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Novel submucosal injection material comprising fully synthetic and self-assembling peptide solution in endoscopic submucosal dissection: A pilot study

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ABSTRACT

Endoscopic submucosal dissection (ESD) requires an injection solution to create a submucosal cushion for safe endoscopic resection. This study evaluated the safety and feasibility of a new injection solution (PuraLift) in ESD for early-stage gastrointestinal tumors. This prospective, single-arm, single-center pilot study included 11 patients with gastrointestinal neoplasms of the stomach (n = 5) or colorectum (n = 6) who underwent ESD. All patients underwent outpatient follow-up at week 4 to confirm presence or absence of adverse events (AEs). All underwent protocol treatment and post-treatment follow-up. None of the AEs were judged to have a cause-and-effect relationship with the study. Questionnaires to the operators who performed the protocol treatment and assistants who performed submucosal injections were evaluated in comparison with saline, and maintenance of mucosal lifting was long, comparable, and short (9/2/0). En bloc and R0 resections were achieved in all patients without intraprocedural AEs. Median size of the specimens was 40 mm (range, 20–70). Median excision time was 52 minutes (range, 22–130). Median volume of PuraLift was 32 mL (range, 22–130). No postoperative bleeding or delayed perforation was observed in any patient. The novel injectable material, PuraLift, can potentially ensure safe and feasible ESD.

Introduction

Compared with conventional endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD) can resect relatively large early gastrointestinal tumors en bloc [1, 2]. ESD requires an injection solution to create a submucosal cushion for safe endoscopic resection [3, 4]. The fully synthetic and self-assembling peptide solution submucosal injection material "PuraLift" (3-D Matrix, Tokyo, Japan) is a non-biological preparation that self-assembles to create a gel of nanofibers when in contact with a neutral pH [5]. It contains the same ingredients as the peptide hemostatic agent "PuraStat" (3-D Matrix). We previously reported two cases wherein PuraLift was used for large, laterally spreading colorectal tumors [6]. Hence, we expect PuraLift to be a useful and safe injection material for humans. This study aimed to investigate the safety and feasibility

of use of PuraLift in ESD for early-stage gastrointestinal neoplasms.

Patients and methods

This prospective, single-arm, single-center pilot study was conducted at the Gunma University Graduate School of Medicine with the approval of the Institutional Review Board (IRB2022–006) in compliance with relevant laws and regulations, including the Declaration of Helsinki and the Japanese Ministerial Ordinance on Good Clinical Practice for Medical Devices. The study is registered in the Japan Registry of Clinical Trials (jRCTs1032220175). Before conducting the study, the principal investigator or sub-investigators explained the details of the study to the patients and obtained their written informed consent.

Patients and lesions

Patients for whom ESD was indicated (following Japanese gastric/colorectal cancer treatment guidelines and gastric/colorectal ESD/EMR guidelines) were included in this study [7, 8]. Perioperative antithrombotic drug management was performed in accordance with guidelines of the Japan Gastroenterological Endoscopy Society [9, 10]. Those aged 20 years or older during the consent provision and those with an epithelial tumor in the stomach (preoperatively diagnosed as intramucosal cancer) or colorectum (adenomas or intramucosal cancers) were included.

Exclusion criteria were as follows: residual or local recurrent lesions; ulceration of the target lesions; multiple lesions for the target procedure; a history of hypersensitivity to peptide preparations or protein preparations; bleeding tendency; pregnant women or women who wished to become pregnant during the study period; nursing mothers; patients presumed to be incapable of hospital follow-up; patients with serious hepatic, renal, cardiac, or vascular diseases; and patients who were considered ineligible by the principal investigator or sub-investigator.

