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## Editorial

## Hemostatic materials in non-variceal upper gastrointestinal hemorrhage

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### Background

Despite that upper gastrointestinal hemorrhage (UGIH) is relatively common, it is an emergent disease of the gastrointestinal system which can threaten the lives of patients.<sup>1</sup> Despite major improvements in endoscopic devices and therapeutic endoscopy for the treatment of UGIH or prevention of rebleeding, higher than a 10% death rate has been reported. Due to the of high incidence of aspirin and nonsteroidal anti-inflammatory agent use, the most common cause of UGIH remains peptic ulcerative bleeding due to gastric and duodenal mucosal injury. In addition to peptic ulcers, the incidence rate of variceal bleeding is 10%–30% and that of Mallory–Weiss tears is 5%–15%. Other common causes of UGIH include esophagitis, erosive lesions, angiodysplasia, Dieulafoy's lesion, and malignant tumors. The goal of UGIH treatment is to maintain the hemodynamic stability of patients, hemostasis, and the prevention of rebleeding. Endoscopic hemostatic intervention is the most important treatment for hemostasis and the prevention of rebleeding for high-risk patients. A variety of endoscopic treatment modalities including hemostatic grasper, thermocoagulation using argon plasma coagulation, hemostatic clipping, mechanical hemostasis with a band material, and injection materials such as epinephrine or histoacryl have exhibited greater impact in terms of reducing the incidence of blood transfusion, emergent surgery, and mortality.<sup>2</sup> However, these conventional endoscopic therapies are often challenging as they depend on lesion location and on the extent and characteristics of bleeding or bleeding deterioration due to mucosal injury or perforation. In recent years, new topical hemostatic modalities have been introduced to allow for easier and more effective hemostasis. This article introduces several hemostatic materials that have been recently used and studied in clinical practice.

### Hemospray

Hemospray (Cook Medical Inc., Winston-Salem, NC, USA) is a highly adhesive proprietary inorganic biologically inert powder which can be sprayed onto bleeding lesions. This mineral powder absorbs liquid from the blood and forms a sticky film when adsorbed by a bleeding lesion.<sup>3,4</sup> The adsorbed powder increases the concentration of the coagulation factor, activates the platelets, and ultimately forms a plug on wounded blood vessels. Following hemostasis, the powder is removed from the intestinal mucosa and is completely removed from the GI track. Although this material forms membranes on the exposed sites which had been actively spurting or oozing blood, it may be less effective on inactive bleeding sites such as nonbleeding visible vessels which are still at high risk of bleeding. Hemospray was first widely used in Asia. In a prospective pilot study conducted by Sung et al,<sup>4</sup> 20 adult male and female with actively bleeding peptic ulcers underwent endoscopic hemostasis within 24 hours of their hospital visit, and 95% (19/20) showed successful hemostasis; however, one patient underwent arterial embolization due to an evidence of pseudoaneurysm. Hemoglobin declined by over 2 mg/dL in two subjects within 72 hours, suspected of rebleeding, but none of the endoscopies revealed bleeding. There were no procedural complications. Holster et al<sup>5</sup> studied the effects of Hemospray on UGIH in patients receiving antithrombotic therapy, the results of which showed no difference in terms of the effect on hemostasis nor rebleeding rates from those patients who had not received antithrombotic agents. The largest study reported so far was conducted in France, involving a total of 202 patients and 64 endoscopists at 20 centers. In the paper 31.7% of the doctors participated in this study answered 'very easy' and 55.4% of them answered 'easy' regarding the application of Hemospray. The initial hemostasis success rate was 96.5% with a rebleeding rate of 26.7% on the 8th day and 33.5% on the 30th day.<sup>5</sup> No procedure-related adverse events were reported on the use of Hemospray. However,

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one of important cautions is not to spray too closely to the lesion. This is because powder can obstruct the sight of the endoscope or block the catheter. Another caution is a trial not to tear the mucous membrane due to the catheter. In addition, the possibility of embolism, intestinal obstruction, and allergic reaction due to the characteristics of the powder are very rare, but remain possible.<sup>7</sup>

## EndoClot

EndoClot Polysaccharide Hemostatic System (EndoClot Plus Inc., Santa Calra, CA, USA), is a powder product made from an absorbable modified polymer with a polysaccharide of vegetable starch. This material features excellent adhesion and high hydrophilicity, so that the injected powder absorbs water rapidly from the blood and concentrates red blood cells, platelets, and coagulation factors on the bleeding site, thereby inducing hemostasis. Much like Hemospray, EndoClot is delivered from an inserted catheter through the endoscope channel and 3 g of powder is injected onto the bleeding sites by an air compressor.<sup>8</sup> Due to that the powder is spread out in multi-directions, it is useful for lesions difficult to access such as the posterior wall of the duodenum. Prei et al<sup>9</sup> performed a prospective open-label study, including 70 subjects, and 64% of patients in the study showed successful hemostasis while rebleeding occurred in 11% (8/70). Park et al<sup>10</sup> by propensity score matching, compared to the conventional endoscopic methods, found that there were no significant differences from the immediate hemostasis success rate of the 30 patients treated with EndoClot nor the incidence of rebleeding rate after 7 and 30 days.<sup>11,12</sup> However, Singh et al<sup>13</sup> conducted a study of hemostatic materials showing that the hemostatic success of commercially available microporous polysaccharide hemispheres was much lower than that of bovine-derived gelatin particles.

