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Development of a hybrid hydrogel for submucosal injection in endoscopic resection of gastrointestinal neoplasm: From laboratory to clinical trial

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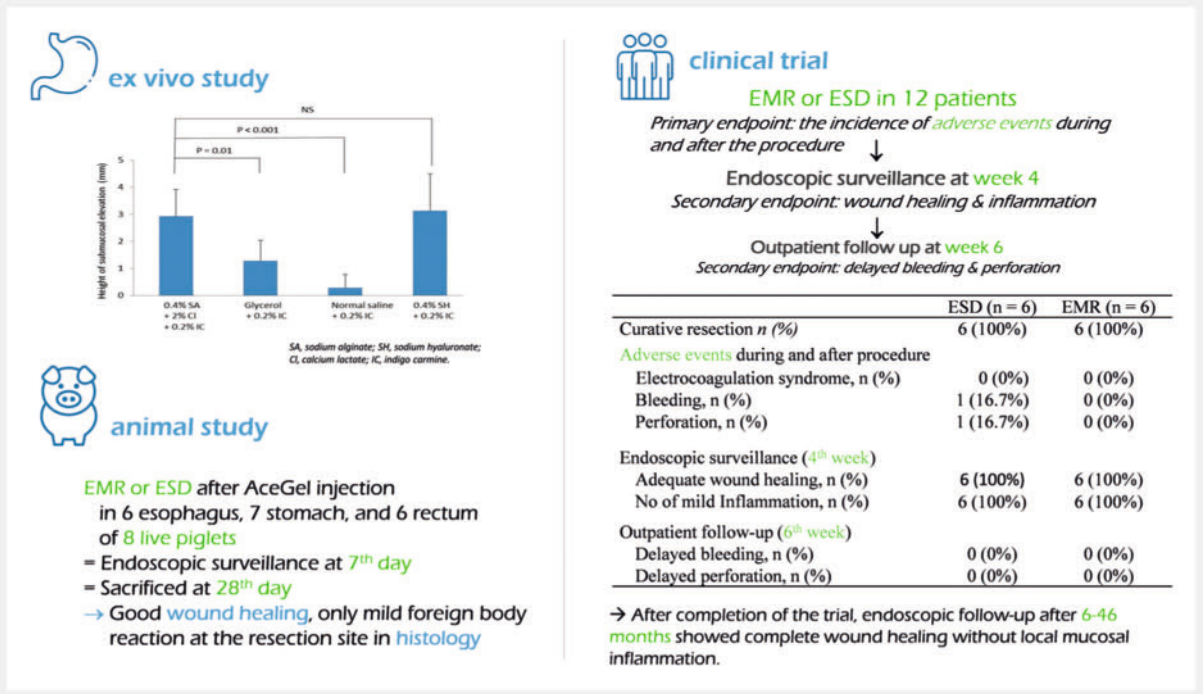
GRAPHICAL ABSTRACT



	ESD (n = 6)	EMR (n = 6)
Curative resection *n (%)*	6 (100%)	6 (100%)
Adverse events during and after procedure		
Electrocoagulation syndrome, n (%)	0 (0%)	0 (0%)
Bleeding, n (%)	1 (16.7%)	0 (0%)
Perforation, n (%)	1 (16.7%)	0 (0%)
Endoscopic surveillance (4th week)		
Adequate wound healing, n (%)	6 (100%)	6 (100%)
No of mild Inflammation, n (%)	6 (100%)	6 (100%)
Outpatient follow-up (6th week)		
Delayed bleeding, n (%)	0 (0%)	0 (0%)
Delayed perforation, n (%)	0 (0%)	0 (0%)

Authors

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Key words

Endoscopy Lower GI Tract, Endoscopic resection (polypectomy, ESD, EMRc, …), Endoscopy Upper GI Tract, Precancerous conditions & cancerous lesions (displasia and cancer) stomach

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ABSTRACT

Background and study aims Submucosal injection solution is essential for successful endoscopic resection of the early gastrointestinal tumor. We evaluated a new endoscopic hydrogel for submucosal injection and its clinical feasibility.

Patients and methods A hydrogel (AceGel) containing 0.4% sodium alginate and 2% calcium lactate was developed for ex vivo and animal studies. Subsequently, a prospective, single-arm study was conducted to assess its feasibility and safety in humans. Patients with gastrointestinal neoplasms undergoing endoscopic resection were enrolled. All patients underwent endoscopic surveillance after 4 weeks and outpatient follow-up at week 6. Afterward, they received endoscopic follow-up according to the medical routine.

