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Endoscopic treatment of esophageal fistulas after esophagectomy with injection of an alpha-cyanoacrylate monomer: a phase II study

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ABSTRACT

Background and study aims Interventional endoscopic treatments including the application of glue are becoming more frequently used for the treatment of esophageal fistulas. However, there are no prospective studies of endoscopic treatment for esophageal fistulas. This prospective study aims to investigate the efficacy and safety of endoscopic injection of alpha-cyanoacrylate monomer for intractable esophageal fistulas.

Patients and methods This single-center prospective phase II trial included patients with more than 1 wk of conservative medical treatment for intractable esophageal fistulas after esophagectomy. In the image-guided therapy suite, a mixture of alpha-cyanoacrylate monomer and oily contrast agent in a ratio of 0.3 to 1.7 mL was endoscopically injected through the fistula.

Results Twenty-five patients who underwent esophagectomy at Wakayama Medical University Hospital were enrolled in this study. The primary disease was esophageal cancer in 16 patients (64 %) and gastric cancer in the remaining 9 patients (36 %). Complete closure of the esophageal fistula was performed in 22 patients after endoscopic injection of alpha-cyanoacrylate monomer. The overall success rate was 88 %. There was no fistula recurrence in any successful closure cases. Three patients with failed esophageal fistula closure had esophageal cancer with cervical esophageal fistulas and required reoperation of the fistulectomy under general anesthesia. No complications associated with this endoscopic treatment were detected.

Conclusions Endoscopic treatment with injection of alpha-cyanoacrylate monomer facilitated healing of post-esophagectomy fistula in 88 % of patients without complications. This suggests that the treatment is effective and safe for patients with esophageal fistulas.

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Introduction

Iatrogenic esophageal fistula after esophagectomy is a serious complication for esophageal and gastric cancers. It can lead to longer hospital stay and high postoperative morbidity and mortality rates. As esophageal fistula is refractory, management of it is often challenging.

Interventional endoscopic treatments including the application of glue and endoscopic clips and stent insertion are increasingly used for treatment of esophageal fistulas [1]. A main limitation of covered stent is the risk of migration, with several studies identifying rates more than 50 % [2, 3]. On the other hand, application of glue has become a promising method in clinical practice for avoiding reoperation after gastro-

intestinal leakage [1, 4]. The use of cyanoacrylate glue was first reported in 1983 as a treatment for tracheoesophageal fistula [5]. Since then, there have been many case reports of successful fistula closures by using glue [1, 6 – 10]. In many of these reports, n-butyl cyanoacrylate polymer or 2-octyl cyanoacrylate polymer was used via endoscopic injection [5 – 7]. We propose that alpha-cyanoacrylate (α-CA) monomer is ideal for glue embolization against intractable esophageal fistulas because α-CA monomer glue spreads faster and thus creates a bond more rapidly than the other polymer glues [1, 10, 11]. We previously demonstrated 4 case series with esophageal fistulas that were successfully treated with endoscopic injection of α-CA monomer [12]. Excluding our preliminary report, only 1 case report has so far examined the usefulness of α-CA monomer for the treatment of esophageal fistulas [8].

This prospective phase II trial aims to test the hypothesis that endoscopic injection of α-CA monomer is effective and safe in patients with intractable esophageal fistulas. We planned this study to apply the endoscopic treatment in a clinical setting.

