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Surgical treatment of perianal and rectal fistula

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Chapter 8

The anal fistula plug treatment compared to the mucosal advancement flap for cryptoglandular high transsphincteric perianal fistulas: A double blinded multicenter randomized trial

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ABSTRACT

Background

The anal fistula plug was developed as alternative treatment for perianal fistulas. The aim was to compare the plug with the mucosal advancement flap for the treatment of high transsphincteric fistulas.

Methods

In a double blinded multicenter randomized trial sixty patients with perianal fistulas were randomized to anal fistula plug or mucosal advancement flap and were blinded for the type of treatment. Outcome parameters were closure rate, postoperative pain (VAS), continence (COREFO, Vaizey, and Wexner score) and quality of life (SF-36 and EQ-5D). Closure was determined by clinical examination by a surgeon blinded for the intervention.

Results

At a follow-up of 11 months the recurrence rates were 71% (n=22) in the anal fistula plug group and 52% (n=15) in the mucosal advancement group, which was not significantly different. There were no significant differences in postoperative pain, in pre- and postoperative incontinence scores, soiling, and quality of life.

Conclusions

The results of the anal fistula plug and advancement flap are disappointing in multicenter setting. There were no significant differences in recurrence, functional outcome and quality of life between de plug and advancement flap. As the plug is simple to apply and minimally invasive it can be considered as initial treatment option for high transsphincteric fistulas.

INTRODUCTION

Perianal fistulas are frequently encountered in today's surgical practice. Surgical treatment of high transsphincteric perianal fistulas results in low success rates compared to treatment of low perianal fistulas.¹ Several new treatment options have been developed over time, however none of these resulted in success percentages above 80%.² The mucosal advancement flap is currently the best available treatment option resulting in a success percentage of around 60%.^{3;4}

The anal fistula plug was developed to treat perianal fistulas. The plug is a FDA and CE approved bioabsorbable xenograft, made of lyophilized porcine intestinal submucosa by Cook Surgical, Inc., Bloomington, IN. The material has inherent resistance to infection. Furthermore, it does not produce a foreign body reaction, and becomes repopulated by own tissue in a period of about three months. The plug is easy to use and could provide a solution for perianal fistulas. Moreover, the anal fistula plug may reduce the recurrence rate, postoperative pain and incontinence. Johnson *et al.* reported 15 patients treated with the anal fistula plug in a prospective study. They compared the results with ten patients using fibrin glue. Patients with high perianal fistulas were included. At a median follow-up of 13.8 weeks they achieved a significant better fistula closure rate of 87% compared to 40% in the fibrin glue group ($P < 0.05$).⁵ Later publications reported less favorable closure rates (24-71%).⁶⁻¹¹ The aim of this randomized prospective multicenter trial was to compare the anal fistula plug with the mucosal advancement flap for the surgical treatment of cryptoglandular high transsphincteric perianal fistulas with respect to fistula recurrence rate and functional outcome.

METHODS

Study design

The study design was a multicenter double blinded randomized trial comparing the anal fistula plug with the mucosal advancement flap in the treatment of high transsphincteric perianal fistula.

Study population

The study population consisted of patients with perianal fistulas eligible for surgical repair. Inclusion criteria were; age above 18 years, high perianal fistulas of cryptoglandular origin as established during surgery (transsphincteric, upper 2/3 of the sphincter complex which was confined by the puborectal sling and the end of the anal canal), and informed consent. Exclusion criteria were; no internal opening found during surgery, HIV-positive patients, Crohn's disease, malignancy or other causes. Patients presenting in the outpatients department with high perianal fistulas of cryptoglandular origin were asked for informed consent when the patient fulfilled the in- and exclusion criteria. Six hospitals participated in this study, including one academic and five non-academic hospitals.

Study outline

Patients were randomized during surgery to either the anal fistula plug or the mucosal advancement flap. During examination under anaesthesia the in- and exclusion criteria were carefully reviewed before randomization. The computer randomization was done centrally in the Academic Medical Center in Amsterdam, the Netherlands. Block randomization with random block sizes (four and six) was used. Stratification was performed for the randomizing centers.

