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Review Article

New endoscopic techniques in treating gastrointestinal bleeding

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A B S T R A C T

Gastrointestinal (GI) bleeding is a common disorder encountered in an emergency department or primary clinical setting. The therapeutic basis for GI bleeding is endoscopic hemostasis. To date, epinephrine injection, through-the-scope clips, monopolar or biopolar coagulation, and band ligation have been established for GI bleeding. Despite the advances in endoscopic techniques, we often experience re-bleeding associated with significant in-hospital mortality in GI bleeding. New devices that complement the disadvantages of these conventional endoscopic techniques have recently been introduced. For example, over-the-scope clip, which has wider and stronger pressure than conventional mechanical devices, can ligate a wide range of surrounding mucous membranes and has been reported to be effective in severe lesions of fibrosis. In addition, hemostatic powders achieved successful hemostasis as primary or rescue therapy in several cases of GI bleeding. Successful application of these new techniques requires appropriate patient selection and understanding of the device and further research is expected in the future.

Keywords: Bleeding; Clip; Hemostasis, endoscopic

Introduction

Gastrointestinal (GI) bleeding is a serious illness, with a high mortality rate observed in clinical practice. Endoscopy plays an important role in risk stratification and treatment of patients with GI bleeding. In cases of GI bleeding, endoscopic hemostasis is usually performed using injection therapy, mechanical therapy with clips, loops, or ligation, and thermal therapy with argon plasma coagulation (APC) and bipolar or monopolar probes. A recent meta-analysis published by Baracat et al[1] recommended the application of hemoclips or the combined use of injection therapy with thermal coagulation for the treatment of peptic ulcer bleeding.

Injecting epinephrine into a hemorrhagic site is a relatively easy procedure, and it is generally used because of its low cost. Injection therapy with epinephrine induces compression of lesion, vasoconstriction, and platelet activation, thus providing a hemostatic effect. Although a local injection of epinephrine diluent is reported to be more effective than a proton pump inhibitor alone, the hemostatic efficacy achieved is lower than that achieved with other endoscopic therapies, and about 20% of re-bleeding is reported when it is used alone. Therefore, a local injection of an epinephrine diluent is generally recommended for temporary endoscopic hemostasis or reduction of bleeding rate prior to other endoscopic hemostasis procedures.

Mechanical therapy using hemoclips is a well-established method of treating patients with GI bleeding. Several randomized studies have demonstrated the clinical efficacy of hemoclips in the treatment of bleeding peptic ulcers, Mallory-Weiss syndrome, and Dieulafoy's lesions.[2-4] However, the use of hemoclips in GI bleeding can be limited due to poor angulation and mobility of the endoscope. If the clip ligation is not performed accurately and delicately, the exposed blood vessels or the surrounding mucous membranes may be torn by the clip, which may thus further promote bleeding. In addition, clips that are ligated in the wrong position may be an obstacle to secondary treatment, if any.

Thermal coagulation is a method of causing hemostasis by applying direct or indirect heat to induce edema of tissue, coagulation of tissue protein, contraction of blood vessels, and the coagulation process. Contact coagulation induces thermal coagulation by direct contact (of hemostatic forceps, an electrocautery probe, or a heater probe) with a hemorrhagic lesion. Noncontact therapy is carried out without contact with tissues, using APC. Contact thermal therapy is effective for spurting bleeding, but achieving

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hemostasis can be difficult where direct contact is difficult. Non-contact methods, such as APC, can be used to obtain hemostasis, without limitation of location, and hemostasis can be achieved in a wide area. However, because deep penetration is limited, it is difficult to achieve hemostasis in deep vein.[5] In addition, rare complications, such as pneumoperitoneum, pneumomediastinum, and perforation may occur.

Although the various hemostatic methods described above are known to effectively induce early hemostasis, there is a risk of re-bleeding. Depending on the location, characteristics, and extent of hemorrhagic lesions, hemostasis in GI bleeding may not be satisfactory. Therefore, in this article, we will review the recently introduced modalities of endoscopic hemostasis and explore their clinical usefulness.

Clip Device for Mechanical Endoscopic Hemostasis

Hemoclips were among the first therapeutic devices for flexible GI endoscopy. The clip design and delivery systems for endoscopic hemostasis continue to evolve. Clip devices are classified into two types according to the delivery system: through-the-scope (TTS) clips, where the clips are pre-loaded with a transparent detachable cap at the distal end of the scope, and over-the-scope clips (OTSC).