## Ankaferd Blood Stopper

Ankaferd Blood Stopper (ABS; Ankaferd Health Products Ltd., Istanbul, Turkey) contains 5 mg of thymine-dried herbal extract, 9 mg of *Glycyrrhiza glabra* (licorice-dried leaf extract), 8 mg of *Vitis vinifera* (grape-dried leaf extract), 7 mg of *Alpinia officinarum* (lesser galangal-dried leaf extract), and 6 mg of *Urtica dioica* (stinging nettle-dried root extract). This material precipitates fibrinogen and forms a protein network which acts on erythrocyte aggregation independent of platelet activity and coagulation in the blood. The topical use of ABS has previously been approved by the Turkish Ministry of Health and is being used to address both dermal and post-surgical bleeding.<sup>14</sup> Gungor et al<sup>15</sup> found that 19 of 26 UGIH patients had successful hemostasis, with a first-stage success rate of 73% and rebleeding rate of 15.8%. In the paper 6 out of 7 subjects who had failed treatments were successful with additional conventional endoscopic treatment. In this study, the authors suggested that alternative techniques such as mechanical compression could be helpful in the application of ABS, rather than spray catheter. However, there has not been much research done on endoscopic hemostasis.<sup>16</sup>

## Nexpowder

While existing products have reported excellent results during several clinical studies, there do exist some disadvantages. Particularly when the powder comes into contact with water and turns into a gel form, the adhesive force is compromised and it often falls off the lesion too quickly to maintain hemostasis. As a result, the hemostatic effect lasts up to a maximum of one day and the

**Table 1 Hemostatic Materials**

Name	Composition	Action mechanism
Hemospray	Mineral	Absorption of water Concentration of platelets and clotting factors
EndoClot	Polysaccharide	Absorption of water Concentration of platelets and clotting factors
Ankaferd Blood Stopper	Mixture of plants	Encapsulated protein network → Erythrocyte aggregation around the network
Nexpowder	Biocompatible natural polymer	Modified of water absorption capacity using coating technology Reversible cross-linking of amine and aldehyde groups

subsequent rebleeding rate is high.<sup>17</sup> In addition, if the powder is not injected with care, the injected powder interferes with the endoscopic field of view, and it could harden into the gel form too early in the catheter, thus hindering the launch. A newly developed hemostatic adhesive powder Nexpowder (Next Biomedical, Incheon, Korea)<sup>18</sup> consists of oxidized dextran and succinic acid modified amino acid, and is thus biodegradable and biocompatible. When Nexpowder comes into contact with water, the aldehyde group of the oxidized dextran reacts with the amine of the succinic acid modified amino acid, and becomes an adhesive gel. The gel physically adheres to the ulcer base creating a mechanical barrier to achieve hemostasis. Nexpowder does not require active bleeding for adhesion because its adhesive characteristics are a result of the reversible cross-linking of amine and aldehyde groups when they come into contact with moisture. For this reason, Nexpowder can be employed to treat non-bleeding visible vessels and prevent delayed bleeding following primary hemostasis having been achieved. In terms of safety, Nexpowder contains no human nor animal derived components. It is biologically inert, non-toxic, and does not appear to interact with tissues. Furthermore, it is not absorbed by the body and it exits via the small intestine within 66 hours. Park et al<sup>18</sup> revealed that 94% (16/17) of initial hemostasis was successful in 17 patients who failed hemostasis with conventional endoscopic procedures, and only 19% (3/16) reported re-hemorrhage within 30 days. We also found that Nexpowder was adherent to hydrogel-like lesions in 69% (11/16) of patients who underwent follow-up endoscopy 24 hours after initial hemostasis. However, since the product has not yet been released, more clinical studies are necessary.

## Conclusion

Several hemostatic materials have been developed to overcome the limitations of conventional endoscopic hemostasis which are presently in clinical use (Table 1). Despite the high success rate of early hemostasis, there is still an insufficient level of hemostasis. There are various problems facing injection which have yet to be resolved. Some materials, on the other hand, overcome these issues of existing hemostatic powders and display higher efficacy with respect to adhesion and durability. In conclusion, hemostatic powder offers immediate hemostasis using a simple, safe, and minimally operator dependent technique. We hope that continued and effective clinical research will lead to an easy and productive hemostatic material.

## Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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## References

- Peery AF, Dellon ES, Lund J, Crockett SD, McGowan CE, Bulsiewicz WJ, et al. Burden of gastrointestinal disease in the United States: 2012 update. *Gastroenterology*. 2012;143:1179-87.e3.
- Hwang JH, Fisher DA, Ben-Menachem T, Chandrasekhara V, Chathadi K, Decker GA, et al.; Standards of Practice Committee of the American Society for Gastrointestinal Endoscopy. The role of endoscopy in the management of acute non-variceal upper GI bleeding. *Gastrointest Endosc*. 2012;75:1132-8.
- Holster IL, van Beusekom HM, Kuipers EJ, Leebeek FW, de Maat MP, Tjwa ET. Effects of a hemostatic powder Hemospray on coagulation and clot formation. *Endoscopy*. 2015;47:638-45.
- Sung JJ, Luo D, Wu JC, Ching JY, Chan FK, Lau JY, et al. Early clinical experience of the safety and effectiveness of Hemospray in achieving hemostasis in patients with acute peptic ulcer bleeding. *Endoscopy*. 2011;43:291-5.
- Holster IL, Kuipers EJ, Tjwa ET. Hemospray in the treatment of upper gastrointestinal hemorrhage in patients on antithrombotic therapy. *Endoscopy*. 2013;45:63-6.
- Haddara S, Jacques J, Lecleire S, Branche J, Leblanc S, Le Baleur Y, et al. A novel hemostatic powder for upper gastrointestinal bleeding: a multicenter study (the "GRAPHE" registry). *Endoscopy*. 2016;48:1084-95.
- Babiuc RD, Purcarea M, Sadagurschi R, Negreanu L. Use of Hemospray in the treatment of patients with acute UGIB - short review. *J Med Life*. 2013;6:117-9.
- Beg S, Al-Bakir I, Bhuvra M, Patel J, Fullard M, Leahy A. Early clinical experience of the safety and efficacy of EndoClot in the management of non-variceal upper gastrointestinal bleeding. *Endosc Int Open*. 2015;3:E605-9.
- Prei JC, Barmeyer C, Bürgel N, Daum S, Epple HJ, Günther U, et al. EndoClot polysaccharide hemostatic system in nonvariceal gastrointestinal bleeding: results of a prospective multicenter observational pilot study. *J Clin Gastroenterol*. 2016;50:e95-100.
- Park JC, Kim YJ, Kim EH, Lee J, Yang HS, Kim EH, et al. Effectiveness of the polysaccharide hemostatic powder in non-variceal upper gastrointestinal bleeding: using propensity score matching. *J Gastroenterol Hepatol*. 2018;33:1500-6.
- Kim YJ, Park JC, Kim EH, Shin SK, Lee SK, Lee YC. Hemostatic powder application for control of acute upper gastrointestinal bleeding in patients with gastric malignancy. *Endosc Int Open*. 2018;6:E700-5.
- Vitali F, Naegel A, Atreya R, Zopf S, Neufert C, Siebler J, et al. Comparison of Hemospray® and Endoclot™ for the treatment of gastrointestinal bleeding. *World J Gastroenterol*. 2019;25:1592-602.
- Singh RK, Baumgartner B, Mantei JR, Parreno RN, Sanders PJ, Lewis KM, et al. Hemostatic comparison of a polysaccharide powder and a gelatin powder. *J Invest Surg*. 2019;32:393-401.
- Uçar Albayrak C, Calişkan U, Haznedaroglu IC, Goker H. Haemostatic actions of the folkloric medicinal plant extract Ankaferd Blood Stopper. *J Int Med Res* 2008; 36: 163-170. *J Int Med Res*. 2008;36:1447-8; author reply 1448-9.
- Gungor G, Goktepe MH, Biyik M, Polat I, Tuna T, Ataseven H, et al. Efficacy of ankaferd blood stopper application on non-variceal upper gastrointestinal bleeding. *World J Gastrointest Endosc*. 2012;4:556-60.
- Barkun A. New topical hemostatic powders in endoscopy. *Gastroenterol Hepatol (N Y)*. 2013;9:744-6.
- Bang B, Lee E, Maeng J, Kim K, Hwang JH, Hyon SH, et al. Efficacy of a novel endoscopically deliverable muco-adhesive hemostatic powder in an acute gastric bleeding porcine model. *PLoS One*. 2019;14:e0216829.
- Park JS, Bang BW, Hong SJ, Lee E, Kwon KS, Kim HK, et al. Efficacy of a novel hemostatic adhesive powder in patients with refractory upper gastrointestinal bleeding: a pilot study. *Endoscopy*. 2019;51:458-62.