Patients and methods

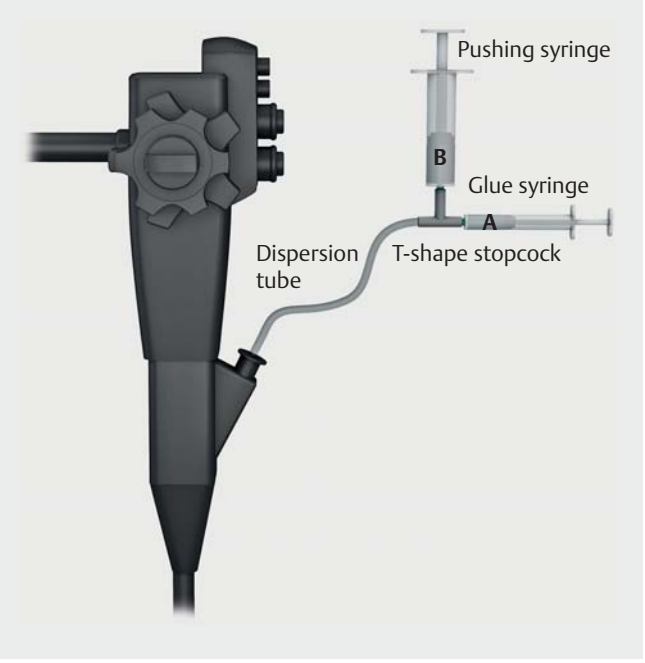
Eligibility criteria

This study was conducted according to a protocol reviewed and approved by the Wakayama Medical University Hospital Ethical Committee on Human Research. All patients gave written informed consent before enrolling in the study. The study protocol was registered at the University Hospital Medical Information Network (UMIN000018486).

Participants were enrolled in the trial between January 2015 and March 2017 and regarded as eligible if they met the following criteria: (i) aged between 20 and 85 years; (ii) invalid cases with more than 1 wk of conservative medical treatment for intractable esophageal fistulas; (iii) had no severe disturbance of liver or renal functions, as indicated by aspartate aminotransferase and alanine aminotransferase levels of < 300 IU/L, and creatinine level of < 3.0 mg/dL. Exclusion criteria were as follows: (i) patients with esophagotracheal fistulas; (ii) patients with pulmonary fistulas; (iii) patients with shock vital.

Surgical procedure (video)

Details of the endoscopic treatment methods performed at our institute have been previously described [12]. In brief, all patients were treated with endoscopic injection of α-CA monomer glue. Endoscopic treatments were performed while patients were under sedation induced by intravenous diazepam. Patients were placed in the left decubitus position. We used a standard endoscope with a single accessory channel (GIF H260; Olympus, Tokyo, Japan). In the image-guided therapy suite, a mixture of α-CA monomer (Aron Alpha A; Sankyo, Tokyo, Japan) and oily contrast agent (Lipiodol; Guerbet, Tokyo, Japan) in a ratio of 0.3 to 1.7 mL was endoscopically injected through the fistula using a dispersion tube and 2.5-mL glue syringe (▶ **Fig. 1**). We used 50 % glucose to push the solution from the syringe into the dispersion tube (▶ **Fig. 1**). We repeated this procedure every 1 or 2 wk until the fistula was closed.



▶ **Fig. 1** Schematic drawing of the endoscopic injection of cyanoacrylate glue. **a** Glue syringe: a mixture of cyanoacrylate and oily contrast agent (lipiodol) in a ratio of 0.3 to 1.7 mL in a 2.5-mL syringe. **b** Pushing syringe: 5 mL of 50 % glucose in a 10-mL syringe.

Study design

We previously confirmed safety of this endoscopic treatment [12]. In this study, we adopted a phase II study design to evaluate the response rate. The primary endpoint of this study was to assess the objective response rate (fistulas closure rate). According to endoscopic findings 4 wk after the endoscopic treatment, we considered the patients with reduction of the esophageal fistula orifice to be successful cases.

Secondary endpoints were to evaluate treatment-related toxicity and the late complications rate. Postoperative complications were analyzed according to the Clavien-Dindo classification [13]; complications higher than grade II were regarded as clinically significant. The planned sample size of the phase II study was 25 patients, a number that was required to confirm the null hypothesis that the 95 % confidence interval of the expected overall response rate (85 %) would be less than 60 % under the condition of α-error of 0.05 and β-error of 0.2.