TTS clip

The TTS clips are available from different manufacturers and may have different opening lengths. The EZ clip is a commonly used device in South Korea. The EZ clip (Olympus Medical, Tokyo, Japan) has a different size with a short clip (5 mm), a standard clip (7 mm), and a long clip (9 mm). There are two types of angles: 90° and 135°. The EZ clip has the advantage of allowing rotation of the arm of the clip according to the position of the lesion, thereby allowing precise positioning, but the disadvantage is that the clip cannot be reopened after the handle operation. Several clip devices have been introduced to overcome these drawbacks. The QuickClip2 (Olympus America, Center Valley, PA, USA) has an opening diameter of 11 mm, and was designed to improve the ease of rotation to orient the clip to a target lesion; it can be opened and closed. The Resolution Clip (Boston Scientific, Natick, MA, USA) can also be opened and closed, and it has an 11-mm opening diameter (Fig. 1).[6]

Over-the-scope clip

In clinical practice, achieving hemostasis by using a TTS clip is limited in the case of bleeding lesions with difficult-to-access locations, arterial spurting in large vessels (of 2–3 mm diameter), and rigid lesions with fibrosis. To overcome the limitation of TTS clips, the over-the-scope clip (OTSC; Ovesco Endoscopy, Tuebingen, Germany) was developed and introduced in 2007.[7] According to the U.S. Food and Drug Administration recommendations, the OTSC is approved for the following hemostatic indications: (1) bleeding ulcers, (2) arteries < 2 mm in diameter, (3) colon diverticula, (4) polyps < 1.5 cm in diameter, and (5) mucosal/submucosal defects < 3 cm.[8]

The OTSC system is mounted onto the distal tip of the endoscope, in a manner almost similar to how it is done with the band ligation device. Since the technique of this system is similar to that of the band ligation used earlier, it would be easy to use if endoscopists are familiar with variceal band ligation. The OTSC is made of nitinol (which has high elasticity) in the form of bear claws. Available clip sizes range from 11 to 14 mm. Three versions of OTSCs are available: a blunt atraumatic type, with pointed traumatic edges, and a clip for gastric wall closure with features of both the traumatic and atraumatic OTSC.[9] Two accompanying aids, the twin grasper and anchor, may be used to approximate the tissue margins of large or fibrotic gaping defects, and to pull these into the transparent cap before releasing the clip (Fig. 2).

In previous studies, the OTSC was mainly used for perforation or closure of fistula, but it can be used effectively for GI bleeding. It can be particularly used in GI bleeding that is recalcitrant to conventional attempts at achieving endoscopic hemostasis. A recent study demonstrated the efficacy and safety of the use of OTSC in GI bleeding, resulting in a salvage endoscopic treatment. Manta et al[10] reported that 30 patients who failed conventional endoscopic hemostasis underwent OTSC-based hemostasis. A total of 29 patients had primary hemostasis. Two patients experienced re-bleeding, requiring repeated endoscopic hemostasis. In one patient with a posterior wall duodenal ulcer, emergency radiological embolization was required to stop the bleeding after failure of the OTSC procedure. In another study, technical success rate was 100% for hemostasis with OTSC, and there were re-bleeding in two cases.[11] Therefore, the authors concluded that the OTSC should be considered in patients with refractory bleeding, after failure of conventional methods of endoscopic hemostasis.

The use of OTSC to achieve primary hemostasis in GI bleeding has been reported in a small case series. Primary hemostasis in

