Horizon Scanning Report

Endoscopic control of gastrointestinal bleeding using sprayed hemostatic powder

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NECA National Evidence-based Healthcare Collaborating Agency
H-SIGHT Horizon Scanning Service for Innovative Global Health Technology

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Basic information	
Identification No.	H-SIGHT-2015-385
Report No.	H-SIGHT-2015-005
Technology type	Medical device and medical practice
Name of technology	Endoscopic control of gastrointestinal bleeding using sprayed hemostatic powder
Product and developer	EndoClot® Polysaccharide Hemostatic System (EndoClot® PHS)
Target group	Patients with gastrointestinal bleeding
Purpose	The medical technology was developed for hemostatic use, and applies styptic powder at lesion sites through gastrointestinal endoscopy when bleeding control in vessels such as capillaries is ineffective or impossible • Hemostatic product for endosomatic absorption: for hemostatic use through gastrointestinal endoscopy when bleeding control in vessels such as capillaries is ineffective or impossible • Air compressor: delivers a hemostatic powder for endosomatic absorption to lesion sites through gastrointestinal endoscopy
Innovativeness	With use of a new hemostatic product for endosomatic absorption, significant improvements are expected in procedural aspects (materials and delivery methods) in comparison with existing/similar technology - A broad range of bleeding can be resolved at once. Endosomatic absorption
Estimated time point of market entry in South Korea	Less than 1 year
Stage of development	Established
Current status of use (domestic and foreign)	• International: After CE approved (June 2012), Currently used in European countries • Domestic: MFDS (Ministry of Food and Drug Safety) approved (No. 14-2138, June 2014) for an ancillary hemostatic product adapted to endoscopic use when bleeding control in vessels such as capillaries is ineffective or impossible. endosomatic absorption (ophthalmology excluded)
Technology setting	General hospital with endoscopist

Summary

This new hemostatic product allows endosomatic absorption, and is differentiated by procedural aspects (materials and delivery methods) in comparison with existing endoscopic hemostasis methods.

The product can be used for hemostatic purposes in gastrointestinal endoscopy when bleeding control in vessels such as capillaries is ineffective or impossible. A broad range of bleeding can be resolved at once.

More clinical evidence is needed to confirm safety and validity: total 7 cases (3 case studies and 4 abstracts published).

1. Background and burden of disease

1.1 Gastrointestinal bleeding

Peptic ulcer accounts for the largest percentage among the types of gastrointestinal bleeding, and is a major cause of hospitalization. However, in recent decades, the causes of disease have changed, treatment drugs have been developed, and various internal treatment methods have been introduced, but the mortality rate has shown little change.

Gastrointestinal tract bleeding can be further categorized into various types according to the major symptoms, such as hematemesis, melena, hematochezia, and occult bleeding, or the minor symptoms, such as dizziness resulting from anemia, loss of consciousness, angina, and difficulty in breathing. Clinical presentation varies in accordance with the degree and rate of bleeding, timing, and whether or not other diseases are present. Bleeding in amounts less than 500 mL rarely reveals systemic symptoms, but in elderly patients, even small amounts of bleeding can bring about hemodynamic changes and result in other symptoms associated with anemia. In a study that investigated upper gastrointestinal bleeding,[1] peptic ulcer was the most frequent cause, accounting for about 50%, followed by variceal bleeding (5-30%), which varies in accordance with population distribution. In addition, other minor causes include hemorrhagic gastric lesions induced by nonsteroidal anti-inflammatory drug (NSAID) or alcohol use, erosive gastritis, and erosive esophagitis. Causes of gastrointestinal bleeding are shown in the table 1.

〈Table 1〉 Upper gastrointestinal tract bleeding induced by diseases.

Bleeding causes	Severity of bleeding	
	Moderate (246 patients)	Severe (140 patients)
Esophagus		
Esophagitis	12%	7%
Ulcer	2%	2%
Mallory-Weiss tear	5%	19%
esophageal varices	5%	31%
Entire esophagus	24%	59%
Stomach		
Stomach ulcer	15%	14%
Prepyloric ulcer	2%	4%
Pyloric channel ulcer	4%	2%
Gastric erosions	2%	0
Gastritis	7%	0
Varices	1%	2%
Portal-hypertensive gastropathy	2%	0
Gastric cancer	2%	0
Polyp	0	2%
Dieulafoy lesion	0	0
Entire stomach	35%	24%
Duodenum		
Ulcer	30%	15%
Duodenitis	8%	0
Aortoenteric fistula	0%	2%
Pancreatic pseudocyst	2%	0
Post-sphincterotomy	1%	0
Entire duodenum	41%	17%

