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Editorial Board Member of *World Journal of Gastrointestinal Endoscopy*, Mohamed H Emara, BM BCh, MD, MSc, Professor, Hepatology, Gastroenterology and Infectious Diseases Department, Faculty of Medicine, Kafrelsheikh University, Kafrelsheikh 33516, Egypt. emara_20007@yahoo.com

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ORIGINAL ARTICLE

Prospective Study

New hope for esophageal stricture prevention: A prospective single-center trial on acellular dermal matrix

Xin-Yu Fu, Zhen-Yu Jiang, Chen-Yang Zhang, Ling-Yan Shen, Xiao-Dan Yan, Xiao-Kang Li, Jia-Ying Lin, Yi Wang, Xin-Li Mao, Shao-Wei Li

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Xin-Yu Fu, Chen-Yang Zhang, Jia-Ying Lin, Department of Gastr-oenterology, Taizhou Hospital of Zhejiang Province, Wenzhou Medical University, Linhai 317000, Zhejiang Province, China

Zhen-Yu Jiang, Department of Gastroenterology, The Second Affiliated Hospital of Baotou Medical College, Inner Mongolia University of Science and Technology, Baotou 014000, Inner Mongolia Autonomous Region, China

Ling-Yan Shen, Xiao-Dan Yan, Yi Wang, Xin-Li Mao, Shao-Wei Li, Department of Gastr-oenterology, Taizhou Hospital of Zhejiang Province Affiliated to Wenzhou Medical University, Linhai 317000, Zhejiang Province, China

Xiao-Kang Li, Shao-Wei Li, Key Laboratory of Minimally Invasive Techniques & Rapid Rehabilitation of Digestive System Tumor of Zhejiang Province, Taizhou Hospital of Zhejiang Province Affiliated to Wenzhou Medical University, Linhai 317000, Zhejiang Province, China

Xiao-Kang Li, Division of Transplantation Immunology, National Research Institute for Child Health and Development, Tokyo 1540001, Japan

Shao-Wei Li, Institute of Digestive Disease, Taizhou Hospital of Zhejiang Province Affiliated to Wenzhou Medical University, Linhai 317000, Zhejiang Province, China

Corresponding author: Shao-Wei Li, PhD, Associate Professor, Department of Gastr-oenterology, Taizhou Hospital of Zhejiang Province Affiliated to Wenzhou Medical University, No. 150 Xinmen Street, Linhai 317000, Zhejiang Province, China. li_shaowei81@hotmail.com

Abstract

BACKGROUND

Given the high incidence of esophageal cancer in China, an increasing number of patients there are undergoing endoscopic mucosal dissection (ESD). Although the 5-year survival rate after ESD can exceed 95%, esophageal stricture, the most common and serious postoperative complication, affects the long-term prognosis of patients and the quality of life. Autologous mucosal grafts have proven to be successful in preventing stricture after ESD for early esophageal cancer.

AIM

To examine the viability of acellular dermal matrix (ADM) as an alternative to autologous mucosa for the prevention of stricture after ESD.

METHODS

This is a prospective, single-center, controlled study. Consecutive patients who underwent ESD surgery and were willing to undergo autologous mucosal transplantation were recruited between January 1 and December 31, 2017. Consecutive patients who underwent ESD surgery and were willing to undergo ADM transplantation were recruited between January 1 to December 31, 2019. A final three-year follow-up of patients who received transplants was conducted.

RESULTS

Based on the current incidence of esophageal stricture, the sample size required for both the autologous mucosal graft group and the ADM group was calculated to be 160 cases. Due to various factors, a total of 20 patients with autologous mucosal grafts and 25 with ADM grafts were recruited. Based on the inclusion exclusion and withdrawal criteria, 9 patients ultimately received autologous mucosal grafts and completed the follow-up, while 11 patients received ADM grafts and completed the follow-up. Finally, there were 2 cases of stenosis in the autologous mucosal transplantation group with a stenosis rate of 22.22% and 2 cases of stenosis in the ADM transplantation group with a stenosis rate of 18.18%, with no significant difference noted between the groups (P = 0.94).

