Communication from the ASGE Technology Committee

TECHNOLOGY ASSESSMENT

ASGE American Society for Gastrointestinal Endoscopy

Devices for endoscopic hemostasis of nonvariceal GI bleeding (with videos)

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This document was reviewed and approved by the Governing Board of the American Society for Gastrointestinal Endoscopy (ASGE).

Background: Endoscopic intervention is often the first line of therapy for GI nonvariceal bleeding. Although some of the devices and techniques used for this purpose have been well studied, others are relatively new, with few available outcomes data.

Methods: In this document, we review devices and techniques for endoscopic treatment of nonvariceal GI bleeding, the evidence regarding their efficacy and safety, and financial considerations for their use.

Results: Devices used for endoscopic hemostasis in the GI tract can be classified into injection devices (needles), thermal devices (multipolar/bipolar probes, hemostatic forceps, heater probe, argon plasma coagulation, radiofrequency ablation, and cryotherapy), mechanical devices (clips, suturing devices, banding devices, stents), and topical devices (hemostatic sprays).

Conclusions: Endoscopic evaluation and treatment remains a cornerstone in the management of nonvariceal upper- and lower-GI bleeding. A variety of devices is available for hemostasis of bleeding lesions in the GI tract. Other than injection therapy, which should not be used as monotherapy, there are few compelling data that strongly favor any one device over another. For endoscopists, the choice of a hemostatic device should depend on the type and location of the bleeding lesion, the availability of equipment and expertise, and the cost of the device. (VideoGIE 2019;4:285-99.)

INTRODUCTION

The American Society for Gastrointestinal Endoscopy (ASGE) Technology Committee provides reviews of existing, new, or emerging endoscopic technologies that have an impact on the practice of GI endoscopy. Evidence-based methodology is used, with a MEDLINE literature search to identify pertinent clinical studies on the topic and a MAUDE (U.S. Food and Drug Administration Center for Devices and Radiological Health) database search to identify the reported adverse events of a given technology. Both are supplemented by accessing the "related articles" feature of PubMed and by scrutinizing pertinent references cited by the identified studies. Controlled clinical trials are emphasized, but in many cases, data from randomized controlled trials (RCTs) are lacking. In such cases, large case series, preliminary clinical studies, and expert opinions are used. Technical data are gathered from traditional and Web-based publications, proprietary publications, and informal communications with pertinent vendors. Technology Status Evaluation Reports are drafted by 1 or 2 members of the ASGE Technology Committee, reviewed and edited by the committee as a whole, and approved by the Governing Board of the ASGE. When financial

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guidance is indicated, the most recent coding data and list prices at the time of publication are provided. For this review, the MEDLINE database was searched through September 2017 for articles related to endoscopic hemostasis devices by using relevant keywords such as "gastrointestinal bleeding," "GI bleeding," "nonvariceal bleeding," "endoscopic hemostasis," and "endoscopic treatment," among others. Technology Status Evaluation Reports are scientific reviews provided solely for educational and informational purposes. Technology Status Evaluation Reports are not rules and should not be construed as establishing a legal standard of care or as encouraging, advocating, requiring, or discouraging any particular treatment or payment for such treatment.

BACKGROUND

Endoscopic intervention is often the first line of therapy for upper- and lower-GI nonvariceal bleeding. Devices used for endoscopic hemostasis in the GI tract can be classified into injection devices (needles), thermal devices (multipolar/bipolar probes, hemostatic forceps, heater probe, argon plasma coagulation, radiofrequency ablation and cryotherapy), mechanical devices (clips, suturing devices, banding devices, stents), and topical devices (hemostatic sprays). This document describes technologies used for endoscopic hemostasis. Cryotherapy and radiofrequency ablation were described in detail in separate recent ASGE Technology assessments and are not reviewed in this document.[1,2]

TECHNOLOGY UNDER REVIEW

Injection needles

Injection needles consist of an outer sheath made of plastic, polytetrafluoroethylene (PTFE, Teflon), or stainless steel, an inner hollow-core needle (19-25 gauge), and a handle. The handle is used to manipulate the needle in or out of the outer sheath. The handle includes a Luer lock connector for a syringe attachment. The needle is kept within the sheath for safe advancement through the working channel of the endoscope. When the target is reached, the outer sheath is advanced beyond the endoscope tip, and the needle is extended to a preset distance. A syringe is then attached to the handle to inject liquid agents into the target tissue.[3] Injection of various solutions achieves hemostasis by mechanical tamponade and/or cytochemical mechanisms. Injection needles of various lengths and diameters have been developed for endoscopic hemostasis in the GI tract (Table 1).

Thermal devices

Endoscopic hemostasis can be achieved by the application of heat or cold at the site of bleeding. Heat causes hemostasis by inducing edema, protein coagulation, vasoconstriction, and indirect activation of the coagulation cascade.[3] Tissue coagulation by heat requires a temperature of approximately 70°C.[3] Thermal devices used for endoscopic hemostasis in the GI tract have traditionally been divided into contact (bipolar/multipolar electrocautery, heater probe, and hemostatic forceps) and noncontact devices (argon plasma coagulation) (Tables 2 and 3).

