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Evolving techniques for gastrointestinal endoscopic hemostasis treatment

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Abstract

With mortality due to gastrointestinal (GI) bleeding remaining stable, the focus on endoscopic hemostasis has been on improving other outcomes such as rebleeding rate, need for transfusions, and need for angiographic embolization or surgery. Over the past few years, a number of devices have emerged to help endoscopically assess and treat bleeding GI lesions. These include the Doppler endoscopic probe, hemostatic powder, and over-the-scope clip. Also, new applications have been described for radiofrequency ablation. In this article, we will discuss these evolving tools and techniques that have been developed, including an analysis of their efficacy and limitations.

Keywords

GI bleed; hemostasis; Hemospray; Doppler endoscopic probe; radiofrequency ablation; OTSC

Introduction

In the past decade, there has been a slight decrease in the hospitalization rate for gastrointestinal (GI) bleeding, while the mortality rate has remained stable at <5%.[1] It has been difficult for studies evaluating medical and endoscopic therapies for GI bleeding to demonstrate a reduction in mortality relative to the standard of care. Therefore, other clinical outcomes—primary hemostasis rate, rebleed rate, length of hospital stay, need for transfusion of red blood cells (RBC), and need for angiographic embolization or surgery—have been used to assess the effect of a particular intervention.

In the past several years, a number of new techniques and devices have become available for endoscopists to use in the risk assessment and treatment of GI bleeding. Collectively, these tools are aimed at improving risk stratification by detection of a vessel underlying the bleeding lesion and guiding improvements of both initial and definitive hemostasis. After providing a background on the standard management of GI bleeding, this review will discuss

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these evolving applications, including their potential role in improving risk stratification and endoscopic hemostasis as well their limitations.

Standard endoscopic considerations

Preparation and evaluation

Patients with active hemorrhage (i.e., a high-volume bloody gastric lavage or ongoing hematemesis, melena, or hematochezia) should undergo emergency endoscopy soon after medical resuscitation, usually in the intensive care unit (ICU). Hemodynamically stable patients can undergo endoscopy, often in the GI endoscopy unit rather than the ICU. For upper GI (UGI) bleeding, therapeutic single- or double-channel endoscopes with large-diameter suction channels should be used to allow quick removal of fresh blood and clots from the GI tract during endoscopy. Additionally, a water pump can be used to target irrigate lesions through the accessory channel and dilute blood for suctioning.

In patients with severe hematochezia and suspected active colonic bleeding, urgent colonoscopy can be undertaken after a rapid purge.[2] Patients should receive 6–8 l of a polyethylene glycol solution either orally or via a nasogastric tube over 4–6 h until the rectal effluent is clear of stool, blood, and clots. Additional polyethylene glycol may be required in some patients, particularly those with active bleeding, constipation, or upon the onset of hematochezia in the hospital. Metoclopramide, 5–10 mg, may be given intravenously before the purge and repeated every 4–6h to facilitate gastric emptying and reduce nausea.

Hemostasis

Thermal contact probes have been the mainstay of endoscopic hemostasis since the 1970s. Contact probes effect hemostasis through two mechanisms: (1) tamponade of a blood vessel to stop bleeding and interrupt underlying blood flow, and (2) application of thermal energy to seal the underlying vessel (coaptive coagulation). They can be used for a variety of bleeding lesions, including peptic ulcers, diverticula, vascular ectasias, and Dieulafoy lesions. The energy level for treating these lesions ranges between 10 and 15 W, and the duration of energy application and amount of pressure applied depends on the depth and size of the vessel being treated.[3,4] The main risk of using a thermal probe is perforation with excessive application of coagulation or pressure, especially in acute or non-fibrotic lesions. Thermal probes can also cause a coagulation injury that can make lesions larger and deeper and may increase the risk of delayed bleeding, particularly in patients with a coagulopathy.[5]

Injection therapy is performed with a sclerotherapy needle to inject epinephrine, diluted to a concentration of 1:10,000 or 1:20,000, submucosally into or around the bleeding site or stigma of hemorrhage. Advantages of this technique are that it is widely available, relatively inexpensive, and safe for use in patients with a coagulopathy. Additionally, it is associated with a lower risk of perforation than thermal techniques. One disadvantage is that it is not as effective for definitive hemostasis as thermal coagulation or endoscopic clips, and typically it is combined with one of these other two modalities.[6,7] Injection therapy can also be

performed with a sclerosant, such as ethanolamine or alcohol, but these agents are associated with increased tissue damage and other risks.