CONCLUSION

In this prospective, single-center, controlled trial, we compared the effectiveness of autologous mucosa transplantation and ADM for the prevention of esophageal stricture. Due to certain condition limitations, we were unable to recruit sufficient subjects meeting our target requirements. However, we implemented strict inclusion, exclusion, and withdrawal criteria and successfully completed three years of follow-up, resulting in valuable clinical insights. Based on our findings, we hypothesize that ADM may be similarly effective to autologous mucosal transplantation in the prevention of esophageal stricture, offering a comparable and alternative approach. This study provides a new therapeutic idea and direction for the prevention of esophageal stricture.

Key Words: Over-the-scope clip; Duodenal subepithelial lesion; Endoscopic resection; Perforation

Core Tip: Preventing esophageal stricture after endoscopic submucosal dissection (ESD) is a critical challenge in the successful treatment of early esophageal cancer. Acellular dermal matrix (ADM) has recently emerged as a potential solution. This study showed that the preventive effect of ADM on esophageal stricture was comparable to that of autologous mucosa. Despite the study's limited sample size, it includes improved postoperative follow-up and holds clinical significance. The results validate ADM as a viable alternative for preventing esophageal stricture. These findings will potentially revolutionize ESD treatment for early esophageal cancer and provide safer and more accessible options for such patients.

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INTRODUCTION

With the maturity of endoscopic technology, endoscopic submucosal dissection (ESD) can now be used to remove large lesions and ensure a negative margin to the greatest extent[1], making it the preferred treatment for early esophageal cancer. Esophageal stricture is one of the most common and serious complications after ESD, with an incidence of approximately 37%-92%[2]. Its incidence is affected by many factors, mainly including mucosal resection > 3/4 of the esophagus circumference[3], resection length > 30 mm, muscular propria injury, and deep resection depth[4].

Among these factors, the one most closely related to the incidence of stenosis was found to be the scope of resection. According to reports, the incidence of stenosis in mucosal resection > 3/4 cases is 60%-100%, while the stenosis rate in near-total resection can reach 88%-100%[5]. Patients with esophageal stenosis may have varying degrees of dysphagia in more stenotic cases. In severe cases, nausea and vomiting may occur after eating, resulting in long-term insufficiency in the nutritional intake, water and electrolyte imbalance, cachexia, and even fatal inhalation[6,7], seriously affecting the long-term quality of life of patients. Furthermore, in severe cases, repeated endoscopic esophageal dilation or even surgical intervention may be required[8]. This increases the financial, physical, and psychological burden on patients.

How to prevent esophageal stricture safely and effectively is thus a key issue influencing the ESD-based treatment of early esophageal cancer.

At present, the commonly used measures to prevent stenosis are mainly local or systemic applications of glucocorticoids[9]. After the application of hormones, the overall incidence of esophageal stricture was 13.5%, thus effectively reducing the incidence of esophageal stricture[6,10]. However, there is a risk of local esophageal perforation or secondary fatal infection, and some patients are contraindicated for hormone application due to their condition, so hormone therapy cannot be used to prevent stricture in all cases.

With the advent of autologous mucosal transplantation technology, relevant studies have explored the effectiveness of mucosal transplantation in preventing esophageal stricture through animal and human experiments[11,12]. However, while the utility of autologous mucosa for preventing esophageal stricture is well-established, autologous mucosal grafts are still subject to many limitations, as the acquisition of autologous mucosa is dependent on the patient and the required slice of mucosal cells, depending on the extent of the lesion. For example, for large lesions, it is necessary to obtain and prepare the appropriate mucosal slices, which can cause secondary damage to the patient. In addition, not all patients are in a condition to accommodate the acquisition and preparation of autologous mucosa. Therefore, such patients may not be able to undergo transplantation and thereby reduce their risk of stenosis.

Several trials have confirmed that cell sheets prepared by culturing oral mucosal cells have the same characteristics as mucosa and can be applied to prevent stenosis. However, the preparation process is time-consuming, which may delay the patient's treatment window and affect the prognosis. Acellular dermal matrix (ADM) is a kind of dermal substitute obtained from the allogeneic dermis after special treatment to remove its cellular components[13]. It is usually made of pig or human skin inactivated by a virus and cobalt-60[14]. It is prepared by sterilization, decellularization, and other processes[14]. The allogeneic dermis that has cellular components removed and retains elastin, keratan sulfate, laminin, and collagen has very low immune activity and will not induce any rejection[15,16]. In addition, studies have shown that ADM can be beneficial for inducing tissue regeneration and promoting cell growth[17]. During this process, ADM is degraded and utilized by local tissues, which is accompanied by the degradation of ADM itself[18]. It is expected to replace autologous mucosa as a graft after ESD for esophageal cancer and thereby prevent the occurrence of esophageal stricture.