Specific details regarding PuraLift

The injection material used in this study, PuraLift, is an aqueous peptide solution in a vial, mainly composed of self-assembling peptides at physiological pH. The peptide solution quickly forms a hydrogel comprising a network of nanofibers when placed under physiological conditions on contact with body fluids, such as digestive fluids and tissue fluids secreted from the stomach and intestines. The injected hydrogel remains in the submucosa and causes a large dissociation between the mucosal and muscular layers. Consequently, lesion elevation occurs and is maintained when EMR or ESD is performed [5]. PuraLift is expected to have less potential to cause infection than conventional injection fluids because it is a non-biological agent. The cost for on vial of PuraLift (20 mL) was ¥5,270/€31.8 (using exchange rates on November 7, 2024), which is comparable to other conventional injection fluids.

Protocol procedure

The protocol involved ESD using PuraLift as a submucosal injection agent without coloring or mixing (▶ **Fig. 1**). PuraLift was injected with a 25G injection needle (Super Grip; Top Co, Kumamoto, Japan). The maximum volume of PuraLift was 180 mL.

Outcome measurements and safety evaluation

Primary endpoints were incidence of defects caused by PuraLift treatment and adverse events (AEs) (including abnormalities in clinical test values and adverse reactions). To confirm the presence or absence of AEs, final observations were made 28 days after ESD. The secondary endpoints were as follows: ease of PuraLift injection, ease of mucosal incision, ease of submucosal dissection, maintenance of mucosal lifting (the four aforementioned parameters were evaluated by the operator who performed the protocol treatment and the assistant who performed the submucosal injection compared with saline), intraoperative AEs, excision time, volume of PuraLift used, and delayed bleeding.

Sample size and statistical analysis

Because this was the first-in-human pilot study, no sample size calculations were performed. This study aimed to collect 10 cases as a safety study and enroll patients prior to ESD, with the expectation that approximately 5% of cases would meet the criteria for discontinuation of the protocol treatment for a total of 11 cases to be enrolled. This study involved a single-arm design, and descriptive statistics were used.

