Randomized controlled trial of minimally invasive surgery using acellular dermal matrix for complex anorectal fistula

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Abstract
AIM: To compare the efficacy and safety of acellular dermal matrix (ADM) bioprosthetic material and endorectal advancement flap (ERAF) in treatment of complex anorectal fistula.

METHODS: Ninety consecutive patients with complex anorectal fistulae admitted to Anorectal Surgical Department of First Affiliated Hospital, Xinjiang Medical University from March 2008 to July 2009, were enrolled in this study. Complex anorectal fistula was diagnosed following its clinical, radiographic, or endoscopic diagnostic criteria. Under spinal anesthesia, patients underwent identification and irrigation of the fistula tracts using hydrogen peroxide. ADM was securely sutured at the secondary opening to the primary opening using absorbable suture. Outcomes of ADM and ERAF closure were compared in terms of success rate, fecal incontinence rate, anorectal deformity rate, postoperative pain time, closure time and life quality score. Success was defined as closure of all external openings, absence of drainage without further intervention, and absence of abcess formation. Follow-up examination was performed 2 d, 2, 4, 6, 12 wk, and 5 mo after surgery, respectively.

RESULTS: No patient was lost to follow-up. The overall success rate was 82.22% (37/45) 5.7 mo after surgery. ADM dislodgement occurred in 5 patients (11.11%), abscess formation was found in 1 patient, and fistula recurred in 2 patients. Of the 13 patients with recurrent fistula using ERAF, 5 (11.11%) received surgical drainage because of abscess formation. The success rate, postoperative pain time and closure time of ADM were significantly higher than those of ERAF (P < 0.05). However, no difference was observed in fecal incontinence rate and anorectal deformity rate after treatment with ADM and ERAF.

CONCLUSION: Closure of fistula tract opening with ADM is an effective procedure for complex anorectal fistula. ADM should be considered a first line treatment for patients with complex anorectal fistula.

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Key words: Acellular dermal matrix; Surgery; Transsphincteric complex fistula

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INTRODUCTION

Anal fistula, an abnormal communication between the anal or rectal lumen and perianal skin, is a common condition in general population, and occurs in 5.6 per 100,000 women and in 12.3 per 100,000 men\(^\text{[1]}\), predominantly in the third and fourth decades of life\(^\text{[2]}\). It is believed that infection of the intersphincteric glands is the initiating event in anorectal fistula, in a process known as the cryptoglandular hyposis\(^\text{[3]}\). It is also commonly believed that surgery is the only way to cure it. Up to now, its treatment is diverse due to lack of standard treatment. Incorrect diagnosis and treatment are the important reason of anorectal surgery failure\(^\text{[4]}\). Traditional surgical procedures include fistulotomy, endorectal advancement flap (ERAF), loose-seton placement, and fibrin glue installation. Anal fistula is described according to the level at which it transgresses the anal sphincter. If the internal opening begins above the anal sphincter, the fistula is described as “high” or transphincteric. Traditional surgery for transphincteric anal fistula often requires staged operations with fistulotomy and seton insertion. The surgery usually results in large and deep wounds which can take months to heal. Moreover, risk of fecal incontinence is inevitable because part of the anal sphincter is divided during surgery. The success rate of these techniques is disappointing. Fistulotomy invariably requires at least some division of the sphincter muscle with risk of incontinence\(^\text{[5]}\), thus leading to a high recurrence and fecal incontinence. It has been reported that the recurrence rate of ERAF for transphincteric anal fistula is 0%-63%\(^\text{[6]}\). Although fibrin glue is an alternative to fistulotomy, its long-term closure rate is low\(^\text{[7]}\). The liquid consistency of fibrin glue is not ideal for closing anorectal fistula, because it is easily extruded from the fistula tract due to the increased pressure\(^\text{[8]}\). Meta analysis indicates that the healing rate of fibrin glue is not significantly different from that of other sphincter saving procedures for fistula\(^\text{[9]}\). Complete closure of primary opening and sphincter preserving are the key to successful anorectal fistula surgery. An alternative strategy is to obliterate the fistula tract.

Using a biological substance to close complex anorectal fistula has attracted attention in recent years. A biological anal fistula plug can securely close the primary opening, thus enabling the surgeon to eradicate the fistula tract with a minimal damage to the sphincter. We report our experience with the management of complex anorectal fistulae using acellular dermal matrix (ADM) which is similar to acellular extracellular matrix (AEM). It is a newly developed biomaterial from pigs that have a collagen structure almost identical to that of humans. During manufacturing of the ADM, living cells are removed by special processes to ensure that no transmittable diseases are present in the tissue.