All the participating surgeons were instructed to obtain uniformity in the use of the plug and the construction of the mucosal flap. Whenever appropriate, surgeons were proctored in the use of the plug by one of the surgeons. Anal fistula plug treatment was done according to the recommendations provided by the consensus panel during the conference held in Chicago in 2007.¹² The plug was purchased from Surgisis (Cook Surgical, Inc., Bloomington, IN). Only in selected cases when the fistula was complex and/or recurrent, MR or anal endosonography was used to outline the fistula tract. All procedures were performed under general or locoregional anaesthesia. Prophylactic broad-spectrum antibiotics were administered only before surgery. During surgery the internal fistula tract opening was identified, followed by cleaning and debriding the fistula tract with hydrogen peroxide. No further curettage was done to minimize trauma to the fistula tract. A suture was attached to the tail of the plug. A probe was inserted into the external opening exiting through the

internal opening and the suture attached to the tail of the plug was grasped. Then the plug was pulled into the fistula tract, tail first. The suture was drawn into the tract until the plug securely blocked the internal opening and fitted snugly within the tract. Any remaining portion of the plug that was not implanted in the tract was trimmed and discarded. The internal end of the plug was sutured in place with at least two Vicryl 3-0 sutures (Ethicon, Amersfoort, the Netherlands). In contrast with former instructions, no external fixation suture was placed. The external opening was left open to allow for drainage of the tract. In case of a wide fistula tract, a second fistula plug was inserted. The mucosal advancement flap was done according to the following technique. The internal opening was excised followed by mobilization of the mucosa, submucosa, and a small amount of muscular fibers from the internal sphincter complex. A rectal flap with a 2 to 3 cm broad base was mobilized. The rectal flap was mobilized sufficiently to cover the internal opening with overlap. Hemostasis was performed to prevent a hematoma under the flap. The fistula tract was curetted. The mucosal flap was sutured in the distal anal canal with Vicryl 3-0 (Ethicon, Amersfoort, the Netherlands). Finally, the fistula tract was excised externally to the anal sphincter in order to ensure an optimal drainage. Patients were blinded for the type of intervention *i.e.* the anal fistula plug or mucosal advancement flap. Postoperatively there was no bowel regimen. Patients in both groups were advised to refrain from physical labour, cycling and sports for two weeks. Patients visited the outpatient department at two weeks, four weeks, and 16 weeks after surgery. Follow-up ended when fistula closure was achieved. At the final follow-up closure rate was determined by clinical examination in the outpatients clinic by a surgeon blinded for the intervention. The fistula was rated closed if the external and the internal opening were closed and no discharge and pain were experienced. Otherwise it was considered as a persistent fistula. No standard endoanal ultrasound or MR was performed at final follow-up.

Primary and secondary endpoints

The primary endpoints of the study were fistula closure rate and continence. Continence was evaluated pre- and postoperatively using the COREFO, the Wexner and the Vaizey score. The COREFO questionnaire has 27 questions to assess colorectal functional outcome.¹³ The Vaizey scale consists of three items about the type

(gas, fluid, solid) and frequency of incontinence (all scored from zero to four) and four additional items that address alteration in lifestyle (zero to four), the need to wear a pad or plug (zero or two), the use of constipating medication (zero or two), and the lack of ability to defer defecation for 15 minutes (zero or four). The total score on the Vaizey scale ranges from zero (complete continence) to 24 (complete incontinence).¹⁴

Secondary endpoints were morbidity, postoperative pain, and quality of life. Postoperatively patients were asked to fill out visual analogue scales (VAS) for pain-measurement. Quality of life was evaluated using the SF-36 questionnaire.¹⁵ The SF-36 measures eight health attributes: physical functioning, social functioning, role limitations due to physical problems, role limitations due to emotional problems, mental health, pain, vitality and general health perception. The higher the score, the better the health rating with 100 points as the maximum for each concept. Health related quality of life was assessed pre- and postoperatively by EQ-5D. This is a simple, self-administered questionnaire in which a patient had to score a one, two or three, reflecting 'no problems', 'moderate problems' and 'extreme problems', respectively. This was scored on five dimensions: mobility, self-care, usual activity, pain/discomfort and anxiety/depression. These scores were generated in a tariff reflecting the preference value associated with a given health state. The utility by Dolan *et al.*¹⁶ was used to calculate the overall health status (= EQ-5D tariff). In which a tariff of -0.6 represented the worst quality of life and 1.0 the best quality of life. Both had to be filled out at postoperative day one till seven and at day 14.

Data collection and monitoring

Data were collected *via* datasheets on paper. Postoperatively questionnaires on pain were filled in by patients. Four months after surgery questionnaires were sent to the patients to assess continence and quality of life.