Endoscopic clips (also known as hemoclips) apply mechanical pressure to a bleeding site, as is done with surgical clips or sutures. Hemoclips offer comparable efficacy to thermal probes in achieving definitive hemostasis.[8] By not causing thermal damage, they are especially useful in patients with malnutrition or coagulopathy.[9] Nevertheless, hemoclips can also be difficult to deploy depending on the bleeding location, the degree of fibrosis of the underlying lesion, and limitations to endoscopic access.

Argon plasma coagulation (APC) uses ionized argon gas to transfer energy to target tissue. It uses a mono-polar current, so a grounding pad is required. It has been used not only to ablate tissue (such as the edges of a post-polypectomy site), but also to treat superficial bleeding or sites for potential bleeding, such as isolated vascular ectasias, gastric antral vascular ectasia (GAVE, watermelon stomach), and radiation proctitis (RP).[10] With superficial coagulation (≤1 mm) and no tamponade capability, there is less efficacy for hemostasis of ulcers with major stigmata of hemorrhage (SRH) and larger or deeper underlying arteries.

With rubber band ligation, mucosal (with or without submucosal) tissue is suctioned into a cap placed on the end of the endoscope, and a rubber band is rolled off the cap and over the lesion to compress its base. This technique is widely used for the treatment of esophageal varices and can be used for other bleeding lesions. Band ligation's main advantage is that it is relatively easy to perform, and it is associated with fewer adverse effects compared to sclerotherapy.[11] Sufficient mucosa must be suctioned into the cap for successful ligation, so lesions involving or surrounded by fibrosis may be difficult to treat with this technique. Some band ligation devices can only fit on diagnostic endoscopes, so the endoscopist may need to switch from the therapeutic to the diagnostic endoscope after the bleeding lesion has been identified.

Evolving techniques in endoscopic hemostasis

Doppler endoscopic probe

The concept of a Doppler ultrasound probe for detecting arterial blood flow during GI endoscopy was first described in 1982.[12] The Doppler endoscopic probe (DEP) can be passed through the working channel of any diagnostic or therapeutic endoscope or colonoscope. The technique has been most commonly described in the evaluation of bleeding ulcers, but any lesion can be interrogated. The base of the ulcer should first be flushed with water to remove any fibrinopurulent exudate. The DEP tip is applied to the ulcer base with light to moderate pressure and at multiple points, including those immediately adjacent to any endoscopic SRH. The Doppler signal moves away from the visual SRH in a straight line. For non-variceal lesions (such as ulcers, Dieulafoy lesions, or Mallory–Weiss tears), the blood flow detected is arterial and not venous. In some cases, the subsurface course of the blood vessel can be traced by following the Doppler signal. A positive DEP signal is defined as a repetitive and similar visual spiking waveform (or audible 'swish-swish' sound) of at least three consecutive cycle durations, indicating pulsatile blood.[13]