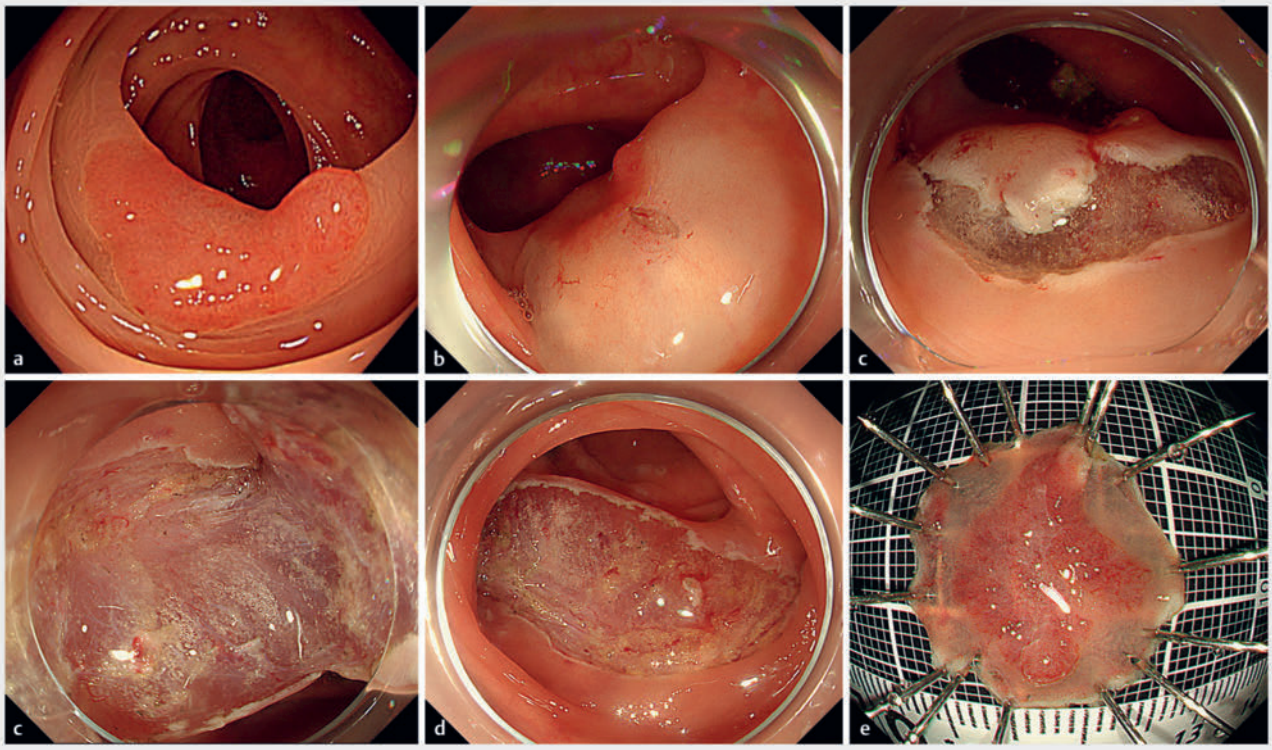
Results

Patients, clinicopathological characteristics, and treatment outcomes

Eleven patients were enrolled in this study between June 2022 and January 2023, all of whom underwent the protocol treatment and post-treatment follow-up. Five endoscopists with more than 100 cases of gastric ESD experience conducted the protocol treatment. ▶ **Table 1** summarizes the clinicopathological characteristics and treatment outcomes regarding the patients. The tumors were located in the upper stomach (n = 1), middle stomach (n = 1), lower stomach (n = 3), ascending colon (n = 1), transverse colon (n = 1), sigmoid colon (n = 3), and lower rectum (n = 1). En bloc and R0 resections were achieved in all patients, without any intraprocedural AEs. Median specimen size was 40 mm (range, 20–70). Median excision time was 52 minutes (range, 22–130). Median PuraLift volume was 32 mL (range, 22–130). Moreover, no postoperative bleeding or delayed perforation was observed in any patient.

Technical and clinical outcomes regarding PuraLift

▶ **Table 2** summarizes the AEs based on the Common Terminology Criteria for Adverse Events regarding PuraLift, which made up the primary endpoint: grade 1 hypoalbuminemia in one case, grade 3 low sodium level in one case, grade 1 low potassium level in one case, grade 1 dizziness in one case, grade 1 nausea in one case, grade 1 vomiting in two cases, grade 1 fever



▶ **Fig. 1** Endoscopic images showing a lateral spreading tumor in the sigmoid colon. **a** In white light. **b** PuraLift is injected into the submucosal layer, and good lifting is achieved. **c** Mucosal incision. **d** Submucosal dissection. **e** Mucosal defect. **f** The resected specimen.

▶ **Table 1** Patient characteristics and treatment outcomes.

Case	Sex	Age (years)	Organ	Location	Macroscopic classification	Tumor Size (mm)	Specimen Size (mm)	Excision time (min)	Volume of PuraLift used (mL)
1	Male	74	Gastric	L	0-IIc	8	31	35	19
2	Male	86	Gastric	L	0-IIc	5	23	30	16
3	Female	81	Gastric	U	0-IIc	5	26	60	32
4	Female	88	Gastric	M	0-IIc	33	56	85	33
5	Male	71	Gastric	L	0-IIa	25	50	69	35
6	Male	70	Colon	S	0-IIa + Is	25	35	33	32
7	Female	76	Colon	S	0-IIa + IIc	15	20	22	21
8	Female	88	Colon	A	0-Is + IIa	37	45	52	40
9	Male	60	Colon	T	0-IIa	60	70	130	75
10	Male	86	Colon	S	0-Is + IIa	39	47	108	70
11	Female	74	Rectum	Rb	0-IIa	35	40	33	20

*All cases were intramucosal lesions, and all endoscopic resections were en bloc resections, negative margins, and curative resections, with no perforation or postoperative bleeding.
A, ascending colon; L, lower stomach; M, middle stomach; Rb, lower rectum; S, sigmoid colon; T, transverse colon; U, upper stomach.

in one case, grade 1 headache in one case, and grade 1 back pain in one case. None of the AEs were judged to have a cause-and-effect relationship with the study, as no findings immediately after treatment indicated allergic reactions or other conditions that had been assumed in advance.

