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Efficacy of a novel hemostatic adhesive powder in patients with refractory upper gastrointestinal bleeding: a pilot study

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ABSTRACT

Background A new hemostatic adhesive powder (UI-EWD) has been developed to reduce the high re-bleeding rates associated with the currently available hemostatic powders. The current study aimed to assess the efficacy of UI-EWD as a salvage therapy for the treatment of refractory upper gastrointestinal bleeding (UGIB).

Methods A total of 17 consecutive patients who had failed to achieve hemostasis with conventional endoscopic procedures and had undergone treatment with UI-EWD for endoscopic hemostasis in refractory UGIB were prospectively enrolled in the study. We evaluated the success rate of initial hemostasis and rate of re-bleeding within 30 days.

Results All patients underwent successful UI-EWD application at the bleeding site. Initial hemostasis occurred in 16/17 patients (94 %). Re-bleeding within 30 days occurred in 3/16 patients (19 %) who had achieved initial hemostasis. In the second-look endoscopy after 24 hours, hydrogel from UI-EWD was found attached at the bleeding site in 11/16 patients (69 %).

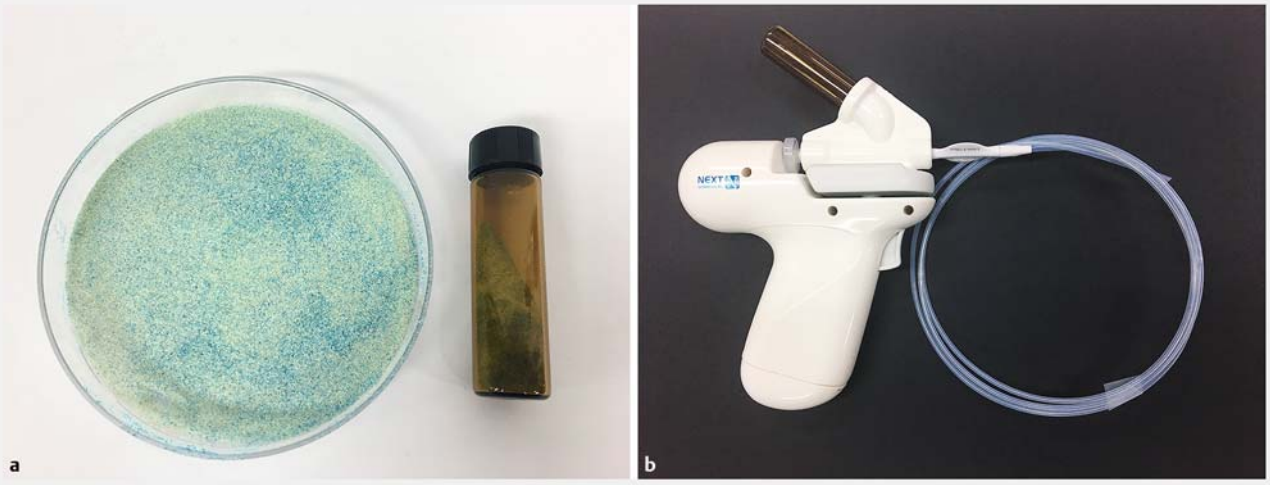
Conclusion UI-EWD has a high success rate for initial hemostasis in refractory UGIB and shows promising results in the prevention of re-bleeding.

Introduction

Upper gastrointestinal bleeding (UGIB) is a common medical emergency that requires hospital admission and is associated with significant morbidity and mortality [1]. The commonly used endoscopic hemostatic methods to control such bleeding presently include injection, thermal devices, and mechanical devices. However, the endoscopic management of UGIB is often challenging because of difficulty in achieving access and the large extent of the bleeding lesions, which result in 8 % – 15 % of patients with UGIB failing to achieve endoscopic hemostasis [2].

Hemostatic powders have recently been studied, and have reported excellent initial hemostatic rates (93 % – 98 %) in UGIB patients [2 – 4]. However, the re-bleeding rate (33 % – 49 %) was found to be high [3, 5, 6] and users of this method are frequently faced with technical challenges in application, such as clogging of the delivery catheter and impairment of adequate visualization due to scattering of powder [7]. A new hemostatic highly adhesive powder (UI-EWD; Nextbiomedical, Incheon, South Korea) (▶ **Fig. 1a**) was developed to overcome these drawbacks of the currently available hemostatic powder.