Overall, as a novel material, ADM has the potential to replace autologous mucosal grafts for the prevention of esophageal stenosis. This prospective, single-center controlled study investigated the role of ADM as a substitute for autologous mucosa in the prevention of post-cancer surgery stenosis, with an aim to provide a new perspective and approach for the treatment of esophageal stenosis.

MATERIALS AND METHODS

Study design

This prospective, single-center, controlled study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Taizhou Hospital, Zhejiang Province, under the Institutional Review Board of Wenzhou Medical University (autologous mucosa transplantation approval number: K20190123; ADM transplantation approval number: X20190603). It was registered with the Center for Clinical Trials under registration number ChiCTR200040119.

Inclusion criteria: A preoperative chromoendoscopy assessment meeting the surgical indications; lesion circumference > 1/2; endoscopic treatment under general anesthesia able to be tolerated; agreed to accept inclusion in the clinical trial and sign the informed consent form for the operation.

Exclusion criteria: Eating disorders and absorption disorders with other causes; complication with diabetes and autoimmune diseases or a recent history of taking hormones and immunosuppressants; a history of serious cardiovascular and cerebrovascular diseases, serious liver and kidney insufficiency, or serious chronic lung diseases; acute or chronic infection.

Exit criteria: Postoperative pathological results indicating the need for further surgery, radiotherapy, chemotherapy, or other treatments; severe postoperative stenosis with a poor effect of repeated endoscopic catheter dilation, necessitating radial esophagotomy and surgery; withdrawing from the trial or being lost to follow-up for any reason; patient death.

At the follow-up evaluation, cases with difficulty swallowing and endoscopy showing that the gastroscope could not pass smoothly through the narrowest part, requiring intervention such as endoscopic dilation therapy, were defined as having postoperative stenosis.

Operation details

The surgery was performed using an Olympus GIF-Q260J gastroscope (Olympus Corporation, Japan), high-frequency electric generator, needle-type incision knife, terminal insulated scalpel (IT knife), triangular terminal scalpel (TT knife), trap, and thermal biopsy forceps.

Eligible patients underwent routine ESD and postoperative stenting. At the same time, autologous mucosal transplantation and ADM transplantation were performed for patients in need. Figure 1 illustrates the surgical procedure in brief. Postoperative fasting was performed for 1 to 2 d, and proton pump inhibitor injections were performed for 3 d. Cases with no gastrointestinal bleeding or esophageal perforation were discharged for follow-up. The stent was removed 1 wk after the operation, and gastroscopy was rechecked at 2 wk and 1 and 6 mo to judge whether or not the ESD wound