Bipolar/multipolar electrocoagulation probes. Hemostasis using electric current passing through a probe to generate heat can be performed using either a monopolar or a multipolar electrocoagulation (MPEC) device.[4] With monopolar devices, the current passes through the patient and back to the unit via a return pad, whereas with MPEC devices, the electric current is confined to the tissue between the electrodes within the instrument tip, obviating the need for a return pad.[4,5]

The MPEC probe can be used tangentially to, or perpendicularly to, the bleeding source. Pressure is applied to compress and seal the walls of the bleeding vessel ("coaptive coagulation").[6] MPEC probes are available in 7F and 10F diameters with an irrigation port at the tip; the 10F probe requires the use of an endoscope with a $\geq$3.2 mm diameter instrument channel. Probe size, wattage, contact pressure and duration, and number of applications will vary depending on the lesion being treated.

Heater probe. The heater probe comprises a PTFE–coated hollow aluminum cylinder with an inner heating coil and an irrigation port at the tip of a 230- to 300-cm 7F to 10F catheter.[3] The probes are reusable and are compatible with the HPU-20 (Olympus America, Center Valley, Pa, USA) power source. The probe transfers heat from its end or sides, causing tissue coagulation. The PTFE coating reduces adherence of the probe to tissue.[7] The probe is placed directly at the site of the bleeding vessel, either perpendicularly or tangentially, with pressure applied for coaptive coagulation. A foot pedal controls heat activation and irrigation. Once the pulse has been initiated, the duration of activation is predetermined and will deliver the entire amount of preselected energy.[3] A power setting of 25 J to 30 J per pulse, using 4 to 5 pulses (total of 100-150 J) per station (before the probe position is changed) has been recommended for peptic ulcer bleeding.[7] Of note, sales of the HPU-20 in the United States were discontinued in 2011, and the manufacturer has communicated its intention to discontinue sales of the compatible probes in 2019 (personal communication).

Hemostatic forceps. Hemostatic forceps are devices that were developed initially for treatment and prevention of bleeding during endoscopic resection (Fig. 1). The bleeding tissue is grasped within the jaws of the forceps, and electrocoagulation is used to coagulate the bleeding source; retraction of the tissue will limit the depth of coagulation injury. Hemostatic forceps are available from

TABLE 1. Injection needles

Manufacturer	Device name	Sheath diameter (French)	Sheath length (cm)	Needle gauge	Needle length (mm)	List price	Special features
Boston Scientific (Natick, Mass, USA)	•Inject sclerotherapy needle	•7	•200, 240	•23, 25	•4, 6	•$70 each	
Medtronic Endoscopic Technologies (Chelmsford, Mass, USA)	•Click-tip injection needle	•7	•180, 230	•19,	•4, 6	•$743.88/ box of 10	
			•180, 230	•22, 25	•4, 6	•$704.64/ box of 10	
	•FlexiTip disposable sclerotherapy needle - standard	•7	•160, 230	•25	•4, 5, 6	•$294.6/ box of 5	
	•FlexiTip disposable sclerotherapy needle - optic yellow tip	•7	•160, 230	•25	•4, 5, 6	•$362.5/ box of 5	•Visible in bloody field
Cook Medical (Winston-Salem, NC, USA)	•AcuJect variable injection needle	•7	•220	•23, 25	•Variable	•$51 each	
	•Disposable varices injector	•7	•200-320	•23, 25	•Variable	•$62-86 each	
		•7	•220	•23, 25	•Variable	•$61 each	•Flush port
Halyard Health (Roswell, Ga, USA)	•Injection needle catheter	•7	•160, 200, 240	•23, 25	•4, 6	•$318.94/ box of 10	
Olympus America (Center Valley, Pa, USA)	•Injector Force Max injection needle	•7	•165-230	•21, 23, 25	•4, 5, 6, 8	•$433.50 (21G)/ box of 5	
US Endoscopy (Mentor, Ohio, USA)	•Articulator Injection needle	•7	•160, 230, 350	•25	•4, 5	•$53/box of 5	
	•Carr-Locke injection needle	•7	•230	•25	•5	•$63/box of 5	
	•iSnare	•10	•230	•23, 25	•5	•$139/box of 5	•2.5- × 4-cm integrated snare

multiple manufacturers: Olympus Coagrasper, Fujifilm Clutch Cutter (Fujifilm Medical Systems USA, Inc, Stamford, Conn, USA), Sumitomo Bakelite SB Knife (Sumitomo Bakelite Co, Ltd, Tokyo, Japan) and vary in features including jaw shape, opening width, rotatability, and working length. Use of electrosurgical current waveforms in which the peak voltage is held below 200 volts, such as Soft Coag mode with the Erbe Vio 300 unit (Erbe USA, Inc, Marietta, Ga, USA) or TouchSoft mode with the gi4000 unit (US Endoscopy, Mentor, Ohio, USA) has been described when using hemostatic forceps.[8-10] Hemostatic forceps that have been cleared by the U.S. Food and Drug Administration (FDA) are monopolar devices; bipolar devices have been developed but are not currently available in the United States.[11,12]