1.2 Burden of disease

In South Korea, the main diseases in which medical technology can be applied are gastrointestinal diseases. Statistical data for diseases and their characteristics from the Health Insurance Review & Assessment Service were used to investigate the domestic disease burden. The total number of gastrointestinal disease patients was approximately 100,000 as of 2014 and the treatment cost was approximately KRW 33,700 million. The data were not limited to gastrointestinal bleeding patients, but the treatment cost for other gastrointestinal diseases appears to be increasing.

〈Table 2〉 Number of patients with other gastrointestinal diseases (K92) and treatment costs.

(Unit: No. of patients, KRW 1,000)

Classification	2014		2013		2012	
	Patients	Medical cost	Patients	Medical cost	Patients	Medical cost
Total	106,298	33,662,295	104,746	28,558,417	109,701	25,596,345

2. Description of the health technology

2.1 Precedure

The medical device for this technology consists of an absorbable powder (composed of an absorbable modified polymer, AMP, to be applied at the bleeding site through gastrointestinal endoscopy) and the application mechanism (air source) to deliver the powder. The device approaches the site through gastrointestinal endoscopy and sprays the hemostatic powder onto the bleeding vessels for hemostasis.

(1) Connect the hemostatic device and air compressor (if needed) to the applicator
(2) Move the gastrointestinal endoscopic apparatus toward the bleeding site and confirm the source
(3) Insert the applicator through the working channel of the gastrointestinal endoscope
(4) Depress the hemostatic device to apply an appropriate amount of hemostatic agent to the bleeding site. If necessary, use the air compressor. If bleeding continues, apply the remaining hemostatic agent after rinsing with saline solution
(5) When hemostasis is accomplished, remove the remaining hemostatic agent after rinsing with saline
(6) Remove the catheter from the endoscope immediately after hemostasis is accomplished

Powder		Biocompatible substance comprising starch-based ingredients with high cell adhesion rate The absorbable modified polymer (AMP) contain no human or animal origin
Applicator		The applicator is a chamber with powder and gas mixed together and is easy to connect to the catheter and tube. Reflux prevention system
Injection device		H (Anti-reflux apparatus): Air pressure at 18 ± 3 kPa L (Powder spraying apparatus): Air pressure at 12 ± 3 kPa

〈Figure1〉 Description of endoscopic hemostatic method for gastrointestinal bleeding application* using sprayed styptic powder.

* Manufacturer: EndoClot Plus, Inc. [http://endoclot.com/EndoClot%20PHS%20Brochure_Revised.pdf]

2.2 Related status

In Korea, this ancillary hemostatic product for endosomatic absorption is used in endoscopic surgery when bleeding control in vessels such as capillaries is ineffective or impossible, since it was approved by the Ministry of Food and Drug Safety (MFDS) (Approval No. 14-2138, June 2014)[2].

This product was CE approved (June 2012) in other countries, and is currently used in Europe; later it was approved and has been used in Singapore (2014), Australia (2013), Malaysia (2012), and Turkey (2012).

3. Alternative or complementary therapy(to the existing health echnology)

Treatment approaches for gastric bleeding patients vary in accordance with bleeding location, degree, and rate. Primary consideration in treatment of bleeding patients is to maintain blood volume and vascular hemodynamic stability. Vital signs must be monitored, and intravenous access must be secured by conducting a blood test to verify the ability to tolerate a large volume of saline solution and plasma extender if necessary. When a patient bleeds a large volume, emergency endoscopic examination and supportive treatment are necessary, in accordance with the type of disease.

3.1 Approach using a nasogastric tube

A nasogastric tube must be left inserted for several hours, even if the aspirate is clean; the aspirate can be clean even when there is active duodenal bleeding. If blood is not detected in the aspirate at the time of active bleeding, then it can be inferred that the stomach and duodenum are not the source and the tube can be removed. However, even if evidence of bleeding is not observed while a nasogastric tube is inserted, it cannot be said with certainty that bleeding is not from the stomach or duodenum. Thus, an endoscopic examination is required. If either bright red bleeding or coffee ground-like aspirate appears, rinsing must be performed with normal saline solution. Rinsing has two purposes: detection of bleeding rate and removal of old clotted blood and blood remaining in the intestine. In addition, small vessels in the stomach can be contracted and have a hemostatic effect.