Results

Patients

Twenty-five invalid patients with more than 1 wk of conservative medical treatment for intractable esophageal fistulas were enrolled in this study between January 2015 and March 2017. ▶ **Table 1** shows the clinical characteristics and surgical outcomes of the 25 patients (male: 22, female: 3), with a median age of 69 years (range: 47 – 83 years). The primary disease was esophageal cancer in 16 patients (64 %), and the cause of the esophageal fistula of these 16 patients was anastomotic leak-

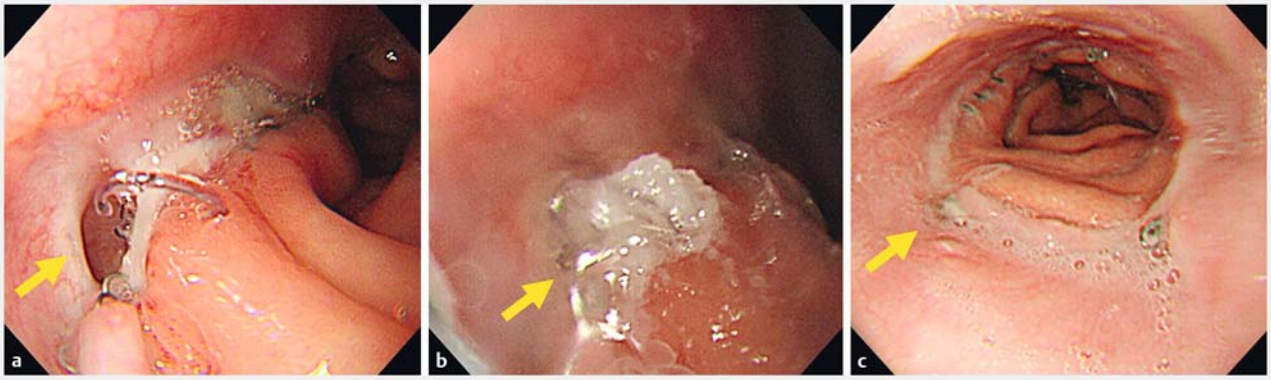
▶ **Table 1** Demographic and clinical data of the patients.

Case	Gender/ age	Primary disease	Primary operation	Site of fistula/ major axis of fistula orifice (mm)	Primary fistula treatment	Time from diagnosis of fistula to injection of CA glue (wk)	Total number of injections of CA glue/ duration of endoscopic therapy	Clinical outcomes of endoscopic therapy	Reoperation procedure after endoscopic treatment	Follow-up (mo)/ clinical course
Failure cases										
1	M/70	Esophageal cancer	Subtotal esophagectomy	Anastomotic site with cervical esophagus/10	Open drainage, antibiotic treatment	2	3T/9W	Failure	Fistulectomy plus muscle flap	24/full recovery
2	M/68	Esophageal cancer	Subtotal esophagectomy	Anastomotic site with cervical esophagus/8	Open drainage, antibiotic treatment	3	6T/6W	Failure	Fistulectomy plus muscle flap	9/full recovery
3	M/65	Esophageal cancer	Subtotal esophagectomy	Anastomotic site with cervical esophagus/12	Open drainage, antibiotic treatment	3	11T/11W	Failure	Fistulectomy plus muscle flap	6/full recovery
Success cases										
4	M/64	Esophageal cancer	Subtotal esophagectomy	Anastomotic site with cervical esophagus/3	Open drainage, antibiotic treatment	2	2T/5W	Completely sealed	None	27/full recovery
5	M/47	Esophageal cancer	Subtotal esophagectomy	Anastomotic site with cervical esophagus/8	Open drainage, antibiotic treatment	1	2T/6W	Completely sealed	None	26/full recovery
6	F/67	Esophageal cancer	Subtotal esophagectomy	Anastomotic site with cervical esophagus/5	Open drainage, antibiotic treatment	5	2T/6W	Completely sealed	None	23/full recovery
7	M/76	Esophageal cancer	Subtotal esophagectomy	Anastomotic site with cervical esophagus/8	Open drainage, antibiotic treatment	3	1T/4W	Completely sealed	None	30/full recovery
8	M/54	Esophageal cancer	Subtotal esophagectomy	Anastomotic site with cervical esophagus/10	Open drainage, antibiotic treatment	2	4T/5W	Completely sealed	None	11/cancer death
9	M/53	Esophageal cancer	Subtotal esophagectomy	Anastomotic site with cervical esophagus/3	Open drainage, antibiotic treatment	1	1T/5W	Completely sealed	None	19/full recovery
10	M/75	Esophageal cancer	Subtota esophagectomy	Anastomotic site with cervical esophagus/5	Open drainage, antibiotic treatment	4	14T/14W	Completely sealed	None	12/full recovery
11	M/68	Esophageal cancer	Subtotal esophagectomy	Anastomotic site with cervical esophagus/7	Open drainage, antibiotic treatment	2	2T/7W	Completely sealed	None	7/full recovery
12	M/62	Esophageal cancer	Subtotal esophagectomy	Anastomotic site with cervical esophagus/5	Open drainage, antibiotic treatment	2	3T/4W	Completely sealed	None	7/full recovery
13	M/65	Esophageal cancer	Subtotal esophagectomy	Anastomotic site with cervical esophagus/6	Open drainage, antibiotic treatment	2	12T/13W	Completely sealed	None	9/full recovery

