by curettage alone in eight (*Table 2*). Extensions were likewise excised and/or curetted. An advancement flap, including the mucosa, submucosa and part of the internal sphincter, was raised from immediately below the internal opening and 3–4 cm upwards. Any defect in the sphincter was sutured with polydioxanone sutures. After trimming off the tip of the flap, including the internal opening, the flap was sutured

Table 1 Baseline patient characteristics

	Surgery only ($n = 41$)	Surgery + gentamicin–collagen ($n = 42$)
Sex ratio (M : F)	24 : 17	28 : 14
Age (years)		
Median (range)	46 (17–67)	51 (27–71)
Interquartile range	36–56	42–55
< 50	25	18
≥ 50	16	24
Previous surgery		
None	10	8
Incision of abscess and/or draining seton	11	12
Fistula surgery	20	22
Intercurrent disease		
No	40	35
Yes*	1	7
Smoker ($n = 82$)		
No	29	34
Yes	12	7
Body mass index (kg/m^2) ($n = 81$)		
Median (range)	26 (18–40)	28 (20–40)
Interquartile range	23–28	25–31
Duration of symptoms (months) ($n = 82$)		
< 3 months	0	1
≥ 3, < 12	11	12
≥ 12	30	28
Antibiotics		
Preoperative prophylaxis	35	35
Preoperative prophylaxis and/or postoperative treatment	2	0
None	4	7

*Diabetes mellitus, six patients; ulcerative proctitis, one; steroid treatment, one.

Table 2 Baseline fistula characteristics

	Surgery only ($n = 41$)	Surgery + gentamicin–collagen ($n = 42$)
Fistula		
Intersphincteric	5	9
Trans-sphincteric	34	32
Suprasphincteric	1	1
Anovaginal	1	0
Primary tract/internal opening		
Ventral	18	15
Dorsal	20	26
3 or 9 o'clock	3	1
Horseshoe fistula		
No	36	39
Yes	5	3
Other extension		
No	37	38
Infralevator	4	0
Supralevator	0	2
Intramural/intersphincteric	0	2
Complex fistula		
No	30	34
Yes	11	8
Treatment of primary tract		
Excision	22	16
Excision and curettage	15	22
Curettage only	4	4
Operating time (min)		
Median (range)	55 (20–90)	55 (23–125)
Interquartile range	35–70	40–75

into place with interrupted polydioxanone sutures. In patients randomized to gentamicin–collagen, half of a 5 × 5 cm sponge was placed under the flap, before tying the sutures; the remaining half was placed deep in the external wound, which was then left open. The median operating time was 55 (range 20–125) min. After surgery patients were given stool softeners and allowed a normal diet from day 1. They were usually discharged the day after surgery.

Follow-up

Patients were evaluated at 1–3 and 12 months after surgery for healing and/or recurrence. Healing was defined as no evidence of external or internal fistula openings, and no recent fistula symptoms. The primary outcome measure was healing rate at 12 months after surgery. The healing rate after 1–3 months, and the relationship between patient characteristics and healing, were also analysed.

Statistical analysis

It was hypothesized that healing would improve after local gentamicin–collagen treatment. The rate of non-healing or recurrence after excision and advancement flap repair for anal fistula was estimated to be 45 per cent[11]. To detect a significant (two-sided $P = 0{\cdot}050$) decrease in recurrence rate to 20 per cent in the treatment group with 80 per cent power, it was estimated that 40 patients were required in each group.

The χ^2 test, Fisher's exact test and Mann–Whitney U test were used for comparison between groups. $P < 0{\cdot}050$ was considered statistically significant. Relative risks and differences in means with 95 per cent confidence intervals were calculated when comparing primary healing and non-healing or recurrence with respect to various patient characteristics and the randomized groups[17].