UI-EWD is a biocompatible natural polymer consisting of aldehyde dextran and succinic acid modified ε-poly. When brought into contact with water, these two materials immediately convert into a highly adhesive hydrogel. Hydrogels are easily formed by the reaction between aldehyde (aldehyde dextran) and amino (ε-poly) groups, leading to the formation of a Schiff base and multiple crosslinking points, and have high adhesive strength. Similarly, dextran and succinic acid modified ε-poly result in the formation of cohesion bonds inherent within the hydrogel by Schiff base reaction. In addition, the coating process is conducted using a fluidized bed granulator with the liquid coating materials, which modifies the water absorption capacity of UI-EWD. This coating technology allows the UI-EWD to be delivered to the bleeding area without catheter clog-



▶ **Fig. 1** Photographs of: **a** UI-EWD; **b** the spraying device.

Video 1 An experiment to demonstrate the ability of UI-EWD to be sprayed. UI-EWD is able to be delivered without catheter clogging even when it is sprayed into water.
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ging and scattering (▶ **Video 1**). The aim of the current study was to evaluate the effect of UI-EWD on refractory UGIB in conventional endoscopic hemostasis, and to assess the re-bleeding rates after initial hemostasis with UI-EWD.

Methods

Patients

Between January 2016 to December 2017, we undertook this prospective, single-center, open-label trial to assess the feasibility of UI-EWD application in refractory UGIB. Consecutive and unselected patients with refractory bleeding undergoing endoscopic UI-EWD spraying were considered for inclusion. The exclusion criteria were: (i) age < 18 years, (ii) pregnancy or suspected pregnancy, (iii) hemodynamic instability (blood pressure < 90/60 mmHg) at the time of endoscopy, and (iv) refusal to agree to the study protocol. Refractory bleeding was defined as confirmation of a Forrest 1a or 1b bleed on endoscopic view after attempted conventional endoscopic hemostasis, including injection therapy (epinephrine 1:100 000), thermal therapy (heater probe, monopolar probe, and/or argon plasma coagulation) and/or clipping (hemoclips). UI-EWD was applied immediately after failure of the conventional endoscopic treatment by the same endoscopist.

Procedure

The application of UI-EWD was performed using a conventional endoscope (Q180 – 1T; Olympus, Tokyo, Japan) by endoscopists who were experienced in therapeutic endoscopy for UGIB. UI-EWD was applied onto the active bleeding site via the spraying device (▶ **Fig. 1b**) under direct endoscopic vision until the bleeding lesion was completely covered with the powder. UI-EWD was applied in bursts, with a maximum release of 6 g of powder.

Successful initial hemostasis was defined as the powder application leading to hemostasis within 5 minutes of visual inspection. If the initial UI-EWD application failed to achieve hemostasis, the application of UI-EWD was repeated or a second conventional endoscopic hemostatic treatment was used, at the discretion of the endoscopist; this was then defined as "failed initial hemostasis."

Standard scheduled second-look endoscopy was carried out at 24 hours after UI-EWD application. Re-bleeding was defined as clinical evidence of bleeding, such as melena or hematemesis, with an associated decrease of 2 g/dL in hemoglobin concentration after the endoscopic procedure.

The study protocol was approved by the Institutional Review Board of our institution (INHAUH 2016 – 13 – 016 – 001).

Results

Patient and bleeding characteristics

Baseline characteristics of the patients and their refractory bleeding episodes are summarized in ▶**Table 1**. A total of 17 patients (median age 76 years, range 41 – 82 years; 76 % male) were enrolled. The cause of bleeding included post-interventional bleeding in 7/17 patients (41 %), a peptic ulcer in 5/17 patients (29 %), tumor bleeding in 4/17 (24 %), and anastomotic bleeding in 1/17 (6 %). Previous endoscopic treatment for hemostasis had failed in all patients; prior endoscopic treatments were mainly thermal therapy (n = 13) or a combination of thermal therapy and clipping (n = 4). In the initial endoscopic examination before applying UI-EWD, spurting hemorrhage (n = 2), and oozing hemorrhage (n = 15) were noted. Five patients were on antithrombotic therapy.

Clinical outcomes

UI-EWD was used as a salvage therapy for refractory bleeding and successfully applied at bleeding sites in all patients (▶**Fig. 2**; ▶**Video 2**). Successful initial hemostasis was achieved using UI-EWD in 16/17 patients (94 %) (▶**Table 2**), with a failure to achieve hemostasis in only one patient. The patient with failure of initial hemostasis had a spurting arterial bleed in the duodenum, which could not be controlled, even using a combination of additional UI-EWD application, coagulation, and injection therapies. The bleeding was finally controlled by interventional angiography.

In the second-look endoscopy 24 hours after the procedure, hydrogel from the UI-EWD was still found attached at the bleeding site in 11/16 successfully treated patients (69 %). Re-bleeding within 7 days occurred in three patients: two had re-bleeds quite early (within 48 hours), which were the result of tumor bleeding, with both being successfully treated with a combination of UI-EWD application and thermal therapy; the remaining patient, who had liver cirrhosis, had a re-bleed at 7 days due to a peptic ulcer. Other than these episodes, no other re-bleeds occurred within 30 days.