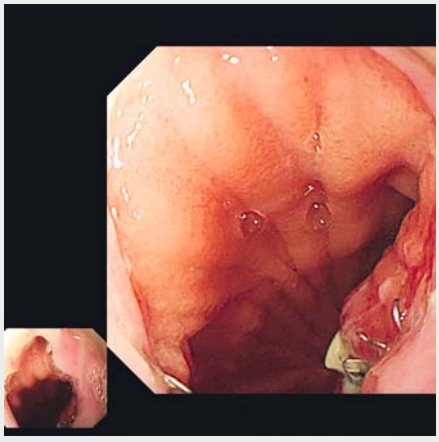
▶ **Table 1** (Continuation)

Case	Gender/ age	Primary disease	Primary operation	Site of fistula/ major axis of fistula orifice (mm)	Primary fistula treatment	Time from diagnosis of fistula to injection of CA glue (wk)	Total number of injections of CA glue/ duration of endoscopic therapy	Clinical outcomes of endoscopic therapy	Reoperation procedure after endoscopic treatment	Follow-up (mo)/ clinical course
14	M/63	Esophageal cancer	Subtotal esophagectomy	Anastomotic site with cervical esophagus/10	Open drainage, antibiotic treatment	3	4 T/8 W	Completely sealed	None	24/full recovery
15	M/70	Esophageal cancer	Subtotal esophagectomy	Anastomotic site with cervical esophagus/3	Open drainage, antibiotic treatment	1	7 T/8 W	Completely sealed	None	21/full recovery
16	M/75	Esophageal cancer	Subtotal esophagectomy	Anastomotic site with cervical esophagus/5	Open drainage, antibiotic treatment	8	13 T/12 W	Completely sealed	None	13/cancer death
17	M/74	Gastric cancer	Total gastrectomy	Anastomotic site with abdominal esophagus/20	Drainage, antibiotic treatment	3	4 T/4 W	Completely sealed	None	30/full recovery
18	M/69	Gastric cancer	Total gastrectomy	Anastomotic site with abdominal esophagus/15	Drainage, antibiotic treatment	2	3 T/4 W	Completely sealed	None	29/full recovery
19	M/81	Gastric cancer	Total gastrectomy	Anastomotic site with abdominal esophagus/10	Drainage, antibiotic treatment	2	1 T/4 W	Completely sealed	None	24/full recovery
20	M/71	Gastric cancer	Total gastrectomy	Anastomotic site with abdominal esophagus/12	Drainage, antibiotic treatment	3	2 T/8 W	Completely sealed	None	19/cancer death
21	M/64	Gastric cancer	Total gastrectomy	Anastomotic site with abdominal esophagus/14	Antibiotic treatment	2	3 T/8 W	Completely sealed	None	14/full recovery
22	M/83	Gastric cancer	Total gastrectomy	Anastomotic site with abdominal esophagus/8	Drainage, antibiotic treatment	3	6 T/6 W	Completely sealed	None	13/full recovery
23	F/79	Gastric cancer	Total gastrectomy	Anastomotic site with abdominal esophagus/4	Antibiotic treatment	2	3 T/4 W	Completely sealed	None	11/full recovery
24	F/77	Gastric cancer	Total gastrectomy	Anastomotic site with abdominal esophagus/3	Drainage, antibiotic treatment	2	2 T/4 W	Completely sealed	None	10/full recovery
25	M/79	Gastric cancer	Total gastrectomy	Anastomotic site with abdominal esophagus/6	Drainage, antibiotic treatment	2	3 T/6 W	Completely sealed	None	6/full recovery