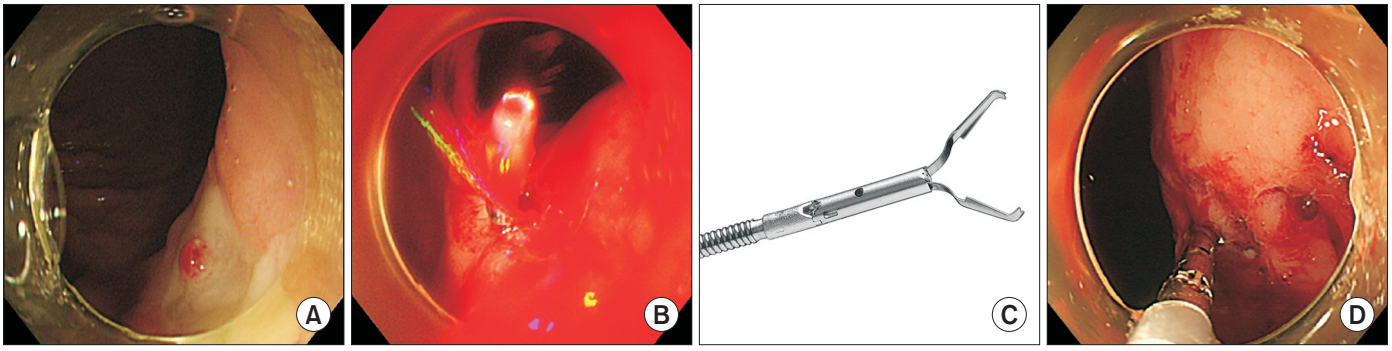

Fig. 1. Resolution Clip (Boston Scientific). (A) Forrest IIa ulcer in the body. (B) Hemostasis failed with conventional clip. (C) Resolution Clip. (D) Appearance following Resolution Clip.

GI bleeding was achieved in 85% to 100% cases.[10,12,13] In a recent study, Wedi et al[14] reported the usefulness of OTSC as a first-line treatment for GI bleeding. In this study, the authors compared the re-bleeding, mortality, and mortality after re-bleeding in the Rockall cohort showing current procedure with the cohort using OTSC as first-line treatment. Primary hemostasis, using OTSC, was successful in 92.4% cases, and the mortality rate after re-bleeding was significantly reduced from 27.9% to 10.9% in the high-risk group with a Rockall risk category of 8 or more. The authors also reported that primary hemostasis using OTSC significantly reduced re-bleeding in the group that had a Rockall risk category 4 and above. Therefore, the authors noted that OTSC could be used as an alternative to standard hemostasis care in high-risk patients. However, this study was not a randomized, controlled study. As a control group, the Rockall cohort had the limitation of past treatment outcome. Therefore, additional prospective, randomized controlled studies are needed.

Severe complications, such as complete lumen closure secondary to clip misplacement and mucosal injury caused by the pointed teeth of the OTSC have been rarely described in the literature.[15,16] Therefore, caution should be exercised when inserting the OTSC into a relatively narrow area, such as the cricopharynx or the pylorus. The main disadvantage of the OTSC is a need to withdraw the endoscope to mount the OTSC. Another disadvantage is that it is difficult to pass it through the upper esophageal sphincter or luminal stricture. Additional treatment is difficult if the OTSC is installed poorly. In addition, prices higher than that of normal clips limit OTSC accessibility. Prospective randomized studies and cost-effective analyses comparing OTSC with conventional clip devices are needed.

Topical Agent

Endoscopic hemostasis using a mechanical device is an effective method, but it has limited efficacy in diffuse bleeding lesions. Therefore, the need for other methods to achieve hemostasis has been suggested. Topical agents for endoscopic hemostasis have been introduced in a relatively simple, safe, and effective way. In recent literature, hemostatic powders that have been introduced for endoscopic hemostasis include Hemospray (Cook Medical, Winston-Salem, NC, USA), EndoClot (EPI, Santa Clara, CA, USA), and Ankaferd Blood Stopper (ABS) (Ankaferd Health Products, Istanbul, Turkey) (Table 1).[8]

Hemospray

Hemospray (also named TC-325) is an inorganic powder that was developed by the armed forces for control of bleeding in military personnel during operations. This mineral powder is highly adhesive, absorbs liquid from the blood, and forms a sticky film when adsorbed on hemorrhagic lesions. The adsorbed powder increases the concentration of coagulation factors, activates platelets, and ultimately forms a plug in the wounded blood vessels.[17] This powder does not contain human or animal proteins or plant substances, and does not have known allergens. Hemospray powder is delivered via a carbon dioxide-powered delivery system through a 7-Fr or 10-Fr catheter, and inserted through the working channel of an endoscope, which provides access to the site of the bleeding.[18]

Sung et al[19] reported a human study in which Hemospray was used in 20 patients with peptic ulcer bleeding. Acute hemostasis was achieved in 95% of the patients (19/20), and bleeding recurred in 2 patients within 72 hours. No mortality, major adverse events, or treatment- or procedure-related serious events were reported during the 30-day follow-up. The clinical outcome of the use of Hemospray in upper GI bleeding, collected in 10 European centers using the multicenter survey in 2013, has been published.[20] A total of 63 patients were included in the study, of