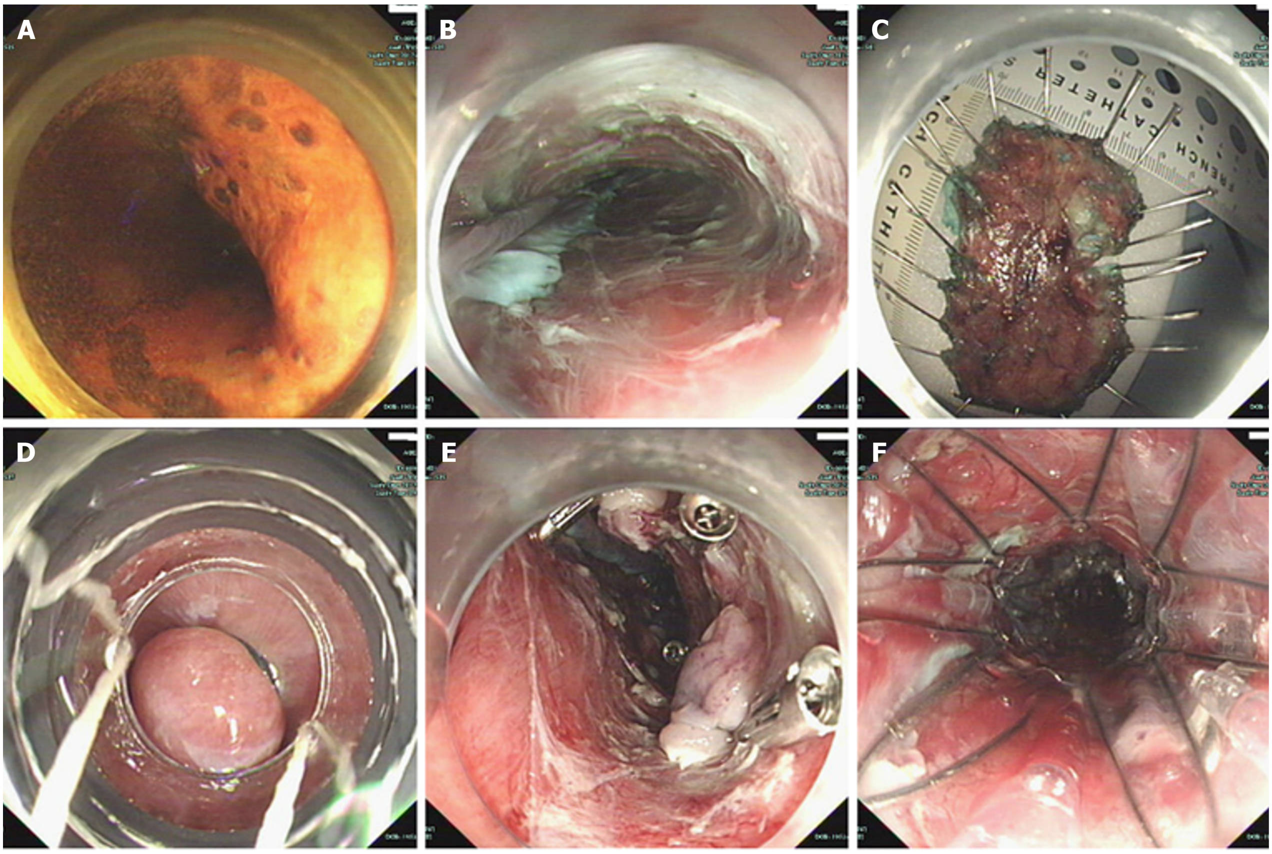

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Figure 1 Operation process of 5/6 periesophageal endoscopic mucosal dissection resection combined with autologous esophageal mucosal transplantation and esophageal covered stent implantation. A: Lugol fluid was sprayed on the whole esophageal mucosa; B: Endoscopic mucosal dissection was performed, and the wound after resection showed an annular mucosal defect; C: The cancerous tissue was removed; D: At the selected normal esophageal mucosa, the mucosa to be transplanted was removed by endoscopic mucosal resection using a polycyclic mucosal resection device; E: A titanium clip was used to secure the excised normal mucosa to the endoscopically peeled mucosal wound; F: The esophageal covered stent was implanted into the compressed transplanted mucosa.

was stenotic using a standard gastroscope entering the gastric cavity to check the survival of the grafted mucosa. Esophageal stenosis was defined as the inability of an Olympus GIF-Q260J gastroscope (with a diameter of 9.9 mm) to pass through the narrow area.

RESULTS

Based on the current incidence of esophageal stricture, a sample of 160 cases was calculated to be required for both the autologous mucosal graft group and the ADM group. A total of 20 patients were recruited in the autologous mucosal transplantation group during the recruitment period from January 1 to December 31, 2017, and a total of 13 patients met the inclusion criteria (excluding 1 with a lesion circumference < 1/2, 1 who refused to sign the informed consent form, 2 with reflux esophagitis, 2 with chronic hepatitis, and 1 with coronary artery disease); of these, 2 patients requested to withdraw from the trial after surgery, 2 were lost to follow-up, and 9 were ultimately included and completed the follow-up.

During the patient recruitment period for the ADM group from January 1 to December 31, 2019, 25 patients were recruited, of whom 14 met the inclusion criteria (excluding 2 with a lesion circumference < 1/2, 3 with reflux esophagitis, 1 with chronic hepatitis, 1 with coronary artery disease, 1 with reflux esophagitis, and 3 with recent aspirin or hormone use), and 3 were lost to follow-up; thus, a total of 11 patients were included and completed the follow-up.