Ethics

The study was conducted in accordance with the principles of the Declaration of Helsinki and 'good clinical practice' guidelines. The protocol was approved by the Medical Ethics Committee of the Academic Medical Center in Amsterdam and the

local ethical committees of the participating centers. Prior the randomization informed consent was obtained from all patients. The article was drafted according to the Consort Statement.¹⁷

Statistical analysis

Data are presented as median values with ranges unless otherwise specified. Categorical data are presented as frequencies or percentages. Differences between groups were tested using Mann-Whitney U test for continuous data. Chi-squared test was used to test for differences between groups in cases of categorical data. $P < 0.05$ was considered as statistically significant. Statistical analysis was done using the SPSS v.15.0.1 package (SPSS, Chicago, IL). The analysis was performed in accordance with the intention to treat principle.

A success percentage of 87% was reported by Armstrong *et al.* for the anal fistula plug.⁵ For the mucosal advancement flap a success percentage of 37% was reported recently by Van der Hagen *et al.* in a series of 41 patients with a follow-up of 72 months.⁴

To detect an increase in success percentage from 40% to 80%, using a significance level of 0.05, at least 46 patients had to be randomized to achieve a power of 80%. In total, 60 patients were randomized.

RESULTS

Patient characteristics

Between October 2006 and 2008, 104 patients were eligible for this study. Sixty patients were randomized during surgery after fulfilling the in- en exclusion criteria. The flow diagram and the patient characteristics at baseline are presented in Figure 8.1 and Table 8.1 respectively. There were no differences between the two groups with respect to sex, age, BMI, previous fistula surgery, smoking, preoperative seton drainage. Thirty-one patients were randomized to the anal fistula plug, and 29 to the mucosal advancement flap. Seton drainage was done in 17 of the 60 patients for a median duration of four months before final surgery (range 1-36).

Drainage of perianal abscesses during surgery was not necessary in any of the pa-

tients. There were no peroperative complications. Three patients had postoperative complications, one in the plug group and two in the advancement group. In the anal fistula plug group one patient was reoperated because of a perianal abscess occurring one day after surgery at the site of the installed fistula plug. The plug was removed and the abscess drained. One patient was readmitted four days after performing an advancement flap with abdominal pain. Retroperitoneal air was seen in the pelvis on CT scan. The patient was admitted for observation and was discharged after one week without a reintervention. The other patient had a postoperative bleeding 10 days after flap repair requiring reoperation. The postoperative pain was assessed by using the visual analogue scale (VAS).

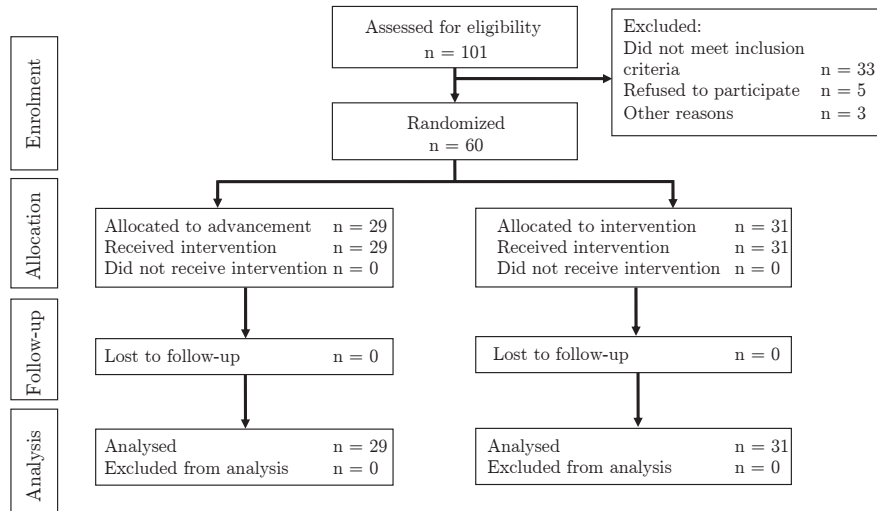


Figure 8.1 – Trial flow diagram.

The mean VAS was 3 (± 3) at day one compared to 4 (± 2.5) in the advancement group (Figure 8.2). Overall there were no differences between both groups ($p=0.143$). Four of the 31 patients (13%) reported that plug had fallen out, all within 10 days after surgery.