3.2 Approach through endoscopic examination and treatment

Endoscopic examination allows identification of the cause of bleeding and the prognosis for rebleeding, and enables endoscopic treatment. In ulcer-induced bleeding, hemostasis can be achieved by endoscopic coagulation, with injection of vasoconstrictors or a sclerosing agent, or use of a heated probe and electrocautery. Variceal bleeding requires more than basic treatment, although ancillary management can be provided with application of pressure using a Sengstaken-Blakemore tube, or injection of vasopressin and the somatostatin derivative octreotide.

3.3 Hemostasis using angiography

Angiography can be performed for the rare causes of upper gastrointestinal bleeding that are not detected by endoscopy. Angiography can be directly used in active bleeding by identifying lesion location and selectively conducting a vasopressin test or coil embolization. However, even if the bleeding location is confirmed, drawbacks exist: the fundamental cause of the lesion cannot be known for sure; angiography is limited to bleeding of at least 30 mL/h; the instruments are expensive; and a prolonged and invasive procedure is required.

4. Evidence

A literature search based on “the hemostatic method in endoscopic gastrointestinal bleeding” and “EndoClot” was conducted to investigate clinical results and the technology itself. No studies from Korea were found, but 7 studies from other countries were identified.

4.1 Effectiveness

Five of these 7 studies were accessed to validate the hemostasis rates using this technology, and the remaining studies provided results for delayed bleeding after application. Each study defined the hemostasis and delayed bleeding rates differently as follows: no bleeding during the time of endoscopic treatment, no rebleeding within 3 days, or no definition provided for the hemostasis rate. The 7 studies with clinical results using this technology had the following characteristics.

〈Table 3〉 Results of endoscopic hemostasis in gastrointestinal bleeding using sprayed styptic powder.

Author (Year)	Number of Subjects	Literature Type	Diseases	Results
Chandrasinghe (2015)	1	case report	Laparoscopic cholecystectomy	Hemostasis in 1 patient
Chedgy (2015)	827	abstract	After EMR and EMR	Delayed bleeding in 33 patients
Huang (2014)	82	case report	After colon EMR	Delayed bleeding in 6 patients
Kasimanickam (2014)	12	abstract	Bleeding induced by duodenal ulcer, gastric lymphoma induced bleeding, ulcer, polyp biopsy	Hemostasis in 12 patients
Patel (2014)	18	abstract	Ulcer, duodenal ulcer, lower gastrointestinal EMR	Hemostasis in 16 patients
Halkerston (2013)	6	abstract	Duodenal ulcer-induced bleeding after EMR, Mallory-Weiss tear	Hemostasis in 5 patients
Müller (2013)	22	case report	Acid reflux, granulation polyps in stomach, stomach biopsy site, duodenal sarcoma, gastric cancer-induced bleeding, ulcer	Hemostasis in 21 patients

Chandrasinghe et al. (2015)[3] reported use of this technology in a 36-year-old with hepatic cirrhosis during laparoscopic cholecystectomy. The subject had liver cancer, hepatic encephalopathy, and recurrent cholangitis, for which laparoscopic cholecystectomy was performed. This technology was successfully applied for bleeding during surgery, with no rebleeding after application.

Chedgy et al. (2015)[4] studied approximately 800 subjects divided into 2 groups, and monitored the occurrence of delayed bleeding after treatment. Group A included 496 upper and 264 lower gastrointestinal patients, in whom the technology was applied as a preventive measure before endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD); delayed bleeding occurred in 21 (4%) and 9 patients (3%), respectively. Group B included 37 lower gastrointestinal and 30 upper gastrointestinal patients. After application of the technology during endoscopic treatment, delayed bleeding occurred in 1 (3%) and 2 patients (7%), respectively. Adverse reactions were not detected in any cases.

Huang et al. (2014)[5] studied 82 patients with colorectal lesions less than 0.5 cm in size after EMR. No bleeding occurred immediately after treatment, and 6 patients showed a positive fecal occult blood test, but all recovered without additional endoscopic or surgical treatment. No side effects were observed.

Kasimanickam et al. (2014)[6] studied 12 patients whose bleeding causes included duodenal ulcer, gastrointestinal stromal tumor (GIST), gastric ulcer, and post-gastric polyp biopsy bleeding. Hemostasis was successful in all 12 patients immediately after surgery, and 1 patient had rebleeding 120 hours later; details on adverse reactions were not reported.