Results In the ex vivo experiments, the submucosal elevation height of AceGel was equivalent to sodium hyaluronate and superior to saline or glycerol. Animal studies showed that the excised wounds healed well without surrounding tissue damage. Twelve patients participated in the clinical trial, including three, two, and seven patients with esophageal, gastric, and colonic lesions, respectively. The mean neoplasm size and submucosal injection volumes were 24.0±8.6 mm and 22.8±19.9 mL, respectively. All patients had adequate wound healing on 4-week surveillance endoscopy, and none had serious adverse events during 6-week follow-up. Moreover, endoscopic follow-up showed complete wound healing after 6 to 46 months without local mucosal inflammation in all patients.

Conclusions AceGel is good for endoscopic submucosal injection and demonstrated its usefulness in durable mucosal elevation for endoscopic therapy in preclinical tests. This clinical trial shows its safety and feasibility in all participating patients.

Introduction

Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) are standard procedures for removing superficial gastrointestinal neoplasms [1, 2, 3, 4, 5]. Both procedures require submucosal injection material (SIM) for mucosal elevation. The ideal SIM should be easy to inject, provide durable elevation, not interfere with ESD procedures, be safe, not damage tissue, and be cheap [6, 7, 8, 9]. However, existing SIMs have limitations [10, 11, 12]. Hypertonic saline and dextrose solutions lift poorly and cause local inflammation and tissue damage[13]. Glycerol lifts better but creates smoke that obscures vision[14]. Hyaluronic acid lifts are great but expensive [6, 11].

Owing to the shortcomings mentioned here, developing more appropriate SIMs to improve the safety and feasibility is necessary. Sodium alginate is a biocompatible natural anionic polymer used in wound healing, drug delivery, and tissue engineering technologies. When sodium alginate is mixed with calcium lactate, the viscosity of the solution increases dramatically and it becomes a hydrogel due to crosslinking of the electrical properties of the two substances. The US Food and Drug Administration (FDA) listed sodium alginate and calcium lactate as Generally Recognized as Safe (GRAS: FDA-21CFR 184.1724 and FDA-21CFR 184.1207, respectively). In addition, calcium lactate has been used in daily clinical practice to correct hypocalcemia. These make this two-solution mixture potentially a better SIM.

Therefore, this study aimed to evaluate an alginate-based ion-responsive hydrogel (named AceGel) as a SIM for superficial gastrointestinal neoplasm resection. We measured the lesion-lifting capacity of AceGel in ex vivo and in vivo animal studies and conducted a human pilot study to investigate its clinical efficacy and safety for endoscopic resection of superficial gastrointestinal tumors.