MATERIALS AND METHODS

**Study design**

Protocol synopsis for this trial and supporting CONSORT checklist were used as supporting information (Figure 1). ADM trial was a single-center, randomized, prospective, single blinded, controlled trial.

**Inclusion/exclusion criteria**

Patients at the age of 12-60 years with 2-6 cm long intra-sphincteric and transsphincteric anorectal complex fistulae identified with a fistula probe during surgery, who gave their informed consent, were included in this trial. Patients with no internal opening found during surgery, and those with positive human immunodeficiency virus, Crohn’s disease, malignant cause, tuberculosis, hydradenitis suppurativa, severe cardiovascular state, diabetes, pregnancy, and sepsis were excluded.

**Patients**

Ninety consecutive patients with complex anorectal fistula, admitted to First Affiliated Hospital of Xinjiang Medical University from March 2008 and July 2009, were randomized into ADM group or ERAF group. Patients were blinded for ADM or ERAF. Demographic data (age and gender of the patients), smoking history, course of disease, fistula types and follow-up time of each patient were recorded (Table 1).
generated random codes were used to produce envelopes containing the information about “ADM” or “ERAF”. These envelopes were prepared by a statistician who was not involved in treatment of patients or in other work specific to the study. Computer randomization was completed at Medical Statistical Center, First Affiliated Hospital of Xinjiang Medical University.

**Ethics**

The trial, conducted in accordance with the Declaration of Helsinki and “good clinical practice” guidelines, local regulations, and China government laws, was approved by the Medical Ethics Committee of First Affiliated Hospital of Xinjiang Medical University. Prior to the randomization, all patients who gave their informed consent were required to comment on the informed consent before the trial.

**Sample size and power**

Before the trial, sample size was calculated using SPSS software 13.0 version. Armstrong reported that the success rate of anal fistula plug is 87% for the closure of fistula opening and van der Hagen et al showed that the success rate of EERAF is 57% for the closure of fistula opening, indicating that to increase the success rate from 40% to 80%, at least 44 patients in each group had to be randomized to achieve a power of 90%.

**Surgical technique**

All patients underwent a proctology at surgery for configuration of the fistula passage. All patients who were given prophylactic broad-spectrum antibiotics underwent preparative regular test, endoscopy, anorectal ultrasound and mechanical bowel preparation before surgery. Anesthesia was induced with broad-spectrum parenteral antibiotics and 500 mg of intravenous metronidazole. Patients were placed in the prone jackknife position under spinal or general anesthesia. Primary opening was located using a fistula probe or by injecting hydrogen peroxide into the fistula tract. All fistula tracts were irrigated with a hydrogen peroxide solution. A fistula probe was passed through the fistula tract from the secondary opening and pulled out through the primary opening. After the fistula tract was identified and cleaned with curettage and hydrogen peroxide, ADM materials were prepared according to the length and lumen of the fistula tract, inserted into the clean fistula tracts, and pulled into a position using a silk suture passed through the fistula tract and secured to the tip of ADM, then via the secondary opening until it fitted snugly into the primary opening. Excess ADM material was trimmed with the secondary and primary openings flushed and secured to the mucosa and internal sphincter with a 3-0 vicryl suture. All data were recorded and analyzed by the same statistician member who did not attend the intervention.

Rectal advancement flap was done for the control group according to the following techniques. In brief, the primary 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 2-3 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 internal opening was not closed before the flap was advanced over the primary opening. Finally, the flap was sutured to the distal anal canal. All patients were not given analgesics after surgery. Patients were followed up at the discretion of the operating surgeon. Per-operative management (including daily activities, diet) of the two groups was identical.

ADM used in this study was an absorbable J-I type (J. Y. Life Tissue Engineering Co., Ltd., China). It is a complex collagen structure manufactured from the submucosa of porcine small intestine. According to the information about the J-I ADM product, its manufacturing is completely similar to Surgisis AFDTM (Cook Surgical Inc., Bloomington, Indiana, USA). These biologically absorbable xenografts including ADM, AEM, Surgisis or other kinds of anal fistula plug consist of an acellular scaffold similar to the human extracellular matrix. In general, integration into the implant begins within a few days after such materials are placed into the fistula tract through penetrating capillaries.