There was no occurrence of any adverse events related to the powder in the current study.

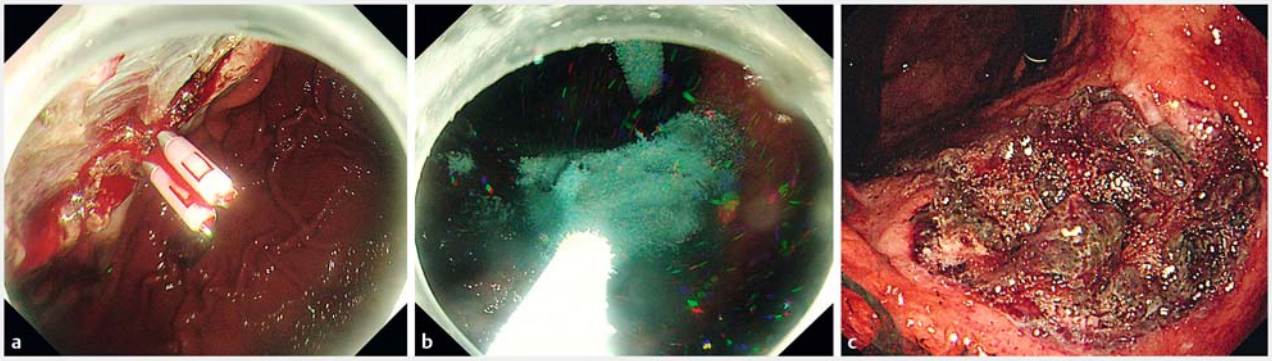
▶**Table 1** Characteristics of the 17 patients and their episodes of upper gastrointestinal bleeding.

Characteristic	
Age, median (range), years	76 (41 – 82)
Sex, male/female, n	13/4
Cause of bleeding, n (%)	
▪ Peptic ulcer	5 (29.4)
▪ Post-intervention bleeding	7 (41.2)
▪ Tumor bleeding	4 (23.5)
▪ Other	1 (5.9)
Location of bleeding, n (%)	
▪ Stomach	13 (76.5 %)
▪ Fundus and cardia	1 (5.9)
▪ Body	8 (47.1)
▪ Antrum	4 (23.5)
▪ Duodenum	3 (17.6)
▪ Anastomotic site bleeding	1 (5.9)
Comorbidity, n (%)	
▪ Hypertension	9 (52.9)
▪ Coronary artery disease	3 (17.6)
▪ Congestive heart failure	3 (17.6)
▪ Diabetes mellitus	2 (11.8)
▪ Chronic kidney disease	2 (11.8)
▪ Liver cirrhosis	1 (5.9)
Anticoagulation, n (%)	5 (29.4)
▪ Warfarin	4 (23.5)
▪ Aspirin and clopidogrel	1 (5.9)
Prior endoscopic treatment, n (%)	
▪ Injection and thermal treatment	13 (76.5)
▪ Injection, thermal, and clipping	4 (23.5)
Forrest classification, n (%)	
▪ Ia	2 (11.8)
▪ Ib	15 (88.2)

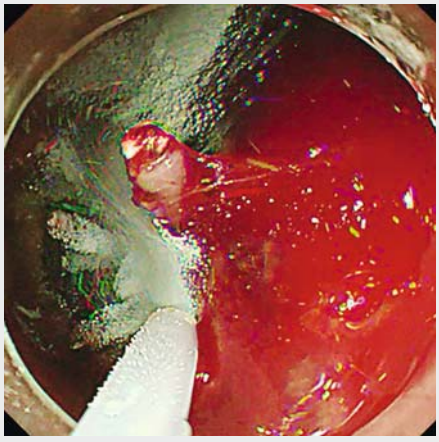
Discussion

Despite the excellent hemostatic rates of the currently available hemostatic powders, high re-bleeding rates after application of the powder are nevertheless concerning. Cahyadi et al. conducted a study with 52 patients who had diffuse or refractory UGIB to evaluate the hemostatic effect of TC-325 (Hemospray; Cook Medical, USA) in a setting similar to ours [5]. TC-325 showed a high rate of immediate hemostasis (98 %) in their study; however, the rate of recurrent bleeding within 7 days was relatively high (49 %) and the powder was not visible in any patient during the second-look endoscopy after 24 hours. Chen et al. also reported a high re-bleeding rate (47 %) with use of TC-325 in patients with high risk non-variceal UGIB [3]. Therefore, because the hemostatic effect of the powders is not durable, some experts do not recommend their use because of the high risk of re-bleeding beyond the 24-hour period [7, 8].