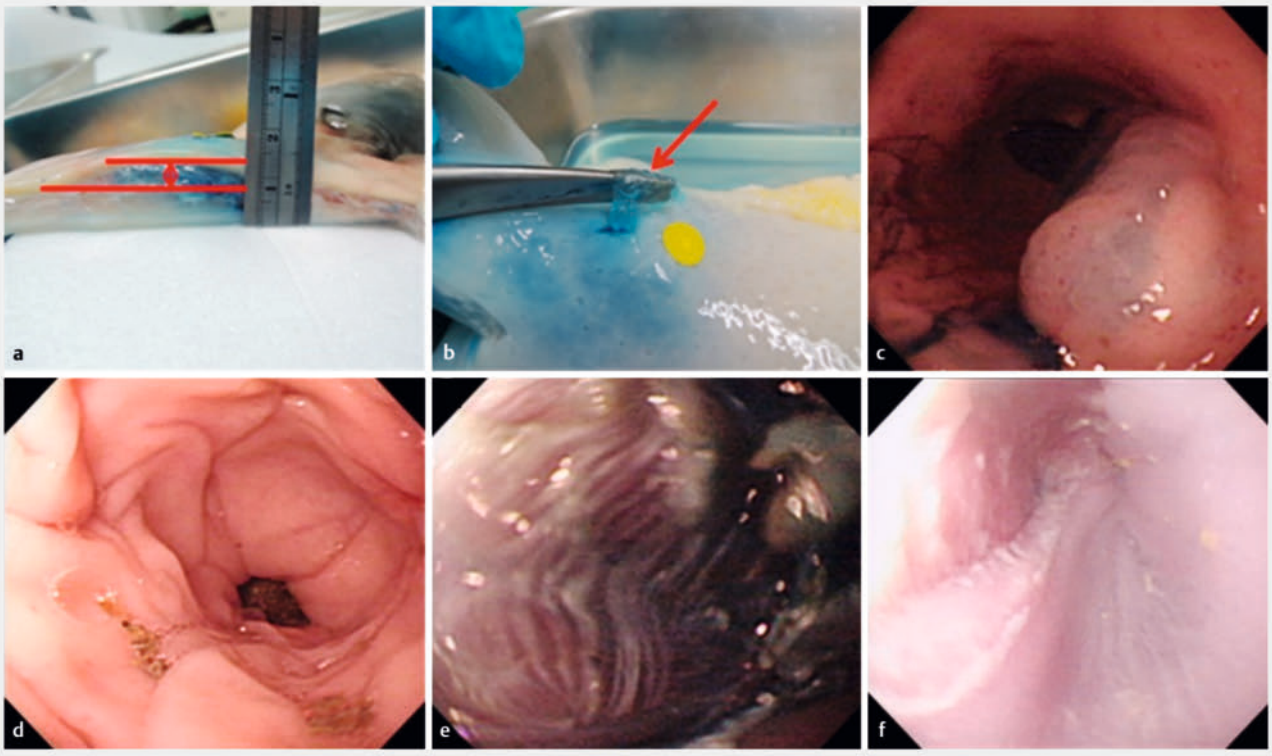
Patients and methods

In vitro study

Appropriate amounts of sodium alginate (Spectrum Chemical, New Brunswick, New Jersey, United States) were used to make 0.2% to 1.0% sodium alginate aqueous solution of different concentrations. The viscosity of the solution of different concentrations was measured in vitro to select the optimal concentration for further study. The examination was performed at 26°C using a DV-E viscometer (AMETEK Brookfield, Chandler, Arizona). Based on viscosity, the candidate solutions were tested by injection through an endoscopic injection needle, gauge 23 (TOP, Ibaraki, Japan). In addition, the sodium alginate solution was mixed with the calcium solution (commercially available 2% calcium lactate and 0.2% indigo carmine in a ratio of 10:1) to test the gelation ability.

Ex vivo piglet stomach study

Piglet stomachs within a few hours of resection were used to compare the submucosal elevation capacity of AceGel and other solutions, including normal saline, glycerol, and sodium hyaluronate. We mixed 0.2% indigo carmine with each solution to dye the submucosal layer blue. Ten milliliters of each solution was injected into different parts of the corpus in the same extracted piglet stomach. A coronal incision was made at the injection site 30 minutes after the injection, and the submucosal elevation height was measured from the plane of the cut. The submucosal elevation height was defined as the vertical distance from the top of the uninjected adjacent mucosa to the top of the injected elevated mucosa (▶ **Fig. 1a**).



▶ **Fig. 1** Ex vivo and animal studies. **a** Measurement of submucosal elevation. **b** Immediate gelation process after submucosal injection. In vivo animal study. **c** Submucosal injection of AceGel in the rectum showed a good cushion effect. **d** Endoscopic surveillance on Day 14 showed normal rectal mucosal, and AceGel was completely absorbed. **e** Successful esophageal ESD in the live piglet. **f** Endoscopic surveillance after esophageal ESD showed good healing with no local tissue damage.

In vivo animal study

We conducted an animal experiment that was approved by the Ethics Committee of the animal center of our university and was performed in accordance with the animal welfare guidelines established by the Agriculture Council of Taiwan. Our animal study included two experiments. First, AceGel submucosal injection was done in the distal esophagus, low corpus of stomach, and rectum of a live piglet. Subsequently, endoscopic surveillance was performed 7 days later to evaluate the resolution of AceGel and local mucosal inflammation. Second, ESD or EMR using AceGel as a submucosal injection solution was performed in eight live piglets, with a total of 19 procedures (6 esophageal, 7 gastric, and 6 rectal cases). Endoscopic surveillance was performed 7 days after the procedure to evaluate AceGel resolution and wound healing status. All piglets were sacrificed after 28 days, and the injection sites were resected and sent for pathological examination to assess tissue damage.

Clinical study

Following the animal study, we conducted a prospective, single-arm interventional study, enrolling patients for endoscopic resection of superficial gastrointestinal neoplasms. The clinical trial was approved by the institutional review board of National Cheng Kung University and the Taiwan Food and Drug Administration (ClinicalTrials.gov ID of NCT 03321396 and Taiwan's FDA ID No.1060013298). All participating patients signed a written informed consent form before enrollment.

Inclusion and exclusion criteria

Our study population comprised patients who were referred for endoscopic resection of early gastrointestinal neoplasm. All patients enrolled in this study fulfilled the following criteria: 1) age ≥20 years; 2) patients with esophageal, gastric, or colonic superficial neoplasm who had not received any other type of endoscopic treatment before; and 3) lesion size ≥10 mm. The exclusion criteria were as follows: patients with 1) advanced cancer; 2) severe thrombocytopenia (<50,000 /μL) or uncorrectable coagulopathy; 3) high risk with antithrombotic agent discontinuation; 4) major comorbidities who were not eligible for clinical trial under physician's consideration; 5) imaging evidence of deep submucosal invasion and/or metastasis; and 6) documented allergy to any of the product compounds.