The flow chart is shown in Figure 2. A total of 20 patients in the two groups included in the analysis had completed ESD surgery and follow-up, including 14 males and 6 females, with a mean age of 63.85 ± 7.66 years old and a median age of 64 years old. Four of the patients had hypertension, with the rest showing no other remarkable medical history, and 10 cases had a lesion circumference ≥ 3/4, while another 10 had a circumference of 1/2 to 3/4. There were 3 cases with a lesion length of 1 to 3 cm and 17 with a lesion length of > 3 cm. Six cases of stage IIa, three stage IIb, four stage IIc, and six stage IIa + IIc were analyzed endoscopically; seven cases showed an infiltration depth to the mucosal layer, three to the lamina propria, five to the myxomucosa, and four to the submucosa. Four patients had stenosis after surgery, with a stenosis rate of 20.00%, including 2 patients in the autologous mucosa group with a stenosis rate of 22.22% and a mean

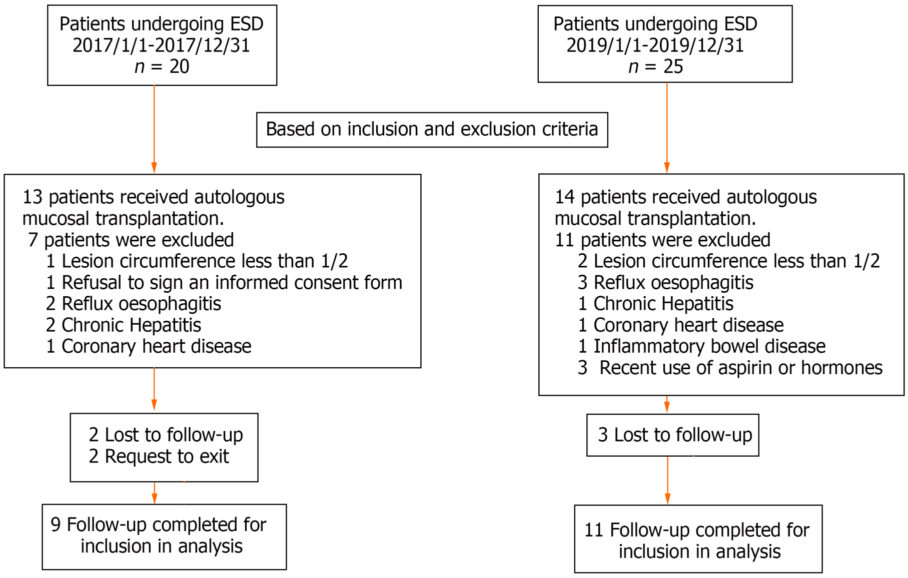

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Figure 2 Flow chart of patient inclusion.

follow-up period of 39.67 ± 2.79 d and 2 patients in the ADM group with a stenosis rate of 18.18% and a mean follow-up period of 43.16 ± 1.77 d (P = 0.94).

Specific details concerning the enrolled patients are shown in Table 1. The comparison between the autologous mucosa group and the ADM group is shown in Table 2.

DISCUSSION

The main components of ADM are collagen and other extracellular matrices, and after modification, it has suitable pore size, porosity, and mechanical strength[19]. It is a scaffold-like repair material with a three-dimensional spatial structure [20]. A large number of studies have confirmed that ADM can induce vascularization and promote cell growth and proliferation when used in the repair of tissues and organs and has good histocompatibility and a low inflammatory response [17,21-23]. Because ADM retains its complete matrix structure and has a unique three-dimensional spatial structure[24], when transplanted into wound repair, it can achieve clinical effects equivalent to autologous full-thickness skin grafting, mainly because ADM plays the role of the dermis when repairing wounds[25]. As a template, ADM can function as a scaffold for cell growth. When ADM is used as an implant, a physical barrier layer can be formed locally to prevent tissue adhesion and pathological proliferation in the local wound so that different tissues can independently complete their healing processes[25].

Some studies have reported the use of ADM as an implant barrier to prevent Frey's syndrome after parotidectomy[26,27], with none of the implants showing rejection reactions. The iodine G-starch test was used one year after surgery, and only two cases were positive, showing a significant difference from the control group[26]. ADM also covers wounds and fills tissue defects. The suitable structure, performance, and function of ADM are a strong guarantee of its utility as a bioremediation material.

ADM has received much attention and been widely used in clinical practice, such as in the repair of burn wounds[28], breast reconstruction[29], and oral mucosa repair[30]. In addition, as a new medical material, it can be degraded and absorbed by the human body. The process of degradation and absorption promotes the regeneration of the patient's own tissues and reduces the occurrence of inflammation. In theory, it can also completely replace autogenous mucosa[18,31].