At a median follow-up of 11 months (range 5-27), the recurrence rate was 71% ($n=22$) in the anal fistula plug group. In the advancement flap repair group the fistula recurred in 52% ($n=15$) which was not significant different from the anal fistula plug group. All patients with a recurrent fistula were symptomatic. Con-

tinence was assessed by COREFO, Vaizey and the Wexner score. The outcome of these questionnaires is presented in Table 8.2. The continence was not significantly different pre- and postoperatively in the COREFO ($p=0.373$), Vaizey ($p=0.618$) and Wexner ($p=0.947$) questionnaires. The same results were found when soiling was assessed. Soiling was reported preoperatively in the fistula plug group and the advancement group in 33% and 36% respectively ($p=0.852$). Postoperatively soiling was reported in the plug group and the advancement group in 29% and 48% respectively ($p=0.143$). The amount of soiling pre- and postoperatively was not statistically significant different in either group. The Wexner score in the plug group was 5.50 (range 0-16) before surgery and was 5.50 (range 0-14) after surgery. In the advancement group the Wexner score was 7.00 (range 0-12) before surgery and 6.50 (range 0-16) after surgery. These results were not significantly different before ($p=0.859$) or after surgery ($p=0.947$) between the anal fistula plug group and the advancement group.

Quality of life was assessed by SF-36 and EQ-5D before surgery and after 16 weeks. In the SF-36 in none of the subscales there were statistically significant differences. The results were equal pre- and postoperative in both groups. The EQ-5D tariff in the plug group was 0.796 (range 0.62-1.00) before surgery compared to 0.830 (range 0.52-1.00) after surgery. The analysis of the EQ-5D the results were also not significantly different pre- and postoperatively.

Table 8.1 – Patient characteristics.

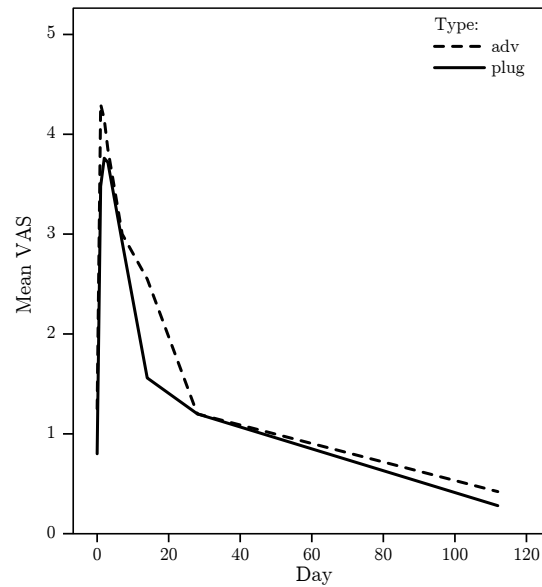
Variable	Plug (n=31)*	Adv (n=29)†	P-value
M:F	23:8	19:10	0.464
Age (median in years)	45 (24-79)	42 (24-61)	0.211
BMI (kg/m ²)	25 (17-35)	27 (21-36)	0.429
Tertiary referral	11	8	0.616
Previous fistula surgery (n)	23	20	0.882
Amount of previous surgery	2 (1-6)	2 (1-5)	0.494
Smoking	14	9	0.469
Preoperative seton drainage	8	9	0.647
Day case surgery	22	22	0.668
Operation time (min)	25 (13-36)	28 (17-50)	0.052

*Anal fistula plug, †Advancement flap

Table 8.2 – Vaizey scale and colorectal functional outcome (COREFO) for patients treated by anal fistula plug or rectal advancement before and after surgery.

Scale, mean (SD)	Fistula plug (pre)	Fistula plug (post)	Advancement (pre)	Advancement (post)
Vaizey[§]				
Incontinence	1.3 (± 1.8)	1.8 (± 2.0)	1.4 (± 2.3)	2.0 (± 2.3)
Social impact	5.4 (± 2.4)	5.4 (± 2.3)	5.6 (± 2.0)	5.7 (± 1.5)
Total	6.7 (± 3.3)	7.2 (± 3.7)	7.0 (± 3.9)	7.7 (± 3.2)
COREFO[¶]				
Incontinence range	14.8 (± 13.1)	19.2 (± 17.2)	16.8 (± 15.6)	13.9 (± 13.7)
Social impact	18.8 (± 21.7)	22.4 (± 21.9)	13.8 (± 19.7)	17.7 (± 21.0)
Frequency	10.0 (± 15.7)	8.5 (± 10.0)	6.0 (± 6.4)	9.5 (± 7.8)
Stool-related aspects	22.3 (± 23.2)	20.3 (± 22.0)	27.8 (± 23.5)	19.8 (± 16.3)
Medication	12.0 (± 23.2)	11.3 (± 22.4)	7.1 (± 17.4)	7.5 (± 17.3)
Total	16.3 (± 14.5)	18.7 (± 16.0)	15.1 (± 13.5)	14.8 (± 12.7)

[§]Mean score ranging from 0-24 (complete continence-complete incontinence) for the total score. Both subscale scores range from 0-12. [¶]Mean score per category after linear transformation to a score from 0-100, higher score represents an increased level of continence disturbance. As the total score, all subscales range from 0-100.