**Postoperative care and follow-up**

All patients were hospitalized with a clear liquid diet and bed rest for 48 h. Activity was restricted to minimal. Patients were required to have a warm Sitz bath, 3 times a day. All patients were given intravenous broad-spectrum antibiotics and metronidazole for 3 d after surgery. Stool softeners were used for 10 d. No activity restriction was requested after discharge. Follow-up examination was performed in the outpatient department 2 d, 2, 4, 6, 12 wk, and 5 mo after surgery, respectively. The primary endpoints of this trial were fistula closure rate. Success was defined as closure of all external openings, absence of drainage without further intervention, and no abscess formation. The presence of one persistent fistula tract was considered surgical failure. Outcomes of ADM and EERAF closure were compared in terms of success rate, fecal incontinence rate, anorectal deformity rate, postoperative pain time, closure time and life quality score.

Continence was evaluated before and after opera-
tions using the Wexner score and Vaizey scale. The Vaizey scale consists of 3 items about the type (gas, fluid, solid) and frequency of incontinence (Table 2) [15]. The secondary endpoints were healing time, postoperative pain time, postoperative deformity rate, incontinence rate and quality of life. Patients after operation were asked to grade their pain on a visual analogue scale (VAS: 0 = no pain; 10 = worst imaginable pain) at different time points during the follow-up. Fecal incontinence was evaluated according to the Williams grade. Quality of life was evaluated using the life quality scale system (Table 3) [16].

Statistical analysis
Statistical analysis was performed using SPSS software 13.0 version. Recurrence rate, fecal incontinence rate and anal deformity rate associated with each intervention option were assessed by χ² test or Fisher’s exact test. Healing time and postoperative pain time were calculated by Wilcoxon’s test or log rank test. P < 0.05 was considered statistically significant.

RESULTS
Three patients were excluded from this trial because of diabetes and Crohn’s disease. All patients completed the follow-up during which their data were collected. No patient was lost to follow-up. No significant difference was found in the characteristics of patients including age, sex, classification of fistula and median follow-up time between the two groups. The median follow-up time of ADM and ERAF groups was 5.7 mo (range 5.1-6.4 mo) and 6.1 mo (range 5.9-6.5 mo), respectively (P = 0.12). No severe adverse effect occurred in the patients.

The fistula occurred in 2 (4.45%) and 13 (28.89%) of the 45 patients in the ADM and ERAF groups, respectively (P = 0.0047), and was healed in 37 (82.22%) and 29 (64.44%) of the 45 patients in ADM and ERAF groups, respectively. Early extrusion of ADM occurred in 4 patients, and late extrusion in 1 patient. The overall fistula healing rate was 82.22% (37/45) in ADM group. Five and 1 patients received drainage surgery in ERAF and ADM groups, respectively. The life quality score was higher, the fistula healing time and postoperative pain time were shorter in the ADM group than in the ERAF group (P < 0.05, Tables 4-7). The recurrence rate of fistula was significantly lower in the ADM group than in the ERAF group. However, no significant difference was observed in incontinence and anal deformity rate between the two groups. In order to clarify the effect of classification on the results, the efficacy and complication rate of intrasphincteric and transsphincteric fistulae were compared (Tables 5 and 6). The recurrence rate of transsphincteric fistula was significantly lower in the ADM group than in the ERAF group. However, no significant difference was observed in the incontinence and anal deformity rate between the two groups.

DISCUSSION
Surgery is considered the predominant and only procedure for anorectal fistula. Although fistulotomy is a simple procedure for fistula, it is not indicated for transsphincteric fistulae because of prohibitive risk of incontinence. Seton cutting, which can slowly divide the sphincter and prevent recurrent abscess formation, is considered a more efficient procedure for transsphincteric fistulae, but can cause incontinence of solid stool in up to 25% of patients [17]. ERAF has become a treatment of choice for most fistulae. However, recent reports sug-

### Table 2 Vaizey score system

| Item                          | Never | Rare | Sometimes | Each week | Everyday |
|-------------------------------|-------|------|-----------|-----------|----------|
| Frequency of incontinence     | 0     | 1    | 2         | 3         | 4        |
| Solid                         | 0     | 1    | 2         | 3         | 4        |
| Liquid                        | 0     | 1    | 2         | 3         | 4        |
| Gas                           | 0     | 1    | 2         | 3         | 4        |
| Alteration in lifestyle       | No    | Yes  |           |           |          |
| Need to wear a pad or plug    | 0     | 2    |           |           |          |
| Use of constipating medication| 0     | 2    |           |           |          |
| Lack of ability to defer defection for 15 min | 0 | 4 | | | |