Compared to ADM, autologous mucosa requires a longer preparation time, which can delay treatment and result in a poor prognosis. In addition, the mucosa can be obtained and prepared in such a way that it can cause secondary damage to the patient, which can be aggravated if the lesion is large; at the same time, since the autologous mucosa is taken from the patient, the quality of the mucosa can be affected if the patient has more underlying diseases, thus affecting the outcome. In addition, if the patient is unable to donate mucosa for the preparation of a mucosal sheet for grafting, the mucosa cannot be grafted postoperatively to prevent stenosis. It has been reported that the same effect can be achieved by preparing mucosal slices from autologous oral mucosa culture. Although this approach reduces the damage and impact caused by the patient's own factors, it also requires a relatively long preparation time.

For early-stage esophageal cancer, early surgery is necessary to obtain a better prognosis. The use of ADM overcomes these issues. The preparation of ADM is not dependent on the patient, so it is not affected by the patient's own condition and does not delay treatment. Furthermore, since the components of the cells that cause the body's immune response are removed, there is basically no immune response.

Table 1 Basic information of 20 patients

Participant	Age (yr)	Gender	Endoscopic morphology	Trauma length (cm)	Circumference of the wound	Infiltration depth	Postoperative stenosis	Occurrence of stenosis time (d)	Number of ADM used (slices)	Follow-up time (mo)	Graft mucosa survival
1	63	Male	IIa + IIc	6	2/3	Mucosal muscle layer	No	No	0	44.13	Yes
2	63	Male	IIb	5	3/4	Submucosa	No	No	0	42.73	Yes
3	58	Male	IIb	2	1/2	Mucosal muscle layer	No	No	0	40.87	Yes
4	67	Male	IIa	4	1/2	Mucosa layer	No	No	0	39.93	Yes
5	73	Female	IIb	4	4/5	Mucosal muscle layer	No	No	0	39.70	Yes
6	58	Male	IIa + IIc	5	1	Superficial submucosa	No	No	0	38.77	Yes
7	69	Female	IIa	6	4/5	Mucosal layer	No	No	0	38.53	Yes
8	69	Female	IIa	5	3/4	Mucosal layer	Yes	98	0	37.83	Yes
9	56	Male	IIa + IIc	8	1	Submucosa	Yes	44	0	34.57	Yes
10	56	Male	IIa	2	2/3	Mucosal layer	No	No	1	44.90	Yes
11	65	Male	IIa + IIc	3	2/3	Mucosal muscle superficial layer	No	No	1	44.90	Yes
12	60	Male	IIc	3	2/3	Mucosal lamina propria	No	No	1	44.43	Yes
13	73	Male	IIc	5	3/5	Mucosal lamina propria	No	No	1	43.97	Yes
14	49	Male	IIc	3	1/2	Mucosal layer	No	No	1	43.97	Yes
15	73	Female	IIa	5	3/5	Mucosal muscle layer	Yes	41	4	43.50	Yes
16	66	Male	IIc	2	4/5	Mucosal layer	No	No	1	43.03	Yes
17	78	Male	IIa + IIc	5	3/4	Mucosal layer	No	No	3	42.57	Yes
18	61	Female	IIa	3	1/2	Mucosal layer	No	No	1	42.57	Yes
19	52	Female	IIa	10	1	Submucosa	Yes	62	4	42.33	Yes
20	68	Male	IIa + IIc	6	1	Mucosal lamina propria	No	No	1	38.60	Yes

ADM: Acellular dermal matrix.

Table 2 Analysis of lesions in the autologous mucosal transplantation group and acellular dermal matrix transplantation group

	Group 1 (n = 9)	Group 2 (n = 11)	P value
Gender			0.77
Male	6	8	
Female	3	3	
Age			0.94
≥ 60 yr	3	4	
< 60 yr	6	7	
Wound circumference			0.23
1/2-3/4 circumference	3	7	
3/4-full circumference	6	4	
Wound length			0.22
< 10 mm	0	0	
10-30 mm	1	2	
> 30 mm	8	9	
Endoscopic morphology			0.81
IIa	3	3	
IIb	3	0	
IIc	0	4	
IIa + IIc	3	3	
Invasion depth			0.19
Mucosal layer	3	4	
Lamina propria	0	3	
Muscularis mucosa	3	2	
Submucosa	3	1	
Follow-up time (mo)	39.67 (34.57-44.13)	43.16 (38.60-44.90)	0.52

Group 1: Autologous mucous membrane transplantation group; Group 2: Acellular dermal matrix transplantation group.