* Dieulafoy lesion, a type of vessel deformity that causes upper gastrointestinal bleeding. It occurs when large tortuous small arteries in the submucosa are exposed, and cause severe bleeding.
** Mallory-Weiss syndrome is a disease associated with ongoing severe nausea and vomiting for hours or days (mainly after drinking), and causes bleeding when the junction between the esophagus and stomach is torn, exposing vessels.

Patel et al. (2014)[7] studied 18 patients and hemostasis was successful in 16 (89%). The subjects had bleeding induced by stomach ulcer, duodenal ulcer, and lower gastrointestinal EMR. Hemostasis was not successful using this technology in 2 patients with a duodenal ulcer and Dieulafoy lesion,* respectively. In these 2 patients, hemostasis was successful immediately after application, but melena occurred 3 days later, and endoscopic adrenaline injection of bleeding site vessels and banding were performed. The course was similar in duodenal ulcer patients in whom hemostasis was successful immediately after application, but who developed melena 2 days later; endoscopic adrenaline injection and hemostasis using clips were performed, followed by high-frequency diathermy. However, this patient was later found to have a GIST.

Halkerston et al. (2013)[8] studied 6 patients, 2 of whom underwent EMR to remove rectal polyps. Since bleeding did not stop with cautery alone, this technology was applied. Another 2 patients had duodenal ulcer-induced active bleeding; adrenaline injection and electrocautery hemostasis were attempted during endoscopic treatment, but bleeding did not stop, and this technology was applied. One patient had a Mallory-Weiss tear** ; this technology was applied to the damaged vessels and bleeding stopped. Hemostasis using this technology was successful in the above 5 patients, with no rebleeding or adverse reactions within 14 days. Another patient had duodenal ulcer bleeding despite adrenaline injection and use of clips, which stopped with this technology. However, rebleeding appeared the next day, and additional diagnostic testing showed carcinoma of the pancreatic head with duodenal infiltration. The authors of this study concluded that application of this technology would be effective in treating broad-based mucosal bleeding induced by EMR.

Müller-Cerbes, et al. (2013)[9] studied 22 patients, and hemostasis was successful in 21 (95.5%). The bleeding causes in these patients included acid reflux accompanying ulcer, granulation polyps in the stomach antrum, biopsy sampling sites for gastric cancer, a broad-based ulcer in the antrum, sarcoma of the duodenum, gastric cancer induced-bleeding, and stomach ulcer. They reported details for 1 unsuccessful case, in which the patient consistently used oral anticoagulants for cardiovascular disease. In this patient, the technology was applied for a broad-based ulcer, but hemostasis was not successful, and bleeding stopped with use of clips. Among the successful cases, 7 patients were using anticoagulants. None of the 22 patients showed rebleeding within 48 hours, and there were no reports of adverse reactions (e.g., aspiration, mucosal damage, additional bleeding, perforation, or allergic reactions).

4.2 Safety

Among search results for studies that applied "the hemostatic method in endoscopic gastrointestinal bleeding using sprayed styptic powder," 4 studies (Chandrasinghe et al. 2015; Chedgy et al. 2015; Huang et al. 2014; Müller et al. 2013) reported that adverse reactions, such as aspiration, mucosal damage, additional bleeding, and allergic reactions, did not occur; in the remaining 3 (Kasimanickam et al. 2014; Patel et al. 2014; Halkerston et al. 2013), only the abstracts were published, with no mention of adverse reactions.

4.3 Results of international health technology assessment

A search was performed for domestic and foreign literature on established and newly developed promising medical technology based on "the hemostatic method in endoscopic gastrointestinal bleeding using sprayed styptic powder." The search found that an evaluation of this technology has not been published.

A search of new medical technology evaluations in Korea found 1 evaluation by the Center for New Health Technology Assessment. The application was resubmitted in January 2016 and is in the process of evaluation.

5. Cost Information

The cost related to this treatment is not currently known. However, the prices introduced at the 2014 meeting of the Belgian Society of Gastrointestinal Endoscopy (BSGIE) were approximately 99 (EUR) for AMP powder and 270 (EUR) for application[10].

6. Ongoing research

Clinical studies related to this method were searched through the website for registered clinical trials operated by the U.S. National Institutes of Health as a service (https://clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (http://apps.who.int/trialsearch/defalt.aspx). Two studies were found (as of November 2015).