Although the DEP does not directly provide hemostasis, its value comes from its ability to help predict both the risk of rebleeding and success/failure of endoscopic therapy. This has been illustrated in several prospective studies of patients with peptic ulcer bleeding, two of which we will describe here in detail. In the first study from 2000, of 52 patients undergoing DEP, endoscopic therapy was performed in 23. Twelve patients had a positive DEP signal prior to endoscopic therapy. Of these patients, nine (75%) were converted to a negative DEP signal after therapy. All three patients with a persistent DEP-positive signal rebled within 30 days compared to only one patient (11%) whose ulcer had been converted to a DEP-negative signal.[14] In the second study from 2015, 163 patients with severe peptic ulcer bleeding underwent DEP evaluation using single-use probes during urgent endoscopy (Figure 1). Patients with major SRH (active arterial bleeding, non-bleeding visible vessel, adherent clot) had a significantly higher DEP-positive rate than those with intermediate SRH (oozing alone or flat spot alone): 87% vs. 42%. After standard, visually guided endoscopic hemostasis with either monopolar electrocoagulation (MPEC) probe or hemoclips (with or without epinephrine pre-injection), there was a significantly higher DEP-positive signal in patients with major SRH vs. intermediate SRH (27% vs. 14%). None of the patients with oozing alone had a positive DEP signal after standard endoscopic hemostasis. The 30-day rebleed rate was 29% in patients with pulsatile or spurting bleeding (Forrest Ia) ulcers and 0% in the oozing (Forrest Ib) ulcer group.[15] Results of a recent randomized controlled trial (RCT) evaluating the use of DEP in non-variceal UGI hemorrhage—including peptic ulcers, Dieulafoy lesions, and Mallory–Weiss tears—reported significantly higher 30-day rates of rebleeding, surgery, and red cell transfusions in the standard therapy group compared with the DEP-assisted treatment group.[16]

The DEP can be used to guide treatment of colonic bleeding such as diverticular hemorrhage. In a prospective cohort of 46 patients with severe hematochezia, the DEP was used in patients with a colonoscopic diagnosis of either definitive or presumptive diverticular hemorrhage. There were 24 patients with definitive diverticular hemorrhage (SRH was identified in a diverticulum during urgent colonoscopy), and 92% had superficial (<4 mm deep) arterial flow detected by DEP underneath the SRH and for 2–4 mm on either side of the SRH along the artery in the diverticulum. No diverticulum had venous blood flow detected with the DEP. The locations of the artery and SRH were used as guides for definitive hemostasis, and no patient in this cohort had recurrent diverticular hemorrhage.[17] This explains why when treatment has been applied away from the SRH in prior studies (such as at the neck of the diverticulum when the SRH is in the base), rebleeding rates are high because the artery underneath the SRH is still patent, leading to persistent blood flow.[18]

Hemostatic powder

The hemostatic powder TC-325, more commonly known as Hemospray (Cook Medical, Winston-Salem, NC), is a granular, mineral, nonabsorbable powder used for management of wounds with bleeding arteries.[19] When it comes into contact with moisture in the GI tract, it becomes cohesive and adhesive, forming a mechanical barrier that adheres to and covers the bleeding site to achieve hemostasis. It is not absorbed or metabolized by mucosal tissue,

so there is no risk of systemic toxicity. In the GI tract, with motility and food, there is eventual separation from the mucosa and passage of the powder from the gut.[20]

The delivery device consists of a syringe containing the powder (21 g per syringe), a delivery catheter that is inserted into the working channel of the endoscope, and an introducer handle with a built-in carbon dioxide canister to propel the powder out of the catheter (Figure 2). The endoscope is positioned near the bleeding lesion, leaving a gap of 1–2 cm between the bleeding site and the catheter tip. The powder is then delivered in short spray bursts (for 1–2 s) until hemostasis is confirmed. Once bleeding is controlled (first application), the bleeding site is observed for 5 min, and if bleeding recurs during this period, the powder is reapplied until hemostasis is achieved again.[21]

Hemostatic powder was first studied in humans in a 2011 prospective pilot study of acute peptic ulcer bleeding. Twenty patients with active ulcer bleeding—one with pulsatile bleeding (Forrest Ia) and 19 with oozing hemorrhage (Forrest Ib) were treated. Overall, acute hemostasis was achieved in 19 patients (95%), all with Forrest Ib lesions, and of these 19 patients hemostasis was maintained in 90% at 72 h. The one patient who did not achieve acute hemostasis had a Forrest Ia ulcer that required angiographic embolization of what turned out to be an underlying pseudoaneurysm.[21]