Given the above, ADM seems to have the same potential as autologous mucosa to prevent esophageal stricture, but no reports or studies on the use of ADM to prevent stricture after human esophageal ESD have yet been published. The present study was conducted to verify the utility of ADM to prevent esophageal stricture in a prospective manner. A total of 9 patients with autologous mucosal grafts and 11 with ADM grafts were enrolled in the study and followed for approximately 3 years with a mean follow-up time of 41.59 mo. There were 2 cases of stenosis in the autologous mucosa, with a stenosis rate of 22.22%, and 2 cases of stenosis in the ADM graft group, with a stenosis rate of 18.18%, with no marked difference noted between the groups (P = 0.94). In this prospective study, strict inclusion and exclusion criteria were established during the experimental design phase, and by estimating the sample size, a sample of 160 cases per group was deemed to be required if the effects of autologous mucosal transplantation and ADM transplantation were to be compared. A total of 20 patients willing to receive autologous mucosal transplantation were recruited from January 1 to December 31, 2017, and 9 patients received autologous mucosal transplantation; a total of 25 patients willing to receive ADM transplantation were recruited from January 1 to December 31, 2019, and 11 patients received ADM transplantation. All of these patients completed a three-year follow-up.

During recruitment, the study failed to enroll sufficient patients who completed the three-year follow-up as required by the trial. Only 9 patients in the autologous mucosa group and 11 patients in the ADM group completed the 3-year follow-up, which is insufficient to draw definitive conclusions. While the stenosis rate did not differ significantly between the groups, it is less than the 37% stenosis rate noted in the relevant study[2]. While it has been shown to have some effect in preventing esophageal stricture, the effect of ADM remains unknown[12,32]. Based on the above results, we can speculate that ADM may exert some preventive effects against esophageal stricture, and its effects may be comparable to those of autologous mucosa. However, due to the many limitations of this trial, including the recruitment of an insufficient number of subjects, the results should be interpreted with caution.

CONCLUSION

Future studies using our established strict inclusion and exclusion criteria and improved follow-up may provide new insight into the prevention of esophageal stricture.

ARTICLE HIGHLIGHTS

Research background

Mucosal autograft transplantation has been reported to be effective in preventing esophageal stricture after endoscopic submucosal dissection (ESD) for esophageal cancer.

Research motivation

The preparation of autologous mucosa is an intricate process that demands a significant amount of time, potentially delaying the treatment of diseases. It is imperative to explore potential substitutes for autologous mucosa.

Research objectives

The efficacy of acellular dermal matrix (ADM) in preventing esophageal stricture is equivalent to that of autologous mucosal transplantation and has a substitutive effect.

Research methods

This is a prospective, single-center controlled study. Patients who underwent ESD surgery and were willing to undergo autologous mucosal transplantation and ADM transplantation were consecutively recruited for the study. A three-year follow-up was conducted for the transplanted patients.

Research results

Autologous mucosal grafts and ADM grafts demonstrated no significant differences in preventing esophageal stenosis, exhibiting similar preventive effects against esophageal narrowing.

Research conclusions

ADM possesses the potential to prevent esophageal stricture, exhibiting comparable preventative efficacy to autologous mucosal grafts while providing substitutive benefits.

Research perspectives

We shall persist in our research endeavors, enlisting additional participants to further validate the efficacy of ADM in preventing esophageal stricture. This shall furnish a multitude of options and avenues towards the treatment of esophageal stenosis.

FOOTNOTES

Co-first authors: Xin-Yu Fu and Zhen-Yu Jiang.

Co-corresponding authors: Shao-Wei Li and Xin-Li Mao.

Author contributions: Fu XY, Zhang CY, Lin JY, Yan XD, Li XK, Wang Y, and Mao XL participated in the design of the study and performed the statistical analysis; Fu XY, Jiang ZY, Zhang CY, Lin JY, and Li SW drafted the manuscript. All authors read and approved the final manuscript.

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Clinical trial registration statement: The study was registered with the Center for Clinical Trials under registration number ChiCTR200040119.

Informed consent statement: All study participants, or their legal guardian, provided written consent prior to study enrollment.

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ORCID number: Xiao-Dan Yan 0000-0002-1493-6817; Yi Wang 0000-0002-9817-1769; Xin-Li Mao 0000-0003-4548-1867; Shao-Wei Li 0000-0002-3276-1037.

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