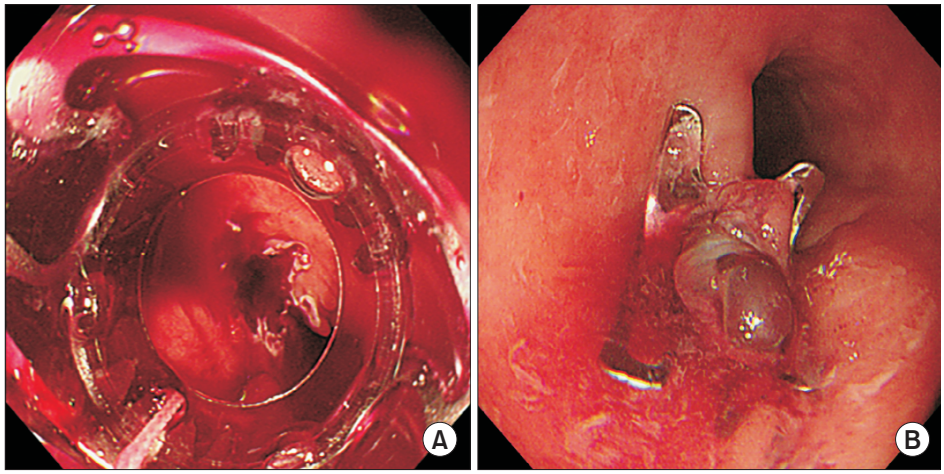

Fig. 2. Over-the-scope clips (OTSC; Ovesco Endoscopy). (A) Tracheoesophageal fistula with active bleeding. (B) Appearance following OTSC placement.

Table 1 Overview on the Commercially Available Substance for Topical Application[17]

	Contains	Mechanism of action	Approved human application	Formulation
Ankaferd blood stopper	Herbal mixture	Protein networks, clotting cascade	Dental procedure	Tampons, sprays, ampoules
Hemospray	Mineral powder	Absorbs H_2O, mechanical tamponade, clotting cascade	Nonvariceal gastrointestinal bleeding	CO_2 pressurized handheld canister
EndoClot	Absorbable polymere	Absorbs H_2O, concentrate cells, clotting cascade	Adjuvant hemostatic therapy	Pressurized air compressor

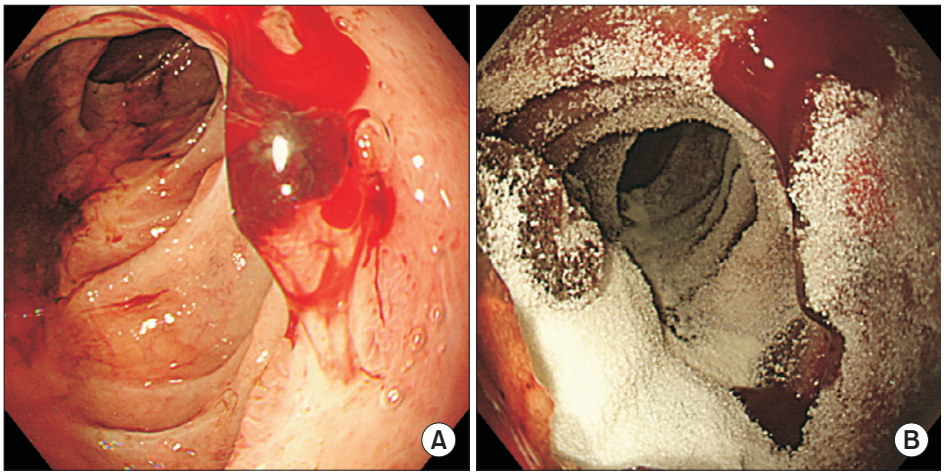

Fig. 3. Endoscopic application of EndoClot (EPI). (A) Duodenal ulcer with active bleeding. (B) Endocopic appearance of EndoClot when applied to a bleeding lesion.

which 30 patients had peptic ulcer bleeding. In upper GI bleeding, use of Hemospray resulted in a primary hemostasis rate of 85% when used as a monotherapy, and re-bleeding rate at 7 days was 15%. Eight patients, who failed conventional endoscopic hemostasis, underwent rescue therapy with Hemospray. The primary hemostasis rate was 100% and the re-bleeding rate at 7 days was 25%.