CA: cyanoacrylate; M: male; F: female; T: times; W: weeks.



▶ **Fig. 2** Endoscopic findings. **a** Endoscopic appearance of fistula opening. **b** A view of the fistula opening after cyanoacrylate glue injection. **c** Fistula closure. Yellow arrows show the fistula site.



Video 1 Endoscopic treatment with injection of α-CA monomer for esophageal fistulas.

age of cervical esophagus after the subtotal esophagectomy with esophagogastrostomy. The remaining 9 patients (36 %) had gastric cancer as primary disease. The cause of esophageal fistula was anastomotic leakage of abdominal esophagus after total gastrectomy with esophagojejunostomy. All patients received conservative medical treatment of over a week, such as fasting and antibiotic administration. In all 16 patients with anastomotic leakage of cervical esophagus after subtotal esophagectomy, we opened the cervical wound and noted the presence of fistula. In 7 of the 9 patients with an anastomotic leakage of abdominal esophagus after total gastrectomy, we performed percutaneous drainage of intra-abdominal abscess. The size of fistula orifice in the esophagus according to endoscopic findings was 8 mm in a median major axis (range: 3 – 20 mm).

Endoscopic treatments

All patients were treated with endoscopic injection of α-CA monomer glue. ▶ **Fig. 2** shows the pre- and posttreatment endoscopic findings of the fistula with the complete healing (case 19). The median duration from diagnosis of esophageal fistula to initiation of the endoscopic treatment was 2 wk (range: 1 – 8 wk). The median number of injections of α-CA monomer glue was 3 times (range: 1 – 14 times), and the median duration of endoscopic treatment was 6 wk (range: 4 – 16 wk).

Primary and secondary endpoints

After treatment, complete closure of the fistula was verified in 22 patients by endoscope. Endoscopic injection of α-CA monomer glue was ineffective in 3 patients. The overall success rate therefore was 88 % (22/25). The 3 patients in which the treatment was ineffective were all esophageal cancer patients with cervical esophageal fistulas. They required reoperation of the fistulectomy plus muscle flap under general anesthesia. During the median follow-up period of 14 mo (range: 6 – 30 mo), 3 patients died of cancer, but the remaining patients completely recovered without recurrence of esophageal fistula.

In both early and late phases, there were no complications higher than Clavien-Dindo grade II in patients who received endoscopic treatments with injection of α-CA monomer glue.

Discussion

This is the first prospective study of endoscopic treatment of an esophageal fistula using α-CA monomer injection. In our study of 25 patients, complete closure of the esophageal fistula was possible in 22 patients after endoscopic injection of α-CA monomer; the overall success rate was 88 %. In addition, there were no complications associated with this endoscopic treatment and fistula recurrence. This phase II study met its primary endpoint of high fistula closure rate and its secondary endpoint of low complication rate. Therefore, we propose that endoscopic injection of α-CA monomer is a feasible and safe procedure for the treatment of nonhealing esophageal fistulas.

Occurrence of esophageal fistula following esophagectomy is a severe complication because gastrointestinal contents drain into the thoracic or peritoneal cavities, leading to intrapleural abscess or peritonitis. The sealing of the fistulas orifice by endoscopic injection of superglue, which is exemplified by α-CA monomer, therefore, is an important step. In addition, α-CA monomer has the advantages of having both stronger adhesive properties and stronger antibacterial properties compared with other polymer glues, such as n-butyl 2-cyanoacrylate polymer and 2-octyl cyanoacrylate polymer [1, 14]. Therefore, α-CA monomer glue is suitable for application in a wet and infected cavity. In this study, the treatment success rate of 88 % is one of the best compared with previous retrospective studies [1, 10, 11, 15]. In 3 case series with 22 [10], 10 [11], and 9 patients [15], respectively, the concomitant presence of fistula with this technique has proven to be associated with a lower success rate. Notably, n-butyl 2-cyanoacrylate polymer was used for glue embolization in the studies. We affirm that using α-CA monomer would be more successful for this technique.