Other studies have supported the use of hemostatic powder in a variety of GI bleeding settings. A registry of 63 patients with non-variceal UGI bleeding, about 50% having peptic ulcer bleeding, were treated with TC-325. Of these 63 patients, 55 were treated with TC-325 monotherapy and eight were treated with TC-325 as second-line therapy after failure of standard endoscopic therapy to achieve hemostasis. In the monotherapy group, 85% achieved primary hemostasis with a 15% rebleed rate by 7 days, and in the second-line therapy group there was 100% primary hemostasis with a 25% rebleed rate by 7 days. Among the patients with peptic ulcers, there was still a majority of Forrest Ib lesions, but 37% of the ulcers were Forrest Ia.[22] A pilot study of nine patients evaluated the use of hemostatic powder in active variceal bleeding (esophagus or esophagogastric junction). All patients achieved hemostasis after application of the powder, and no patient had rebleeding within 24 h after which a planned second endoscopy at which time all patients underwent elective band ligation without any interference from the initial treatment.[20] A number of case reports and series have suggested that the hemostatic powder might have potential for treating other GI bleeding lesions, including actively bleeding post-variceal banding esophageal ulcers [23], gastroenteric anastomotic ulcers [24], refractory duodenal diverticular bleeding [25], and refractory bleeding from ischemic colitis.[26]

Over-the-scope clip (OTSC)

The over-the-scope clip (OTSC) (Ovesco Endoscopy GmbH, Tübingen, Germany) was introduced in 2007 and has been used for treatment of bleeding GI lesions and closure of GI perforations. It has the ability to grasp the full thickness of the GI tract wall. The clip consists of a nitinol alloy, which allows for significant elasticity. It fits onto a cylindrical cap in the open state, and the cap is mounted onto the tip of the endoscope. The clips are available in a variety of sizes to fit endoscopes with diameters ranging between 8 and 11.5 mm (cap sizes 11–14 mm). There are different teeth types, and the ‘atraumatic’ type with its

blunt teeth is used for cases of GI bleeding. The clip is applied by stretching a wire with a hand wheel, installed on the entrance of the working channel, similar to rubber band applicators. The tip of the endoscope approaches the lesion, which is then suctioned, into the applicator cap (Figure 3). Additional devices, such as an anchor that is made by same company, can be used to facilitate better tissue accumulation in the cap. Stretching the wire with the hand wheel then fires the clip.[27]

Since its introduction, there have been a few case series evaluating the use of the OTSC in GI bleeding. A retrospective study assessed its effect after failure of conventional techniques (injection of saline/epinephrine along with through-the-scope hemoclips). Out of 30 patients (23 with UGI bleeding and seven with lower GI (LGI) bleeding), primary hemostasis was achieved with the OTSC in 29 (97%). One patient with a duodenal bulb ulcer required angiographic embolization to achieve hemostasis. Two patients had recurrent bleeding within 24 h, which was treated with endoscopic injection therapy.[28] A smaller retrospective study of 12 patients with UGI bleeding, undergoing OTSC treatment after two failed attempts at conventional endoscopic therapy, showed similar results. Hemostasis was achieved in all patients, and two patients demonstrated rebleeding within 7 days, requiring either further conventional endoscopic therapy or surgery.[29] A prospective study evaluated OTSC as first-line therapy for UGI bleeding in 40 patients. Hemostasis was achieved in all patients, and there were no rebleeding events or complications at 30 days of follow-up.[30] In all of these studies, the majority of patients had peptic ulcer bleeding, while Dieulafoy lesions were encountered in 6–17% of patients.