Study endpoints

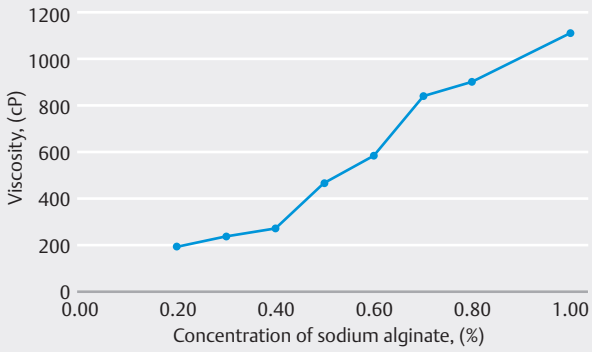
The study's primary endpoint was the incidence of adverse events (AEs) during and after the procedure, including post-procedure electrocoagulation syndrome, significant bleeding, or perforation. The secondary endpoints were wound healing and local mucosal inflammation detected by endoscopy after 4 weeks and delayed bleeding or perforation within the 6-

week follow-up period. Significant bleeding or delayed bleeding was defined as hematemesis, melena, or hemoglobin levels dropped >2 g/dL within 3 days or 6 weeks of the procedure, respectively. Perforation was defined as observing a gross defect noted during the procedure or the presence of free air in the radiological finding. Electrocoagulation syndrome was defined as the development of abdominal pain, fever, leukocytosis, and peritoneal irritation symptoms/signs in the absence of peroration. Wound healing was defined based on the following criteria: 1) complete healing: completely healed wound with no visible ulcers; 2) adequate healing: incompletely healed ulcer but with a diameter less than half of the original neoplasm diameter; and 3) insufficient healing: residual ulcer with a diameter more than half of the original neoplasm diameter. Local mucosal inflammation was classified as follows: 1) no inflammation: normal mucosa around the wound/scar; 2) mild inflammation: the area of mucosal redness around the wound/scar was <0.5 cm; 3) moderate inflammation: the area of mucosal redness was 0.5 to 1 cm; and 4) severe inflammation: the area of mucosal redness was >1 cm. We also recorded procedure time, times of needle exchange, en bloc resection rate, and complete resection rate to assess AceGel's performance. En bloc resection was defined as complete resection of the target lesion in one piece. Complete resection was defined as the complete removal of the lesion without any residual remnants and with pathologically negative margins of high-grade dysplasia.

Endoscopic procedures and follow-up

All endoscopic resections were performed using CO_2 insufflation and a water-jet endoscope (PCF-260AZI or GIF-260 J, Olympus, Tokyo, Japan) with patients under intravenous general anesthesia with propofol infusion. An electrosurgical knife, either a Dual knife (KD-650 L/U) or IT-nano knife (KD-612 L/U), was used to perform ESD. The electrosurgical generator used was ESG-100 (Olympus, Tokyo, Japan). The total injection volume of AceGel, procedural time, number of times the needle injection was changed, and intraprocedural and late AEs were recorded. Furthermore, submucosal fibrosis was recorded when either a non-lifting sign after submucosal injection or a white web-like structure in the transparent submucosal layer was observed during ESD. In addition, for patients undergoing gastric EMR/ESD, proton pump inhibitor was administered 4 to 8 weeks after endoscopic resection.

According to our study design, all patients underwent further endoscopic monitoring after 4 weeks to assess wound healing and any evidence of local tissue injury. At 6 weeks after endoscopic resection, an outpatient evaluation was scheduled to evaluate the delayed adverse events, which marked the completion of the clinical trial. After this point, further follow-up was conducted based on the clinical routine and patient preferences, with individualized intervals determined on a case-by-case basis. Data collection continued until the manuscript preparation stage, allowing us to capture potential long-term effects and outcomes of AceGel usage.



▶ **Fig. 2** Viscosities of different concentrations of sodium alginate solutions. The viscosity of sodium alginate was measured at 26°C using a Brookfield DV-E Viscometer.