The injection of α-CA monomer often causes endoscopic troubles because of the strong fast-acting adhesive characteristics associated with the superglue. In general, α-CA monomer is an acrylic resin that rapidly polymerizes in the presence of a little water. Because the presence of moisture causes the glue to set, exposure to normal levels of humidity in the air causes polymerization to start within several seconds. Therefore, we mixed the α-CA monomer and oily the contrast agent (lipiodol) at a ratio of 0.3 to 1.7 mL in a 2.5-mL syringe. We developed this mixture ratio in terms of efficiency of the infusion [12]. Lipiodol has the added benefit of allowing radiological confirmation of the injection and identification of embolization to be performed. If the glue syringe containing the α-CA monomer and lipiodol is made air-tight, we could endoscopically inject the solution safely in the image-guided therapy suite. On the other hand, it is generally accepted that the polymerization of α-CA monomer is delayed in the presence of a large quantity of water. Therefore, we used a 50 % glucose solution to push the solution from the syringe into the endoscopic dispersion tube. In our experiments, 50 % glucose solution was suitable for the pushing of the embolic solution [12]. We succeeded in performing the endoscopic injections of α-CA monomer in all cases using the above-mentioned devices and methods.

In our study, the endoscopic treatment for esophageal fistulas closure failed in 3 patients (12 %). In these patients, the size of the fistula orifice in the esophagus was larger than 8 mm of the median (8, 10, and 12 mm, respectively). In addition, the fistula sites were all located in the flexion of the cervical esophagus. The hold of endoscopic position during this treatment was therefore difficult, and the infusion volume of α-CA monomer glue during endoscopic treatment may be insufficient. The strong pressure exerted on the flexion of the cervical esophagus during swallowing may have caused the nonhealing fistulas. Furthermore, the systemic inflammatory reactions in failed patients were high. We postulate that stable patients who have fistulas in the abdominal esophagus after total gastrectomy with esophagojejunostomy may be managed by this endoscopic treatment. While the majority of patients with cervical esophageal fistulas after subtotal esophagectomy with esophagogastrostomy are candidates for this endoscopic treatment, it has its limitations in certain patients – for example, patients with fistula larger than 8 mm, patients with fistula that render it difficult to hold an endoscopic position, and unstable patients with evidence of sepsis. In these patients, other endoscopic treatments, such as endoscopic clips and stent insertion, are also inadequate adaptations [1, 16]. In our series, all 3 patients in which this endoscopic treatment was refractory were cured by surgical reinterventions with fistulectomy plus muscle flap. However, a more aggressive surgery, such as esophagectomy with proximal and distal stoma, is advisable before this endoscopic treatment is planned in unstable patients with a septic condition.

This phase II study had several limitations. It was conducted in a single institution without randomized controlled study. Due to the small sample size, findings from this do not allow established clinical application. Indeed, many patients with esophageal fistulas can be treated conservatively, and their fistulas may close during follow-up even when endoscopic intervention was not performed. Therefore, in our 22 success cases who received endoscopic injection of α-CA monomer, the patients who were available for conservative treatment and the patients who really needed endoscopic treatment to make the fistula closure might be mixed. In order to prove the clinical application of this endoscopic treatment with injection of α-CA monomer, we are going to plan a large multicenter, randomized, double-blind, placebo-controlled phase III clinical trial in the future.

In conclusion, endoscopic treatment with injection of α-CA monomer facilitated healing of post-esophagectomy fistula in 88 % of patients without complications. This suggests that the treatment is effective and safe for patients with esophageal fistulas.

Competing interests

None

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