The OTSC appears to be a very promising tool in GI endoscopic hemostasis. An RCT is needed to better assess its effectiveness in severe, refractory, and/or recurrent UGI bleeding compared to conventional endoscopic therapy, as well as to better assess its effectiveness in LGI bleeding. The clip's main limitation is in accessing lesions that are not en-face, such as in the duodenum, or are very firm and cannot be suctioned or pulled into the cap prior to OTSC deployment. It is possible that the clip cannot be used in patients with cricopharyngeal or esophageal stenosis, which would prohibit passage of the endoscope having a larger diameter after the clip and cap have been placed on it. Use of the augmenting devices, such as the anchor, can exacerbate the bleeding from these lesions during clip placement, so caution should be taken if they are employed to assist with achieving hemostasis. Also, it is contraindicated in the treatment of esophageal and gastric varices. Rarely, the OTSC might need to be removed due to clip migration or misplacement. There has yet not been described a standard method for OTSC removal. Several techniques have been described, including an Nd:YAG laser [31], threading a hydrophilic tip guidewire around the clip and then pulling it out [32], and clip fragmentation using DC current pulses. [33]

New uses for radiofrequency ablation

Radiofrequency ablation (RFA) is an endoscopic technique that has been used primarily in the treatment of Barrett's esophagus. The HALO ablation system (Covidien, GI Solutions, Sunnyvale, CA) delivers a consistent amount of energy to the surface using well-defined and reproducible increments of energy (Figure 4). This limits the energy penetration to the

superficial mucosa and reduces the possibility of operator dependence and overtreatment, which could cause perforations.

RFA has an emerging role in the treatment of GAVE (watermelon stomach). The conventional endoscopic therapies for this condition have been thermal contact probe and APC. These techniques can be effective but are operator-dependent and bleeding recurrence is common. RFA for this indication was first described in a pilot study of six patients with GAVE who had bleeding and transfusion dependence. After RFA treatment, five patients (87%) no longer required transfusion, although the follow-up period was only 2 months.[34] In a larger, retrospective study of 24 patients, RFA treatment of GAVE led to a significant reduction in the number of units transfused, and 65% of patients were no longer transfusion-dependent at 6 months of follow-up. There were no complications observed.[35] The most compelling study to support the use of RFA in GAVE has come from a prospective study of 21 patients with GAVE that was refractory to treatment with APC. This was defined as recurrent GI bleeding and/or persistent iron deficiency anemia despite having at least two previous APC treatments. In this study, after a median of two RFA sessions, 86% of patients no longer required transfusions and had no evidence of GAVE on follow-up 6 months after completing RFA treatment. One patient had minor acute bleeding and superficial ulcerations found incidentally at follow-up endoscopy and did not require any intervention.[36]

RP is another chronic cause of GI bleeding that might be managed with RFA. Initial observations of its success in RP came from case reports and small series. [37,38] More recently, a retrospective study looked at 17 patients with chronic RP (heavy bleeding with clots or bleeding requiring transfusion) who underwent RFA treatment. After a median of two RFA sessions and at 6 months of follow-up, significant improvement was seen in symptoms (bleeding and tenesmus) and mean hemoglobin concentration, and 69% of patients who previously required transfusions no longer needed them.[39]

RFA has potential advantages over APC, in that it does not involve high-volume gas insufflation (reduced risk of bowel overdistension), and, with its direct contact against the mucosa, it can treat systematically a wide area with less risk of overtreatment or missing areas that need to be treated. Risks of RFA for treatment of GAVE or RP have been reported, including bleeding as well as mucosal and submucosal tears.[36,40]

Conclusion

In recent years, new tools have emerged for endoscopists to use in the assessment and treatment of bleeding GI lesions. The DEP has demonstrated its utility in better predicting the risk of rebleeding and success of therapy, and also can allow for ‘mapping’ of the underlying artery to provide targeted and definitive hemostasis. The emerging therapeutic tools (Hemospray and OTSC) have shown promise for treating a variety of bleeding causes, and new indications are being identified for endoscopic RFA. It remains to be seen whether these devices will have more of a complementary or rescue role, or if they can be considered as first-line therapies.