Statistical analysis

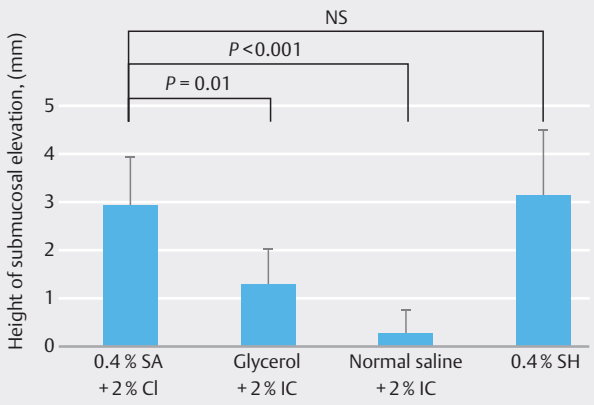
Because this was a first-in-human pilot study, no sample size calculation was performed. The outcomes of AceGel performance were summarized using means±standard deviation for continuous variables and counts (percentages) for categorical variables. The differences of submucosal elevation height in were analyzed using the Student *t* test. Statistical significant was defined as P <0.05.

Results

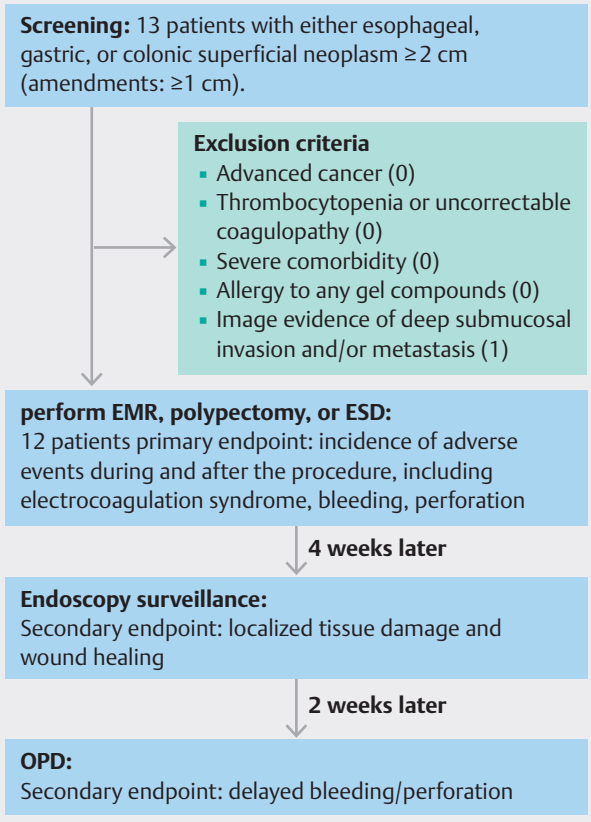
In the in vitro experiment of this study, as shown in ▶ **Fig. 2**, the viscosity of sodium alginate was positively correlated with its concentration, from 197.2 centipoises (cP) in a 0.2% to 1113 cP in a 1% solution. We noticed a rapid increase in viscosity from 0.4% to 0.5% solutions. In addition, when injecting the solution through the catheter using a 23G injection needle, it took great effort to push 0.5% sodium alginate through the catheter. In contrast, it was much easier for the 0.4% solution. Therefore, a 0.4% sodium alginate solution was used for further studies.

In the ex vivo study, ▶ **Fig. 1b** shows an immediate gel formation after the submucosal injection of both alginate and calcium solution. ▶ **Fig. 3** shows the submucosal elevation height at 30 minutes after the ex vivo injection of different injection regimens. The submucosal elevation height of AceGel (2.93 ±0.99 mm, n = 14) was significantly higher than that of the normal saline (0.29±0.49 mm, n = 7, P <0.001) and glycerol (1.29 ±0.76 mm, n = 7, P = 0.01) groups, but it showed no difference when compared with that of the sodium hyaluronate group (3.14±1.35 mm, n = 14, P = 0.89).

In the first part of the in vivo animal study, ▶ **Fig. 1c** demonstrates the good cushion effect after submucosal injection of AceGel in the esophagus, stomach, and rectum of a live piglet; the endoscopic surveillance after 7 days showed complete resolution of AceGel (▶ **Fig. 1d**) and no obvious mucosal inflammation. In the second part of the in vivo animal study, all eight piglets underwent ESD or EMR safely. Endoscopic surveillance 7



▶ **Fig. 3** Height of submucosal elevation in different injection solutions. The height of AceGel was 2.93±0.99 mm, which was significantly higher than that of the normal saline (0.29±0.49 mm, P <0.001), and glycerol (1.29±0.76 mm, P = 0.01) groups; however, it showed no difference when compared with that of the 0.4% SH + 0.2% IC group (3.14±1.35 mm, NS). SA, sodium alginate; SH, sodium hyaluronate; Cl, calcium lactate; IC, indigo carmine. NS, non-significant.



