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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 eleven 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 the presence or absence of adverse events. All underwent protocol treatment and post-treatment follow-up. None of the adverse events 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 to 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 adverse events. The median size of the specimens was 40 (range, 20–70) mm. The median excision time was 52 (range, 22–130) min. The median volume of PuraLift was 32 (range, 22–130) mL. No postoperative bleeding or delayed perforation was observed in any patient. The novel injectable material, PuraLift, can potentially ensure safe and feasible in ESD.

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Introduction

Compared to 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 the 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 the 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 the 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 the 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.

The 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 PuraLift (20ml, one vial) cost was ¥5,270/€31.8 (using the 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

The primary endpoints were the 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

As 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. The median size of the specimens was 40 mm (range, 20–70 mm). The median excision time was 52 min (range, 22–130 min). The median PuraLift volume was 32 mL (range, 22–130 mL). 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 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 the experience with PuraLift, which included the secondary endpoints. The ease of use of PuraLift injection was comparable in all 11 cases, ease of mucosal incision was easy in 2 cases and comparable in 9, ease of submucosal dissection was comparable in all 11 cases, and maintenance of mucosal lifting was long in 9 cases and comparable in 2.

Discussion

The previous report included two cases involving only colorectal lesions, and there has been no coherent report of this novel submucosal injection material [6]. This report includes a new evaluation of efficacy, adverse events, and questionnaires to the operators and assistants, including 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 the use of PuraLift in any of the

cases. The 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 the experience regarding PuraLift use. The 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. The safety and feasibility of the use of PuraLift were not a concern.

As 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.

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

Figure legends

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.

Table1. patient characteristics and treatment outcomes

Case	Sex	Age (years)	Organ	Location	Macroscopic classification	Tomor Size (mm)	Size of Specimen (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, postoperative bleeding.

U: upper stomach, M: middle stomach, L: lower stomach, A: ascending colon, T: transeverse colon, S: sigmoid colon, Rb: lower rectum

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 to saline.

References

1 Gotoda T, Yamamoto H, Soetikno RM. Endoscopic submucosal dissection of early gastric cancer. J Gastroenterol 2006; 41: 929 – 942

2 Kobayashi N, Saito Y, Uraoka T et al. Treatment strategy for laterally spreading tumors in Japan: before and after the introduction of endoscopic submucosal dissection. J Gastroenterol Hepatol 2009; 24: 1387 – 1392

3 Uraoka T, Saito Y, Yamamoto K et al. Submucosal injection solution for gastrointestinal tract endoscopic mucosal resection and endoscopic submucosal dissection. Drug Des Devel Ther 2009; 2: 131 – 138. DOI: 10.2147/dddt.s3219

4 Jung YS, Park DI. Submucosal injection solutions for endoscopic mucosal resection and endoscopic submucosal dissection of gastrointestinal neoplasms. Gastrointest Interv 2013; 2: 73 – 77

5 Nakata K, Pioche M, Kuribayashi S et al. The feasibility of a fully synthetic and self-assembled peptide solution as submucosal injection material: a preliminary animal study. Scand J Gastroenterol 2021; 56: 984 – 989

6 Kasuga K, Sato K, Nakata K et al. A novel submucosal injection material comprising a fully synthetic and self-assembling peptide solution for endoscopic resection of large colorectal laterally spreading tumors. Endoscopy 2023; 55: E621 – E622

7 Ono H, Yao K, Fujishiro M et al. Guidelines for endoscopic submucosal dissection and endoscopic mucosal resection for early gastric cancer (second edition). Dig Endosc 2021; 33: 4 – 20

8 Tanaka S, Kashida H, Saito Y et al. Japan Gastroenterological Endoscopy Society guidelines for colorectal endoscopic submucosal dissection/endoscopic mucosal resection. Dig Endosc 2020; 32: 219 – 239

9 Fujimoto K, Fujishiro M, Kato M et al. Guidelines for gastroenterological endoscopy in patients undergoing antithrombotic treatment. Dig Endosc 2014; 26: 1 – 14

10 Kato M, Uedo N, Hokimoto S et al. Guidelines for gastroenterological endoscopy in patients undergoing antithrombotic treatment: 2017 appendix on anticoagulants including direct oral anticoagulants. Dig Endosc 2018; 30: 433 – 440