Expert commentary

Endoscopic therapies remain the mainstay for GI bleeding. It has been difficult to demonstrate a significant reduction in GI bleeding-associated mortality for two likely reasons: (1) the mortality rate is already relatively low, and (2) as the general population gets older, develops more health conditions, and takes more medications that increase the bleeding risk, the increased risk of death will offset any impact that improved endoscopic therapies can provide. With that said, the focus of GI endoscopic hemostasis is on non-mortality outcomes such as primary hemostasis rate, rebleeding rate, need for transfusions, need for angiographic embolization surgery, and length of hospitalization.

The current methods of GI endoscopic hemostasis have been very effective, but there is always room for improvement. Better understanding factors that lead to failure of endoscopic treatments to achieve definitive hemostasis are crucial to improving outcomes. The DEP focuses on identifying an underlying artery and can potentially track the path of the vessel such that more targeted therapy can be performed. It is simple to use, does not significantly prolong procedure time, and, based on the studies discussed, can identify which lesions are more likely to rebleed and serve as a predictor of and guide to definite hemostasis. One limitation, however, is that because epinephrine injection may only transiently reduce arterial blood flow by vaso-constriction and not obliterate it, Doppler interrogation immediately after this treatment is not reliable for predicting reduction in rebleeding risk of non-variceal GI lesions with major SRH.

Hemostatic powder is a very appealing option for GI endoscopic hemostasis, in that it is quick and appears to be quite effective. However, it has its limitations. It is a temporizing measure and does not treat the underlying vessel, which is likely why monotherapy with it seems to be associated with a relatively low rate of primary hemostasis and high rate of rebleeding.[22] Definitive therapy of both variceal and non-variceal UGI bleeding needs to be performed within 1–2 days of initial endoscopy, so it becomes time-consuming and more costly to routinely perform two endoscopic procedures when definitive hemostasis could be achieved during the first endoscopy. Studies have mainly included oozing lesions that have a lower risk of rebleeding after standard endoscopic therapies. It might be promising for tumor-related bleeding or diffuse bleeding, in which other focal hemostasis techniques are not effective, such as in diffuse portal hypertensive gastropathy, ischemia, and inflammatory bowel disease (IBD). Currently, it is not available in the United States.

The OTSC has been shown to be a very powerful option for treatment of various bleeding GI lesions. The question that arises is: when should it be used? This question has yet to be answered, but RCTs comparing its use with standard therapies will help. We believe that it will have a role as first-line treatment for Dieulafoy lesions—in which the submucosal location of the artery requires greater depth of treatment than what conventional treatments can reliably achieve—as well as rescue therapy for refractory ulcers. It might also be an option for treatment of diverticular hemorrhage, although this will require inversion of the diverticulum in order to achieve hemostasis, particularly if the SRH is located in the base.

RFA appears to be a feasible option for both GAVE and RP, particularly for cases in which standard therapies have been unsuccessful. It remains to be seen whether RFA should be considered as first-line therapy for these conditions. RCTs comparing RFA with APC would help determine this.

Five-year view

In the era of improving health-care quality, the GI endoscopic hemostasis research will focus even more on improving outcomes demonstrating reduced morbidity and cost (length of hospitalization, transfusion requirements, need for surgery, etc.). With newer technologies emerging, it will need to be determined whether they can either replace or complement the conventional therapies for treating GI bleeding that are more cost-effective than the current standards. RCTs comparing these technologies will be crucial in determining this.

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Key issues

- While mortality associated with GI bleeding has remained stable, the focus on endoscopic hemostasis is on other outcomes, including primary hemostasis, rebleeding rate, and need for other interventions.
- Conventional therapy for most types of non-variceal GI bleeding—epinephrine injection in combination with thermal probe or hemoclips—is the standard by which new techniques for GI endoscopic hemostasis will be compared.
- The DEP can help predict both the rebleeding risk and success/failure of endoscopic treatment.
- Hemostatic powder might be useful in cases of GI bleeding that are refractory to other endoscopic therapies, but this modality does not treat the underlying lesion.
- Hemostatic powder also might be appropriate for treatment of diffuse bleeding lesions, such as those related to portal hypertensive gastropathy or ischemic colitis.
- The OTSC can be used for a variety of bleeding GI lesions, either as a primary treatment option or in cases of refractory bleeding.
- RFA appears to be a promising technique for treatment of superficial GI bleeding lesions, including GAVE and RP.
- RCTs are needed to compare these new treatment modalities with conventional treatment to better their roles in GI endoscopic hemostasis.