▶ **Fig. 4** Flow chart of the clinical trial in this study. EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; OPD, outpatient department.

days after the endoscopic intervention showed good wound healing (▶ **Fig. 1e**, ▶ **Fig. 1f**). As expected, evaluation after sacrifice revealed only mild foreign body reaction at the resection site.

▶ **Fig. 4** illustrates a flow chart of the clinical trial. Altogether, 13 patients were screened and one was excluded for highly suspicious invasive colon cancer. The endoscopic resection using AceGel was performed by three endoscopists. Patient clinical characteristics and procedure types are presented in ▶ **Table 1**, with a mean age of 62.5±9.2 years and a mean lesion size of 24.0±8.6 mm. Six patients underwent ESD, and the rest received either EMR or polypectomy. None of the patients had submucosal fibrosis, and complete resection was achieved. Two immediate intraprocedure events were reported. One patient with early colonic cancer who received ESD had a perforation, and immediately, the mucosa defect was closed successfully using hemoclips. In another patient undergoing colonic ESD, we experienced difficulty in endoscopic manipulation and easy bleeding; therefore, the procedure was converted to piecemeal EMR.

During endoscopic resection, AceGel was able to maintain an adequate, long-lasting mucosa elevation either in the esophagus, stomach, or colon. The AceGel performance is described in ▶ **Table 2**. The ESD group had larger neoplasms, resulting in more AceGel injection volumes and longer procedure times. As shown in ▶ **Table 2** and Supplementary Table S1, endoscopic follow-up at Week 4 revealed complete wound healing in five patients (3 and 2 patients in the EMR and ESD groups, respectively) and adequate healing in the remaining seven patients. Further, eight patients had mild local mucosal inflammation around the wound/scar (3 and 5 patients in the EMR and ESD groups, respectively), four had no inflammation.

Fig. S1 a-c shows a gastric neoplasm that EMR resected with a good cushion effect after AceGel injection. Fig. S2 a-d illustrates an esophageal ESD that surveillance endoscopy at 4 weeks later showed good wound healing and no residual bluish AceGel. Moreover, ▶ **Fig. 5** shows a colonic lateral spreading tumor had good mucosa elevation (▶ **Fig. 5b**) and a sustained cushion effect during ESD (▶ **Fig. 5c**). All resected specimens underwent histological analysis, and the presence of retained AceGel in the submucosal layer did not interfere with the specimen evaluation (▶ **Fig. 5d**).

After completing the clinical study, nine of 12 patients underwent follow-up endoscopy as per the standard medical protocols 6 to 46 months after undergoing EMR or ESD (Table S1). Endoscopic examinations revealed complete wound healing with no local mucosal inflammation. Two patients diagnosed with T1b cancer were unwilling to undergo surgery. Endoscopy and computed tomography performed at the 11- and 25-month follow-ups revealed no local recurrence or distant metastasis.

▶ **Table 1** Baseline demographics and characteristics of 12 enrolled patients.

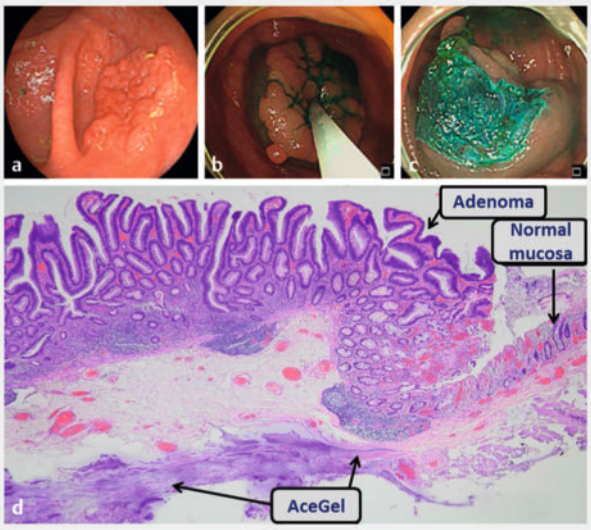
	Age	Gender	Neoplasm location	Size (mm)	Macroscopic appearance	Submucosal fibrosis	Endoscopic procedure	Histological diagnosis
Esophagus	54	Male	Upper third	15	Type 0-IIb	No	EMR	Mild dysplasia
	50	Male	Middle third	35	Type 0-IIb	No	ESD	Carcinoma in situ
	52	Male	Middle third	20	Type 0-IIb	No	ESD	Squamous cell carcinoma, T1b
Stomach	61	Female	Corpus	15	Type 0-Is	No	EMR	Leiomyoma
	65	Female	Antrum	15	Type 0-Is	No	EMR	Tubular adenoma
Colon	52	Female	Sigmoid	10	Type 0-Is	No	Polypectomy	Tubular adenoma
	60	Female	Rectum	30	LST-G-M	No	ESD	Adenocarcinoma, T1b
	70	Male	Sigmoid	28	Type 0-Isp	No	EMR	Traditional serrated adenoma
	71	Female	Ascending	30	LST-G-H	No	ESD	Villous adenoma
	66	Female	Sigmoid	25	LST-G-M	No	EPMR	Villous adenoma
	67	Female	Cecum	30	LST-G-H	No	ESD	Villous adenoma
	80	Female	Hepatic flexure	25	LST-G-M	No	EPMR	Villous adenoma with high-grade dysplasia