### Table 3 Life quality scale system

| Question                                                                 | Score |
|--------------------------------------------------------------------------|-------|
| Physical                                                                 |
| P1 It is difficult for me to get out and do things like going to a movie or to church |       |
| P2 I avoid travelling                                                     |       |
| P3 Whenever I am away from home, I try and stay near a toilet as much as possible |       |
| P4 I can’t hold on to my bowel motion long enough to get to the bathroom |       |
| P5 I try to prevent bowel accidents by staying very near a bathroom      |       |
| P6 I cut down on how much I eat before I go out                          |       |
| P7 Whenever I go somewhere new, I make sure I know where the toilets are |       |
| Social                                                                   |
| S1 I avoid visiting my friends                                           |       |
| S2 I avoid staying the night away from home                              |       |
| S3 It is important to plan my daily activities around my bowel habit     |       |
| S4 I leak stool without even noticing it                                 |       |
| S5 I can’t do many things I want to do                                   |       |
| S6 I have sex less often than I would like                               |       |
| S7 I feel different from other people                                   |       |
| S8 I avoid travelling by plane or public transport                       |       |
| S9 I avoid going out to eat                                              |       |
| S10 I am afraid to have sex                                              |       |
| Emotional                                                                |
| E1 I am afraid to go out                                                 |       |
| E2 I worry about not being able to get to the toilet in time             |       |
| E3 I feel unhealthy                                                      |       |
| E4 I feel ashamed                                                        |       |
| E5 I worry about bowel accidents                                         |       |
| E6 I feel depressed                                                      |       |
| E7 I worry about the smell                                               |       |
| E8 I enjoy life less                                                     |       |
| E9 The possibility of bowel accidents is always on my mind               |       |
| E10 During the past month have you felt so sad, discouraged, hopeless, or had so many | |
| Overall sense of well-being                                             |       |
| Problems that you wondered whether anything was worthwhile?             |       |
| General, would you say your health is excellent/very good/good/fair/poor?|       |


Table 4 Recurrence, fecal incontinence, anal deformity, postoperative pain time, and healing time of patients with ADM or ERAF \( n (\%) \)

|          | ADM | ERAF | \( P \) value |
|----------|-----|------|--------------|
| \( n \)  | 45  | 45   |              |
| Recurrence | 2 (4.45) | 13 (28.89) | 0.0047 |
| Fecal incontinence | 1 (2.22) | 4 (8.89) | 0.3574 |
| Anal deformity | 0 (0) | 3 (6.76) | 0.2402 |
| Postoperative pain time (d) | 1.5 ± 0.5 | 7.5 ± 1.8 | 0.0000 |
| Healing time (d) | 7.6 ± 3.6 | 25.9 ± 5.5 | 0.0000 |

Table 5 Recurrence, fecal incontinence, anal deformity, postoperative pain time, and healing time of patients with intrasphincteric fistula, ADM or ERAF \( n (\%) \)

|          | Intra ADM | Intra ERAF | \( P \) value |
|----------|-----------|------------|--------------|
| \( n \)  | 19        | 17         |              |
| Recurrence | 0 (0.00)   | 3 (17.65) | 0.1907 |
| Fecal incontinence | 0 (0.00) | 0 (0.00) |          |
| Anal deformity | 0 (0.00) | 0 (0.00) |          |
| Postoperative pain time (d) | 1.2 ± 0.4 | 5.5 ± 1.9 | 0.0000 |
| Healing time (d) | 7.1 ± 3.4 | 24.6 ± 5.4 | 0.0000 |