Results

Between September 1998 and January 2004, a total of 106 patients underwent endoanal advancement flap repair for anal fistula at this centre, of whom 87 agreed to participate in the study and were randomized to surgery alone or surgery with local gentamicin–collagen treatment (*Fig. 1*). Two patients, who were randomized the day before surgery early in the study period, did not undergo advancement flap repair and were excluded. Thereafter randomization was not performed until during surgery. One patient declined further follow-up after the first postoperative evaluation and another, with doubtful healing at 3 months after

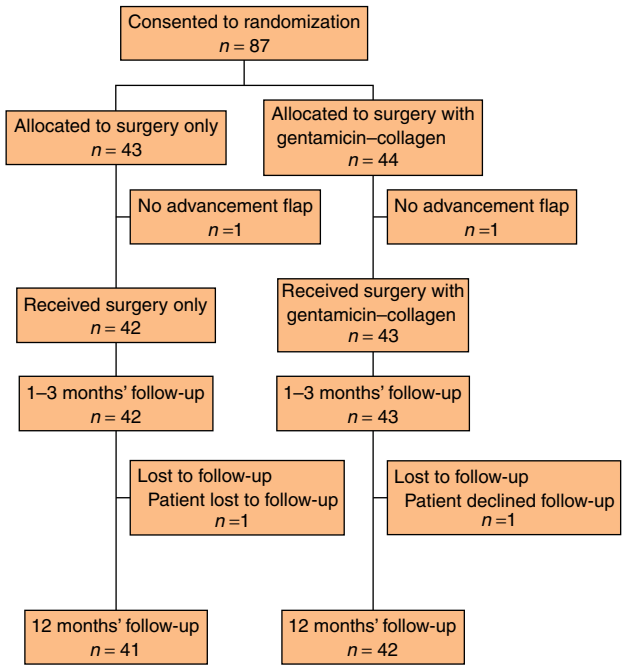

Fig. 1 Study flow chart

surgery, was lost to follow-up. Thus 83 patients remained for analysis 12 months after surgery. With the exception of the two patients excluded because they did no undergo advancement flap repair, the analysis was by intention to treat. There were no adverse events related to the study treatment in either group.

Early follow-up

At early follow-up, 41 (48 per cent) of 85 patients were completely healed. There was no difference between patients randomized to surgery alone (20 of 42 healed) and those who had surgery with gentamicin–collagen (21 of 43 healed). Nine patients who had not completely healed by 1–3 months after surgery had healed by 1 year without further treatment, whereas three patients whose fistula was healed at early follow-up developed a recurrence within 12 months.

Late follow-up

A total of 47 patients (57 per cent) had healed primarily with no recurrence by 1 year after surgery. The healing rate for patients randomized to gentamicin–collagen was 26 of 42, compared with 21 of 41 for those who had surgery alone; the difference was not statistically significant.

Prognostic factors for healing

Healing rates in different subgroups of patients were analysed in an attempt to identify possible prognostic factors. There was no significant difference between healing rates in men (30 of 52 healed) and women (17 of 31). There was a tendency towards a lower healing rate in patients who had undergone previous fistula surgery with curative intent (21 of 42) compared with patients who had undergone incision of an abscess and/or draining seton only or no surgery (26 of 41), but this was not statistically significant. Likewise, there was no significant difference in healing rate of complex (ten of 19) and simple (37 of 64) fistulas. Patients aged 50 years or more tended to have a higher healing rate (27 of 40) than younger patients (20 of 43), but the difference was not significant. The relative risk of non-healing or recurrence was 1·6 (95 per cent confidence interval (c.i.) 0·98 to 2·7) for patients younger than 50 years and 1·4 (95 per cent c.i. 0·8 to 2·2) for those who had undergone fistula surgery previously. There were no differences in overall healing rate in relation to the duration of symptoms, body mass index (BMI) or smoking habit. The operating time was similar in the two randomized groups, and in patients with primary healing compared with those whose fistula recurred.

Discussion

Published randomized studies on fistula surgery are sparse. The dilemma in anal fistula surgery is that the risk of incontinence increases with the radicality of surgery. However, a high recurrence rate may also lead to incontinence owing to scarring and repeated dilatation of the sphincters.

The present study did not demonstrate any significant difference in recurrence rate between the two randomized groups, although there was a tendency towards a lower recurrence rate after local application of gentamicin–collagen. The difference might become significant if a larger number of patients were analysed, but this would require a multicentre study. Such a study was not practicable because the advancement flap technique was in use in few hospitals at the beginning of the present trial. Ideally, this randomized trial should have included a group with a collagen implant without gentamicin, but this would have required an even larger number of patients. Collagen in itself has a haemostatic effect and could theoretically promote wound healing by interacting with platelets, fibroblasts and macrophages.