ESD, endoscopic submucosal dissection; EMR, endoscopic mucosal resection; EPMR, endoscopic piecemeal mucosal resection

▶ **Table 2** AceGel performance in endoscopic resection of superficial gastrointestinal neoplasm.

	ESD (n = 6)	EMR/polypectomy (n = 6)
Neoplasm size *(mm)*	30.0±5.5	18.0±6.9
AceGel volume *(mL)*	34.3±21.9	10.8±7.8
Needle exchange *(n)*	5.8±3.3	1.7±0.8
Procedural time *(minutes)*	101.3±44.1	13.8±6.9
En bloc resection *n (%)*	5 (83.3%)	5 (83.3%)
Complete resection *n (%)*	6 (100%)	6 (100%)
Adverse events during and after the procedure		
▪ Electrocoagulation syndrome, n (%)	0 (0%)	0 (0%)
▪ Significant bleeding, n (%)	1 (16.7%)	0 (0%)
▪ Perforation, n (%)	1 (16.7%)	0 (0%)
Endoscopic surveillance (4th week)		
▪ Complete or adequate healing, n (%)	6 (100%)	6 (100%)
▪ No or mild inflammation, n (%)	6 (100%)	6 (100%)
Outpatient follow-up (6th week)		
▪ Delayed bleeding, n (%)	0 (0%)	0 (0%)
▪ Delayed perforation, n (%)	0 (0%)	0 (0%)

ESD, endoscopic submucosal dissection; EMR, endoscopic mucosal resection.



▶ **Fig. 5** Endoscopic image of a patient with colon neoplasm. a White light image of the neoplasm. b Prominent submucosal cushion effect after injecting 10 mL of AceGel. c A sustained submucosal cushion effect was observed before additional injection during ESD. d The histological slide showed AceGel retained in the submucosal layer.

Discussion

We developed a novel alginate-based hydrogel as SIM, named AceGel. Our ex vivo study showed that AceGel has mucosal lifting capabilities comparable to that of commercially available sodium hyaluronate, which is widely used in ESD but is expensive. Our animal study and clinical trial have also demonstrated its feasibility and safety. AceGel contains two solutions of 0.4% sodium alginate and 2% calcium lactate plus blue dye (i. e., FDC #1). Because calcium lactate's viscosity is lower than sodium alginate's, calcium lactate with dye was first injected to locate the appropriate layer of the submucosa. After formation of submucosal bulb, viscous sodium alginate was injected to induce a gelation process in the submucosal layer and properly elevate the mucosa. This injection sequence can prevent mis-injection of viscous sodium alginate into muscular layer. A mixing ratio of 1:1 was optimal, but a ratio of 0.5:1 to 2:1 can still successfully trigger gelation.

The major advantage of AceGel is its high viscosity and long-lasting gelation process. Sodium alginate itself has a high viscosity and has already been used in animal studies and clinical trials as a SIM [15, 16]. Our study added calcium into sodium alginate to achieve a higher viscous cushion. We selected 0.4% sodium alginate as the main component of AceGel for clinical trials. This is because the viscosity increased rapidly after the concentration was increased from 0.4% to 0.5%, resulting in excess injection force needed (▶ **Fig. 2**). This viscosity issue directly affects the ease of injection during endoscopic resection. To tackle this challenge, we chose a lower concentration of sodium alginate to maintain its injectability. By mixing sodium alginate with calcium lactate, we initiated a gelation process in the submucosal layer, which enhanced mucosa elevation. This approach ensures both easy injectability and adequate viscosity. The choice of sodium alginate concentration varies in the literature. Kusao et al. suggested 0.6% as the optimal concentration [15]. Nonetheless, Hirose et al. chose the same 0.4% sodium alginate concentration as our study's optimal concentration because the injection force needed of 0.4% sodium alginate was similar to that of 0.4% sodium hyaluronate commonly used in the clinic [17]. Hence, both the Hirose et al study and ours confirm that 0.4% sodium alginate is the best choice for balancing viscosity and injectability.