In accordance with the previous hemostatic powders, UI-EWD also showed excellent initial hemostatic effect (94 %) in patients with refractory bleeding in the current study. On the other hand, re-bleeding occurred in only three patients (19 %), and the adhesive hydrogels were found to be still attached at the bleeding site in 69 % of the second-look endoscopies performed 24 hours later. This greater adhesion of UI-EWD could



▶ **Fig. 2** Endoscopic images showing: **a** a Forrest Ib bleed from the gastric antrum 1 day after endoscopic submucosal dissection, which could not be controlled with thermal therapy and clipping; **b** application of UI-EWD at the bleeding site; **c** on second-look endoscopy 24 hours after application of the powder, hydrogel still firmly attached at the bleeding site with no further signs of bleeding.



Video 2 A representative video clip of UI-EWD being applied in a patient with refractory bleeding.
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▶ **Table 2** Clinical outcome of the application of UI-EWD hemostatic adhesive powder in 17 patients with refractory bleeding.

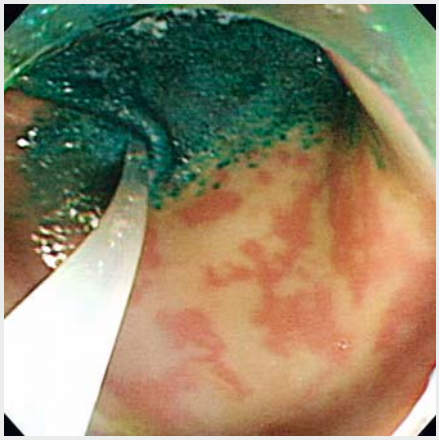
Characteristic	
Success of initial hemostasis, n (%)	16 (94.1)
Overall re-bleeding at day 7, n (%)	3 (18.8)
Spurting hemorrhage (Forrest type Ia), n	2
▪ Success of initial hemostasis, n (%)	1 (50)
▪ Re-bleeding, n (%)	0 (0)
Tumor bleeding, n	4
▪ Success of initial hemostasis, n (%)	4 (100)
▪ Re-bleeding, n (%)	2 (50)

originate from the Schiff base reaction between polymer components, with the hydrogel having the ability to remain firmly attached even when mechanical force is applied to pull it off (▶ **Video 3**). Therefore, we believe that UI-EWD provides greater adhesion than the commercially available hemostatic powders and would prove very useful in rescuing patients with refractory bleeding and reducing the re-bleeding rate.

Nevertheless, in patients with a spurting arterial bleed, the initial hemostasis rate of UI-EWD remained unsatisfactory (50 %). Therefore, we propose that UI-EWD should be used as bridging therapy in spurting arterial bleeds: after applying UI-EWD for hemostasis, alternative treatment options, such as surgery or interventional radiology, should be prepared in case UI-EWD application fails.

Tumor bleeding represents a challenging clinical situation and conventional endoscopic hemostasis is not always effective [9]. The failure of conventional hemostatic treatment may be related to the large size of the bleeding tumor, its underlying tissue friability, pathological angiogenesis, and tumor-induced necrosis [10, 11]. The mechanism of tumor bleeding is explained by erosion of the raw surface of a malignant site. In addition, acidic conditions from the stomach can promote more bleeding because the acid dissolves the clot and digests the tumor tissue, which lacks a barrier of mucus and epithelium [12]. The non-contact application of UI-EWD makes it desirable in situations that involve its application over a large area with complex neo-angiogenesis or that are difficult to access, meaning they would not otherwise be amenable to conventional targeted therapies. Moreover, the UI-EWD that persists on the surface for a period of time may protect the tumor tissue from further erosion by gastric acid.

There were four tumor bleeds included in the current study and UI-EWD showed promising results in initial hemostasis (100 %). Given the character of the powder, UI-EWD is able to cover a large area with non-contact, non-thermal, non-traumatic, and technically easy application. Therefore, we assume that UI-EWD may be considered a salvage hemostatic modality in selected patients where surgery is not indicated because of



Video 3 An experiment to show the ability of UI-EWD to remain attached in a porcine model. The hydrogel stays firmly attached to the normal mucosa even when mechanical force is applied to pull it off.
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the high risk of associated morbidity or mortality. However, UI-EWD can be considered as a bridging therapy rather than a salvage hemostatic modality in tumor bleeding because the rebleeding rate was relatively high (50 %).

The current study is limited by the small number of patients and the diverse causes of refractory bleeding. However, recruitment of a larger number of patients with refractory bleeding is very difficult, and further prospective multicenter studies would be useful to confirm our results.

In conclusion, this study demonstrates the effectiveness of UI-EWD as a salvage therapy in the treatment of refractory UGIB. The inclusion of these patients in future trials is recommended to increase the generalizability of these results.

Acknowledgments

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Competing interests

Don Haeng Lee is the developer of UI-EWD and the founder of Nextbiomedical Co. Ltd. He declares that he has no conflict of interest. Other authors declare no potential conflict of interest.

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