Earlier larger studies on endoanal advancement flap repair for anal fistula described low recurrence rates of 1–16 per cent[1–3], but in three later studies by Sonoda *et al.*[9], Mizrahi *et al.*[10] and Zimmerman *et al.*[18], each of which included around 100 patients, recurrence rates were 36, 40 and 31 per cent respectively. In a smaller previous study that included 42 patients with mostly cryptoglandular, trans-sphincteric fistulas, the rate of non-healing was 45 per cent[11].

Several factors may influence healing rate and those commonly noted include previous fistula surgery or recurrent fistula, inflammatory bowel disease and complexity of the fistula. Others factors that have received less attention are patients' age, BMI or body surface area, smoking habit, duration of symptoms and antibiotic treatment. In most studies that included both cryptoglandular and Crohn's fistulas, patients with Crohn's disease had higher recurrence rates[2,9,10,19]. Schouten *et al.*[20] found that patients with more than one previous fistula repair had significantly higher recurrence rates than those with one or no previous repair (50 *versus* 13 per cent respectively), but in a later study by the same group there was no difference[18]. In other studies, in which the proportion of patients with previous repairs varied between 15 and 47 per cent, earlier repair had no impact on the recurrence rate[3,9–11]. The use of a draining seton before advancement flap repair resulted in lower recurrence rate in a study by Sonoda *et al.*[9], whereas Zimmerman *et al.*[18] noted that this practice made no difference. In the present study there was a

tendency towards a lower recurrence rate in patients with no previous repair.

Results in relation to fistula complexity are difficult to evaluate as patient groups are often heterogeneous or not comparable. In studies that compared results for repair of rectovaginal and anorectal fistulas, one group found that rectovaginal fistulas had a worse outcome[9], but this was not the case in another study[10].

Sonoda *et al.*[9] noted that greater age was associated with a lower recurrence rate. This result might have been attributable to a higher proportion of patients with Crohn's disease in the younger age groups. The presence or not of Crohn's disease is also a possible explanation for their finding that larger body surface area was associated with a lower recurrence rate. In the study by Zimmerman *et al.*[18], which did not include patients with Crohn's disease, outcome was not related to either age or BMI. In another series age had no impact on recurrence rate, whereas in the present series the recurrence rate tended to be lower among older patients.

Although the advancement flap technique is described in detail in earlier papers, comprehensive information on preoperative preparations and postoperative treatment is not always available. The use of mechanical bowel preparation, postoperative immobilization with or without oral feeding, constipating agents, stool softeners, antibiotic prophylaxis and postoperative treatment varies widely. Some centres use antibiotics only prophylactically[3,18], whereas others continue parenteral antibiotics for 3–5 days after surgery[2,18,20,21] or discharge patients on oral antibiotics[9,21]. Some keep patients on parenteral[2,3] or oral[22] fluids for the first few days, sometimes in combination with constipating agents, whereas others allow an early normal diet[11,18,21]. There are not many comments on the use of antibiotic treatment, but postoperative antibiotics did not have an impact on healing rate in two large retrospective studies[9,10]. In a smaller series, patients who had preoperative prophylaxis and postoperative treatment had better results than those with prophylaxis alone or no antibiotics at all[11]. In a recent study by Zimmerman *et al.*[18] no difference in outcome was noted between similar patients from two centres, one of which administered parental antibiotics for 5 days and the other used antibiotic prophylaxis. In the present study there was a tendency towards better outcome after local gentamicin–collagen treatment, but this was not statistically significant.

There was no clear selection of patients in this study and failure to include patients was based on practical issues such as availability of agent and clinicians' awareness of the study. The results should therefore be applicable to the general population of patients with fistula judged suitable for sphincter-saving surgery. The dropout frequency was low and an intention-to-treat analysis would have yielded similar results.

This study has demonstrated that primary recurrence rates after advancement flap for anal fistula are fairly high and that healing is not significantly improved by local application of gentamicin–collagen.

Acknowledgements

This work was supported by the Swedish Research Council, project no. K2002-73X-14221-01A.

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