Figure 1.
Doppler endoscopic probe (DEP).

Figure 2.
Hemostatic powder delivery device.

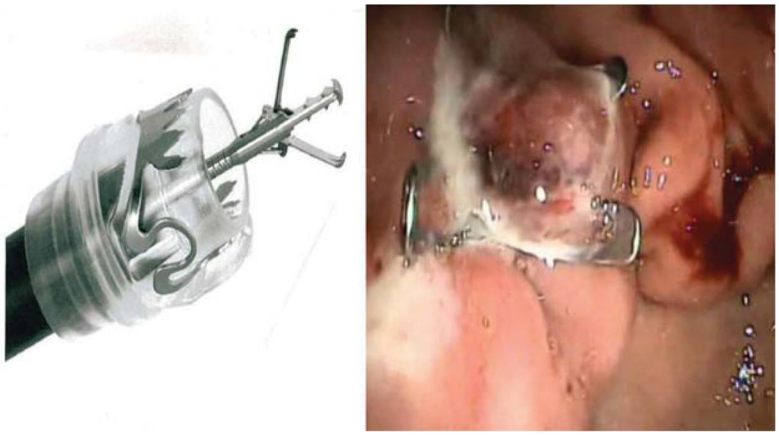

Figure 3.

Over-the-scope clip. Left panel: the clip, in the open position, on the loading cap. A grasping device is seen protruding through the cap. Right panel: the clip is in the closed position over an ulcer.

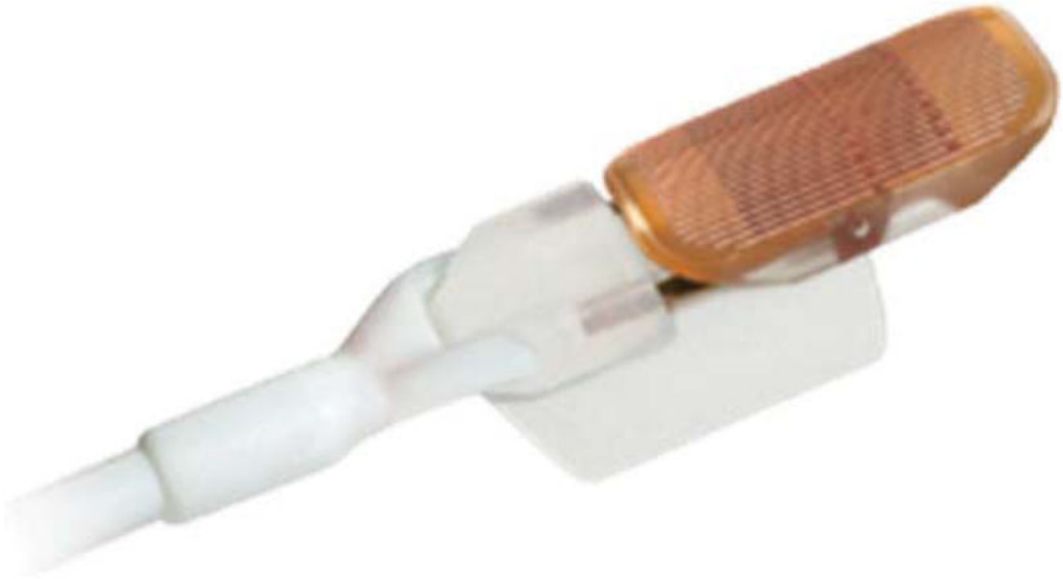

Figure 4.
Radiofrequency ablation (HALO-90) catheter.