A novel fully synthetic and self-assembled peptide solution for endoscopic submucosal dissection-induced ulcer in the stomach

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Background and Aims: Endoscopic submucosal dissection (ESD) can remove early stage GI tumors of various sizes en bloc; however, success requires reducing the relatively high postprocedure bleeding rate. The aim of this study was to assess the safety and efficacy of a novel, fully synthetic, and self-assembled peptide solution that functions as an extracellular matrix scaffold material to facilitate reconstruction of normal tissues in ESD-induced ulcers.

Methods: Consecutive patients who underwent gastric ESD were prospectively enrolled. Immediately after the resection, the solution was applied to the site with a catheter. Gastric ulcers were evaluated by endoscopy and classified as active, healing, or scarring stages at weeks 1, 4, and 8 after ESD.

Results: Forty-seven patients with 53 lesions, including 14 (29.8%) previously on antithrombotic therapy and 2 (4.3%) requiring heparin bridge therapy, were analyzed; 2 patients were excluded, 1 with perforations and 1 with persistent coagulopathy. The mean size of the en bloc resected specimens was 36.5 ± 11.3 mm. The rate of post-ESD bleeding was 2.0% (1/51; 95% CI, 0.03–10.3). Transitional rate to the healing stage of ESD-induced ulcers at week 1 was 96% (49/51). Subsequent endoscopies demonstrated the scarring stage in 19% (9/48) and 98% (41/42) at weeks 4 and 8, respectively. No adverse effects related to this solution occurred.

Conclusions: The use of this novel peptide solution may potentially aid in reducing the delayed bleeding rate by promoting mucosal regeneration and speed of ulcer healing after large endoscopic resections in the stomach. Further studies, particularly randomized controlled studies, are needed to fully evaluate its efficacy. (Clinical trial registration number: 000011548.)

INTRODUCTION

Endoscopic submucosal dissection (ESD) can remove early stage GI tumors of varying sizes en bloc; the procedure can be curative or at least reduce local recurrence and facilitate more accurate histopathologic assessment.[1-3] However, delayed bleeding can occur days after the procedure and success requires this relatively high postprocedure bleeding rate to be reduced, particularly in the stomach (4.6%–15.6%).[4-7] Although gastric ESD-induced ulcers are treated with proton pump inhibitors (PPIs) for at least 8 weeks in most hospitals, this treatment does not eliminate the risk of bleeding.[8] Prevention of post-ESD bleeding is important because it can potentially result in significant morbidity from acute blood loss and the need for

Abbreviations: ESD, endoscopic submucosal dissection; PPI, proton pump inhibitor; ECM-SM, extracellular matrix scaffold material; HBT, heparin bridge therapy; PGA, polyglycolic acid.

This work was supported by MEXT KAKENNHI Grant-in-Aid for Scientific Research (C), grant number 24591028.

DISCLOSURE: *All authors disclosed no financial relationships relevant to this publication.*

0016-5107/$36.00
http://dx.doi.org/10.1016/j.gie.2015.11.015

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additional endoscopic intervention and extended hospitalization.

Recently, tissue engineering and regenerative substances, such as extracellular matrix scaffold material (ECM-SM), have been developed to target the reconstruction of structurally and functionally normal tissues.[9] In addition, a fully synthetic and self-assembled peptide solution that functions like ECM-SM to replace collagen has been developed.[10,11]

We conducted this clinical trial with the aim of assessing the safety and efficacy of this novel peptide solution for the management of ESD-induced gastric ulcers.

TABLE 1. Baseline characteristics

Patients	**45**
Age, mean (SD)	71.9 (8.8)
Male sex (%)	73.3
Current use of antithrombotic agents, n (%)	14 (29.8%)
Administration of heparin bridge therapy, n (%)	2 (4.3%)
Gastric lesions	51
Location: U/M/L	16/17/18
Outcome of ESD	
En bloc resection (%)	51 (100)

SD, Standard deviation; *U*, upper third of the stomach; *M*, middle third of the stomach; *L*, lower third of the stomach; *ESD*, endoscopic submucosal dissection.

METHODS

The study protocol was approved by the institutional review board of Keio University Hospital. Consecutive patients who underwent ESD for intraepithelial gastric tumors[12] performed by 8 endoscopists of various levels of experience were enrolled.

Patients receiving antithrombotic therapy were included in this study; however, this was discontinued before the procedure in patients at low risk for thromboembolism according to the current guidelines of the Japan Gastroenterological Endoscopy Society.[13] Heparin bridge therapy (HBT) was administered to patients who were considered high risk for thromboembolism up to 6 hours before ESD, and restarted on the first postprocedure day. Patients with a platelet count <50,000/mm^3 were excluded from this trial. In addition, cases with coagulopathy (international normalized ratio >2) despite appropriate management and those with perforations were excluded from the analysis.

Informed signed consent for the procedure and use of the peptide solution was obtained from all patients.

Fully synthetic and self-assembled peptide solution

A novel fully synthetic material consisting of a 16-amino acid peptide solution (PuraMatrix; 3-D Matrix, Tokyo, Japan) self-assembles at physiologic pH and forms a hydrogel comprising a network of nanofibers. This rapidly seals open blood vessels when exposed to blood or tissue fluids. In addition, the important feature of PuraMatrix is its nanostructure, which is equivalent to natural ECM-SM (nanofiber) and results in adequate adherence of cells and tissue.[14]

Study protocol

For every 1 cm of resected tumor, 1 mm^3 of PuraMatrix was applied immediately to the resection site using a catheter (TOP Endoscopic Spraying Tube; Top, Tokyo, Japan). All patients received a single-dose PPI for 8 weeks beginning on the morning of the procedure.

Post-ESD bleeding was defined as bleeding that required endoscopic or surgical intervention, or a decrease in hemoglobin level of 2 g/dL and hemodynamic instability. Images of ESD-induced ulcers were collected prospectively and digitally stored, and post-ESD gastric ulcer stages were evaluated by endoscopy and classified as active, healing, or scarring at weeks 1, 4, and 8. The healing stage of gastric ESD-induced ulcer was defined as an ulcer without a mucous coating and increased margin according to the Sakita and Fukutomi classification.[15] The stage was classified at follow-up endoscopy after careful inspection and thorough review by 2 experienced endoscopists who did not participate in the ESD procedure. Although this classification is generally used to assess the healing process of a peptic gastric ulcer, we used this classification for ESD-induced ulcers in this study because it is the most objective guide published. When the opinions on stage differed between the 2 endoscopists, they discussed their findings until consensus was reached on a mutually agreeable and best staging. Although the Sakita and Fukutomi classification is directly related to peptic ulcer disease, the pathophysiology of which is certainly different from that of an iatrogenic-induced ulcer/mucosal defect after ESD, tissue regeneration and healing requires the same process from a histologic perspective. Therefore, given that it is the only objective staging guide available, this classification was used in this study to reduce interobserver interpretation variability.

The primary end point was the rate of post-ESD bleeding. The secondary end points included the transitional rate to the healing and scarring stages of gastric ESD-induced ulcers.

Statistical analysis

The continuous values were expressed as means ± standard deviation (SD). JMP, version 8, software (SAS Institute, Cary, NC) was used to analyze the data and the significance level was set at 5% for each analysis; $P < .05$ was considered statistically significant.