Hemospray is reported to be effective in diffuse bleeding lesions. Smith et al[21] reported endoscopic hemostasis using Hemospray in four patients with non-variceal diffuse portal hypertensive bleeding. Chen et al[22] describes the first 5 cases of malignant diffuse GI bleeding managed with Hemospray. Initial hemostasis was achieved in all patients, with only one case of re-bleeding. Other bleeding sources treated by Hemospray in upper GI bleeding include varices, post-procedure bleeding (sphincterotomy, endoscopic submucosal dissection).[23–26]

No procedure-related complications were associated with the use of Hemospray. Theoretically possible side effects of Hemospray include embolization, intestinal obstruction, and allergic reaction to the powder. Because of the low pressure of carbon dioxide used for spraying the Hemospray powder, the actual risk for embolism is very low.[27] GI obstruction is another possible risk as it is sloughed off from the GI wall and passes into the small intestine. If hemostasis fails, there is the disadvantage that the powder attached to the mucous membrane may limit the use of other hemostatic modalities, and Hemospray works only on active bleeding.[18]

Ankaferd Blood Stopper (ABS)

ABS is a plant-derived hemostatic agent used in Turkey as a topical treatment for dental and postsurgical external bleeding. ABS consists of a mixture of five herbs and can be dispensed in the form of ampoules, pads, and sprays. A preparation of 100 mL of ABS is composed of a standardized mixture of plants, including 5 mg *Thymus vulgaris* (dried grass extract), 9 mg *Glycyrrhiza glabra* (dried leaf extract), 8 mg *Vitis vinifera* (dried leaf extract), 7 mg *Alpinia officinarum* (dried leaf extract), and 6 mg *Urtica dioica* (dried root extract).[28] Although the exact hemostatic mechanism of action of ABS is unknown, it is understood that erythrocyte aggregation and the formation of an encapsulated protein scaffold network have a hemostatic effect.[29,30]

The endoscopic hemostasis effect produced by ABS was reported in case reports and series for treatment of post-polypectomy bleeding, Mallory-Weiss syndrome, Dieulafoy lesions, radiation colitis, and bleeding from tumors.[31] The hemostatic efficacy of ABS in published case reports is promising. However, additional prospective randomized controlled studies are needed.

EndoClot

The EndoClot polysaccharide hemostatic system is a non-contact endoscopic device that has recently been developed and sprays hemostatic powder. Its exact component is not known but consists of absorbable modified polysaccharides derived from plant starches that do not contain animal or human components. The EndoClot is observed as a white powder, and when this powder is sprayed on a bleeding lesion, it rapidly absorbs water from the blood. This dehydration process increases the concentration of platelets, red blood cells, and coagulation proteins (thrombin, fibrinogen, etc.) and forms a gelled, adhesive matrix that acts as a mechanical barrier to prevent bleeding.[32]

EndoClot has a powder in the chamber that works through a 2,300-mm delivery catheter through the working channel of the endoscope. The external air compressor produces sustained pressure that forces the powder in the chamber through the catheter to reach the bleeding lesion. Generally, particles of EndoClot are widely sprayed, so they can be easily used even in a difficult position to access the endoscope. In addition, there is no need to contact the catheter directly with the bleeding lesion during powder distribution, so it does not promote additional mucosal injury or bleeding (Fig. 3).

Huang et al[33] first applied EndoClot for controlling and preventing bleeding related to endoscopic mucosal resection in 181 lesions in 81 patients. Delayed bleeding was observed in 3 patients that did not have immediate post-procedural bleeding. No major adverse events of the EndoClot therapy during a 30-day follow-up reported. In an observational study, endoscopic hemostasis using EndoClot was performed in 21 patients and immediate hemostasis was achieved in all patients. The 30-day re-bleeding rate in these patients was 4.8%.[34] Recent studies have compared EndoClot and conventional hemostatic therapies using propensity score matching in non-variceal upper GI bleeding. In this study, 40 patients who received EndoClot therapy and 303 patients who received conventional therapy were compared. The rate of immediate hemostasis and re-bleeding of 7-day and 30-day did not differ between the two groups. Complications associated with EndoClot were not reported in this study.[35]

Conclusions

Recently, mechanical devices such as OTSC and various hemostatic powders have been introduced as a new method for endoscopic hemostasis in GI bleeding. These techniques and devices have been reported to be useful as primary therapy as well as rescue therapy in cases of failure of conventional hemostasis. Successful application of this technique depends on the appropriate indication and the endoscopist's experience in using this device. Therefore, additional experience and comparative studies of the new techniques are warranted.

Conflicts of Interest

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

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