**Figure 8.2** – Postoperative pain was assessed by using the visual analogue scale (VAS). Adv=Advancement flap group

DISCUSSION

The present randomized multicenter trial was conducted to assess the value of the anal fistula plug for the treatment of high perianal fistulas in comparison to the mucosal advancement flap. At a median follow-up of 11 months the recurrence rates in both groups were not significantly different. In the plug group the recurrence rate was 71% compared to 52% in the group treated by the mucosal advancement. There were no differences in terms of postoperative pain scores and quality of life after surgery. The continence was not significantly different pre- and postoperatively for COREFO, Vaizey, or the Wexner score in both groups.

The main objective in the treatment of perianal fistula is healing of the fistula by closing the internal opening while preserving anal continence. The treatment currently most often used is the mucosal advancement flap. However, this technique does not result invariably in high success rates.¹ The anal fistula plug appears to be a promising alternative to the current treatment options for high perianal fistulas. The initial results indicated potential advantages with respect to recurrence rate, postoperative pain and continence. Furthermore the plug is minimally invasive as it is technically easy to install in the fistula tract.

In this series, the results of the anal fistula plug placement were disappointing. The recurrence rates found in literature for the anal fistula plug vary and range from 12% to 86%.^{7;18–21} Ortiz *et al.* conducted a randomized clinical trial that was discontinued due to a high amount of early recurrences in the fistula plug group.¹¹ In a series of 31 patients with high transsphincteric fistulas the fistula recurred in 12 of 15 patients (80%) treated with anal fistula plug. It is believed that inadequate fixation and early fall out of the plug is responsible for the failures.¹⁰ In the current study this occurred only in four patients, all within the first 10 days. All plugs were fixed according to the guidelines as presented after the consensus meeting.¹²

One of the features of plug placement was the expected reduction of postoperative pain compared to the advancement flap. Part of the pain and discomfort after mucosal flap advancement is caused by the excision of the fistula tract externally to the anal sphincter in order to ensure optimal drainage. Surprisingly no differences were found. A subanalysis was done assessing the pain in the first days following surgery. Also in these groups no differences were found.

Continence was assessed by COREFO, Vaizey, and Wexner questionnaires pre-

and postoperatively. There were no differences between the groups before or after surgery. In both groups soiling was reported in a significant amount of patients, however this was not significantly different from the situation before surgery. In a recent study describing the results of the surgical treatment of perianal fistulas of cryptoglandular origin soiling was reported following surgery in 40% of the patients.²² However, in these series 109 patients were treated with fistulotomy for low perianal fistulas and a rectal advancement flap was performed in 70 patients for high transsphincteric fistulas. In a series of 61 patients with perianal fistulas as result of Crohn's disease between 54% and 75% of the patients reported soiling.²³ In neither of these two studies the preoperative amount of soiling was known.

In the current study the quality of life was assessed by SF-36 and EQ-5D questionnaires. The results were comparable in both groups. A possible drawback from the quality of life assessment in patients with perianal fistulas is the small impact of the anal disease in overall quality of life. None of the used questionnaires is directed towards perianal disease. Currently there is no data in the literature on quality of life in perianal fistulas.

The sample size calculation²⁴ was based on the first study available on the anal fistula plug in which the success rate was 87%.⁵ Looking at the current available literature probably if the trial would be conducted at this moment the sample size would be larger which could result in significant results.

Another important aspect of the plug is the cost of the device. Besides the plug itself, the materials used for the installation of the plug are identical to the advancement flap. When the plug is compared to the conventional treatment option it is considerably more expensive. The price of the anal fistula plug is 690 euro. As a result, the cost of the placement of the plug is 690 euro more than the mucosal advancement flap.

In conclusion, both the results of the anal fistula plug and mucosal advancement flap are disappointing in multicenter setting in a group of patients with only high transsphincteric fistulas. There were no significant differences in recurrence, functional outcome and quality of life between de plug and advancement. As the plug is technically simple to install and minimally invasive, it can be considered to use as an initial treatment option for high transsphincteric fistulas despite of the high costs.

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