▶ **Table 3** summarizes experience with PuraLift, which included the secondary endpoints. Ease of use of PuraLift injec-

▶ **Table 2** Frequency of adverse events based on CTCAE.

Case	Location						
1	Gastric	Vertigo	Grade 1	Nausea	Grade 1		
2	Gastric	Vomiting	Grade 1				
3	Gastric	Fever	Grade 1				
4	Gastric	Vomiting	Grade 1				
5	Gastric						
6	Colon	Headache	Grade 1	Back pain	Grade 1	Hyponatremia	Grade 3
7	Colon						
8	Colon						
9	Colon						
10	Colon						
11	Rectum						

CTCAE, Common Terminology Criteria for Adverse Events.

▶ **Table 3** Experience regarding PuraLift.

	Value
Ease of PuraLift injection, n (soft/comparable/hard)	0/11/0
Ease of mucosal incision, n (easy/comparable/difficult)	2/9/0
Ease of submucosal dissection, n (easy/comparable/difficult)	0/11/0
Maintenance of mucosal lifting, n (long/comparable/short)	9/2/0

The results were evaluated by the operator who conducted the protocol treatment and the assistant who performed the submucosal injection compared with saline.

tion was comparable in all 11 cases, ease of mucosal incision was easy in two cases and comparable in nine, ease of submucosal dissection was comparable in all 11 cases, and maintenance of mucosal lifting was long in nine cases and comparable in two.

Discussion

The previous report included two cases involving only colorectal lesions, and there has been no coherent report about this novel submucosal injection material [6]. This report includes a new evaluation of efficacy, AEs, and surveys of the operators and assistants, including information about gastric and colorectal lesions. This prospective, single-center study demonstrated that PuraLift was safe for use, with no intraoperative complications or serious AEs. In addition, there were no discontinuations in use of PuraLift in any of the cases. Maintenance of submucosal elevation was good, and feasibility was not a concern.

We previously reported two cases wherein PuraLift was used for large laterally spreading colorectal tumors without AEs (Cases 7 and 11) [6]. In the present study, no AEs due to PuraLift occurred in the other nine patients, including gastric lesions. We also investigated experience with PuraLift use. Ease of injection was similar to that of saline and did not show the rigidity observed with hyaluronic acid. In addition, PuraLift did not interfere with ESD procedures, and maintained mucosal lifting in the stomach and colorectum. Safety and feasibility of use of PuraLift were not a concern.

Because PuraLift is a non-biological agent, it is expected to have a lower potential for infection than conventional injectable solutions. Furthermore, because PuraLift is composed of the same components as the hemostatic agent PuraStat, it is expected to have additional effects, such as hemostatic action, which will be clinically evaluated in the future.

Our study had some limitations. It was a single-center study with a small sample size and was not a controlled trial. Secondary endpoints were subjective and unblinded. Hence, additional case studies and comparative blinded studies are required.

Conclusions

In conclusion, the novel submucosal injection material, PuraLift, is potentially safe and feasible for use in ESD. Further research with a larger sample size, multicenter comparison, and long-term follow-up is needed to confirm its efficacy and safety.

Conflict of Interest

Dr. Yoji Takeuchi is a member of the Endoscopy Editorial Board. Prof. Toshio Uraoka received consulting fees from 3-D Matrix Co, Ltd. The other authors declare no conflicts of interest.

Clinical trial

Japan Medical Association Clinical Trial Registry (http://www.jmacct.med.or.jp/)
Registration number (trial ID): jRCTs1032220175
Type of Study: prospective study

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