The possible reason why our success rate was much lower than the reported findings \(^{[38]}\) is that all the procedures were performed by 4 surgeons. Another possible explanation for this difference may be the selection bias of patients. Contrary to our results, however, Zubaidi et al.\(^{[35]}\) found that transsphincteric fistula is more likely to heal after plug placement. Ky et al.\(^{[38]}\) and Ellis\(^{[39]}\) have reported a high success rate of plug placement for transsphincteric fistula. We focused on fistula channel debridement and complete drainage during surgery in order to prevent abscess formation as previously described\(^{[40]}\). Because more granulation tissues in the fistula tract can function as a barrier to cellular infiltration into ADM, it is difficult to imagine that simple irrigation with hydrogen peroxide without thorough curettage of the tract can clean the tract and allow incorporation of ADM material into its surroundings. We believe that the low success rate in the study by Safar et al.\(^{[31]}\) is due to inadequate debridement and curettage of granulation tissue. Complete debridement, curettage of the tract, and hydrogen peroxide irrigation may be important for the surgery to achieve a greater success rate. This point differs from that of Schwandner et al.\(^{[41]}\). In our study, 5 patients (11.11%) experienced ADM dislodgement, which may be due to the poor ADM fixation to the sphincter in the primary opening. Technical failure associated with plug-falling out is an important reason for surgery failure\(^{[41]}\).

In our study, the success rate of ADM for complex fistula was 82.22% (37/45), indicating that placement of ADM is a safe, beneficial, minimally invasive procedure for fistula, and can protect the anal function.

Laws et al.\(^{[41]}\) proposed to combine anal fistula plug and advancement flap for fistula. However, we hold that selection of patients, complete debridement, tract prepa-
ration and plug fixation are closely associated with the final success rate.

It is essential to use antibiotics before surgery. It was reported that anorectal abscess is not formed in patients after treatment with AEM[39] or Surgisis[36]. However, early infection occurred in our study. Although use of Surgisis is not associated with perianal sepsis[36], it has been shown that the incidence of severe perianal sepsis is 23%[41]. Although the sepsis rate of ADM (1/45) was significantly lower than that of ERAF (5/45) in our study, more evidence is needed for the evaluation of ADM. Safar et al[37] suggested that the success rate of plug for fistula is not associated with the preoperative bowel preparation, but we performed mechanical bowel preparation before surgery to avoid possible constipation or infection after surgery.

In our study, ADM could obviously shorten the postoperative pain time and the fistula healing time, but not the deformity and incontinence rate of transsphincteric fistula. Transsphincteric fistula recurred in 2 patients, suggesting that it is necessary to perform multicenter randomized controlled trial to evaluate the efficiency of ADM on transsphincteric complex fistula.

A significant number of patients in ERAF group in this study had long-term continence disturbances in forms of gas and liquid stool incontinence, which may be associated with ERAF or fistulotomy, abscess drainage, and other anorectal treatment modalities.

An adequate follow-up time is essential in a comparative study of ADM and ERAF for complex fistula. Only one study is available with a long follow-up time[35]. The follow-up time in our study is similar to that in previous studies[32,44,49]. The success rate of ADM for fistula (82.22%) was associated with the ADM itself and the adequate follow-up time in our study. Zubaidi et al[32] showed that a longer follow-up time and over an 80% success rate of biologically absorbable substance for fistula provide better evidence for the use of ADM. Song et al[39] reported convincing results based on 6.3 mo follow-up time. However, Wang et al[35] showed that the success rate of biologically absorbable substance for fistula is only 34% after a follow-up time of 18 mo.

In conclusion, closure of the fistula tract primary opening using ADM is an effective and acceptable procedure for complex anorectal fistula. ADM is a safe, beneficial, minimally invasive procedure for fistula, and can protect anal function. ADM dislodgement is associated with the closure techniques. Further longer-term multicenter randomized controlled clinical trials are needed to evaluate its efficacy on complex anorectal fistula.

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COMMENTS

Background

Anal fistula is an abnormal chronic communication between the anal or rectal lumen and perianal skin. Surgery usually results in large and deep wounds which can take months to heal. Moreover, risk of fecal incontinence is inevitable because part of the anal sphincter is divided during surgery. The success rate of different techniques is disappointing. Using a biological substance to close complex anorectal fistula is attractive.

Research frontiers

Acellular dermal matrix (ADM) is a bioabsorbable xenograft for tissue defect. Application of different kinds of ADM in treatment of anorectal fistula is a hotspot in the World.

Innovations and breakthroughs

Closure of the fistula tract primary opening using ADM is an effective and acceptable alternative to complex anorectal fistula. ADM is a safe, beneficial,
minimally invasive procedure for fistula, and can protect anal function. It should be considered a first line treatment for patients with complex anorectal fistula.

**Applications**

This method can reduce postoperative pain, shorten fistula healing time, and improve the postoperative life quality of patients.

**Peer review**

This is an interesting and generally well written paper with the effects of endorectal mucosal advancement flap and acellular dermis plug on complex fistula compared. The results are striking.

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