〈Table 4〉 Clinical study summary of the endoscopic hemostatic method in gastrointestinal bleeding using sprayed styptic powder.

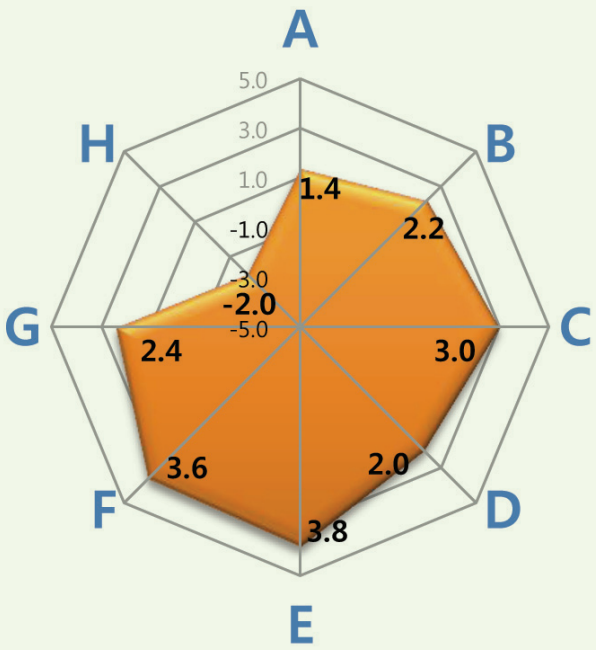
No	Year	Main ID	Target condition	Subjects (N)	Intervention method	Tracking period	Result variables	Status
1	2011	NCT 0149 6781	EMR subjects for colon polyps and submucosal cancer	164	EndoClot application for hemostatic purposes after EMR.	1month	1st result: Hemostasis rate after EMR. 2nd result: Mucosal restoration after EMR, time to hemostasis, rebleeding rate, gastrointestinal blockage	Complete
2	2012	NCT 0173 5786	EMR subjects for colon polyps and submucosal cancer	164	EndoClot	1month	1st result: Hemostasis rate after EMR. 2nd result: Mucosal restoration after EMR, time to hemostasis, rebleeding rate, gastrointestinal blockage	Complete

7. Social impact (expert opinion)

These are opinions those of 5 experts in relevant clinical department selected randomly in the pool of National Evidence-based Collaborating Agency (NECA) comprising 800 health technology assessment experts.

Potential impacts in consideration of diverse aspects (such as disease burden, innovativeness, economic effects, acceptability, and social ripple effect), as well as clinical effects of endoscopic hemostasis in gastrointestinal bleeding using sprayed styptic powder were achieved with the input of professional advice.

This technology will be recognized as an innovative treatment method, with possible benefit for unmet medical needs and health conditions. However, if the effects are minor, the possibility increases that insurance coverage will consider this to be a high-cost item, in which case there might be an adverse effect on healthcare access. Thus, symptom improvement alone might be insufficient to justify the cost. Furthermore, the current study results are insufficient to prove the hemostatic effect in gastric bleeding, and clinical acceptability might thus be decreased. In patients who use anticoagulants, this technology might be very useful for those with high risk of clots resulting from drug interruption for endoscopic treatment. More study evidence supporting the use of this technology will be clinically useful. Furthermore, this technology may be useful when the bleeding site is uncertain, or in the case of broad-based multicentric bleeding. However, the area needed to visualize the bleeding site could be difficult to attain because of the large area of antihemorrhagic application. One opinion stated that the powder application dose in clinical use was not easy to determine, and a learning period to control the application amount is therefore necessary. It can be inferred that the product is safe for human use because the main ingredient is a polysaccharide. However, the results are insufficient to determine whether the effect is naturally hemostatic or antihemorrhagic. The treatment cost has not been published, but it is inferred that high cost is unlikely, considering the main device components and product composition.



A. Fulfillment of unmet needs; B. Improvement in patients' health; C. Impact on health disparities; D. Impact on health care delivery system; E. Acceptability to patients; F. Acceptability to clinicians; G. Changes in healthcare costs; H. Social, Ethical and legal impact. (This graph presents mean values of results on positive or negative potential impact assessment by medical professionals with ±1~5 points of scale.)

〈Figure 2〉 Result of analysis of the potential effects for the endoscopic hemostatic method in gastrointestinal bleeding using sprayed styptic powder.

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