In our ex vivo experiment, the mucosal elevation ability of AceGel was significantly better than that of normal saline or glycerol and similar to that of hyaluronic acid. A longer duration of mucosal elevation could theoretically reduce the operative time as it saves time in changing needles and knives. Hirose et al. conducted a similar ex vivo study using dual-solution SIM with 0.4% sodium alginate, but they obtained a higher submucosa height using their dual-solution than by using hyaluronic acid [17]. This variation in the results can probably be attributed to the difference in the molecular weight and ionic strength of solutions used, because these factors influence the water-holding capacity of alginate hydrogel. Their study also compared the ESD outcomes of different SIMs in an ex vivo porcine colon model. In this investigation, their results support our hypothesis that the new SIM with alginate plus calcium led to a fewer injection number (1.3±0.5 vs. 2.8±0.4), injection volume (7.0±0.9 vs. 17.2±3.4 ml), and procedural time (14.2±6.1 vs. 29.2±9.1 minutes) [17]. Nevertheless, their study did not include clinical trials in patient populations to investigate the feasibility and safety of the new SIM.

The clinical trial in our study is a first-in-human study to demonstrate that this hybrid hydrogel, AceGel, can be used for ESD or EMR and provide a sufficiently durable submucosal cushion in the esophagus, stomach, and colon. In addition, AceGel preserves lesion tissue for accurate histological assessment, further emphasizing its important properties as an ideal solution for submucosal injection. Importantly, this study showed that this hybrid hydrogel was safe for patients up to 28 days after the procedure and did not result in tissue damage. Furthermore, although complete healing of the wounds was not observed in five patients during the 4-week endoscopic surveillance, they exhibited adequate healing, with the wound diameter being less than 50% of the original neoplasm diameter. Furthermore, upon completing the clinical trial, endoscopic follow-up conducted 6 to 46 months after neoplasm resection revealed complete wound healing without local inflammation or foreign body reactions. AceGel is biodegradable after injection because Na^+ can be exchanged with Ca^{2+} that is dynamically found in surrounding tissues, which is consistent with our findings that wounds healed well without local tissue damage [18, 19].

There are some limitations to our study. First, our ex vivo study primarily focused on comparing the mucosal elevation heights between various SIM at the initiation and 30 minutes after injection. We recognized that this timeframe might be insufficient to illustrate the dynamic time-course change in mu-

cosal elevation beyond the initial 30 minutes. Nevertheless, in the existing literature, various studies have compared the mucosa elevation abilities of different solutions, and these studies typically assessed mucosal elevation height at intervals of 5 to 15 minutes within 30 or 60 minutes. Moreover, these studies revealed a consistent trend in elevation capacity throughout the observation period [15, 16, 19]. Second, a small sample size of only 12 patients was used in the study, as it was a "first-in-human" trial that usually involved a limited number of participants. Nevertheless, this pilot study evaluated the application and feasibility of AceGel in different sites of neoplasms by various endoscopic resection methods. Third, this study did not compare the efficacy of AceGel with other common injection solutions used in therapeutic endoscopic procedures. However, our animal study demonstrated that AceGel exhibited a better submucosal cushion effect than normal saline and glycerol and a similar cushion effect as hyaluronic acid. Fourth, the cost can influence the selection of a SIM, and the commercial cost of AceGel has not been released yet, as it is still in the regulatory process. However, a relevant study by Hirose et al. reported that sodium hyaluronate was 17.3 times more expensive than sodium alginate and calcium [17]. This significant cost difference underscored the cost-effectiveness of alginate-based hydrogel compared to sodium hyaluronate.

Conclusions

In conclusion, the hybrid hydrogel (AceGel) is suitable for endoscopic submucosal injection. This study demonstrates its usefulness and advantages for ESD or EMR, including durable mucosal elevation, patient safety, and no damage to surrounding tissues. Further investigation is warranted to compare AceGel with other mucosal lifting materials in advanced endoscopic resection, with a specific focus on ESD procedures.

Conflict of Interest

The assignee of the AceGel patent is National Cheng Kung University. KJW is one of the contributors and owns 15% rights. The other authors declare no conflicts of interest.

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National Science and Technology Council MOST 107-2823-8-006-003

Clinical trial

Trial registry: ClinicalTrials.gov (http://www.clinicaltrials.gov/)
Registration number (trial ID): NCT 03321396
Type of Study: Interventional (Clinical Trial)

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