Argon plasma coagulation. Argon plasma coagulation (APC) is a noncontact thermal method of hemostasis. An APC delivery system consists of an argon gas cylinder, a computer-controlled, high-frequency electrosurgical generator with a gas flow-controlling valve, and an endoscopic probe.[4] Inert argon gas is converted to ionized argon gas (plasma) by a monopolar electrode at the tip of the probe. The probe tip is placed close to the bleeding lesion, with the optimal distance ranging from 2 to 8 mm.[3] High-frequency monopolar current is then conducted through the gas, resulting in tissue coagulation.

Variables of system setup include power (watts), gas-flow rate, and mode of energy delivery.[4] Increased power results in more rapid devitalization of tissue and deeper penetration. Gas flow should be set at the lowest possible rate for desired tissue effect to reduce the risk of gas embolization and argon-related pneumoperitoneum.[4] The mode of current delivery can be set to either forced or pulsed. Forced mode entails continuous delivery of energy, resulting in more rapid tissue devitalization and hemostasis. By contrast, pulsed mode sends intermittent bursts of energy to the tissue, resulting in a more superficial effect.[4] APC is particularly well suited for superficial treatments because the penetration depth of the coagulation is limited to only a few millimeters.[13] APC probes are available in a variety of lengths and diameters with forward, side, or circumferential ports allowing forward, tangential, or circumferential applications, respectively.[3]

Mechanical devices

Clips. Clips are metallic devices that effect hemostasis by mechanical approximation of tissue and subsequent tamponade. Two broad categories of clips are currently available for endoscopic hemostasis in the GI tract: through-the-scope (TTS) clips and cap-mounted clips.

TABLE 2. Contact thermal devices

Manufacturer	Device name	Sheath diameter (French)	Sheath length (cm)	List price	Special features
Multipolar electrocautery probes					
Boston Scientific (Natick, Mass, USA)	•Gold probe	•7, 10	•300, 350	•$359	
	•Injector gold probe	•7, 10	•210	•$519	•Integrated 25-gauge injection needle
Medtronic Endoscopic Technologies (Chelmsford, Mass, USA)	•Bicap superconductor, multielectrode bipolar probe	•5, 7, 10	•200, 300, 350	•$396.48	
		•7. 10	•300	•$240	
Cook Medical (Winston-Salem, NC, USA)	•Quicksilver bipolar probe	•7, 10	•350	•$328	
Olympus America (Center Valley, Pa, USA)	•BiCOAG bipolar probe	•7, 10	•350	•$370.30	•Bipolar coagulation provides coagulation at any angle
		•7, 10	•350		
US Endoscopy (Mentor, Ohio, USA)	•Bipolar hemostasis probe	•7, 10	•350	•$300	
Heater probes					
Olympus America (Center Valley, Pa, USA)	•HeatProbe	•7, 10	•230, 300	•$812	•Reusable
Hemostatic grasper					
Olympus America (Center Valley, Pa, USA)	•Coagrasper (upper/gastric)	•7	•165	•$278	•Opening width 5 or 6.5 mm •Rotatable
	•Coagrasper (lower)	•7	•230	•$320	•Opening width 4 mm •Rotatable
	•SB Knife (Jr, Short, Standard)	•7	•230, 195, 180	•$1695	•JR: opening width 4.5 mm; scissor-like jaw •Short: opening width 6 mm, angled tip design •Standard: opening width 8 mm, angled tip design •Rotatable
Fujifilm Medical Systems (Wayne, NJ, USA)	•ClutchCutter	•7	•180	•$670	•Serrated, rotatable jaws

TABLE 3. Noncontact thermal devices

Manufacturer	Device name	Sheath diameter (French)	Sheath length (cm)	Fire direction	List price	Special features
Canady (Hampton, Va, USA)	•Canady plasma GI probe	•5, 7	•230, 340	•Straight, side	•$1650/box of 10 $165/probe	
Medtronic Endoscopic Technologies (Chelmsford, Mass, USA)	•Beamer argon probe	•5, 7, 10	•160, 230, 320	•Straight, fire	•$3202.80/box of 10	
	•Beamer argon snare probe	•7	•160, 230	•Straight, fire	•$2241.60/box of 5	•Combination APC probe and snare
ERBE USA, Inc. (Marietta, Ga, USA)	•APC probe	•5, 7, 10	•150, 220, 300	•Straight, side, circumferential	•$2139.50 to 2459.50/box of 10*	
	•FiAPC probe	•5, 7, 10	•150, 220, 300	•Straight, side, circumferential	•$2139.50 to 2459.50/box of 10†	•Integrated filter

*Endoscopy size.
†Endoscope cap depth.

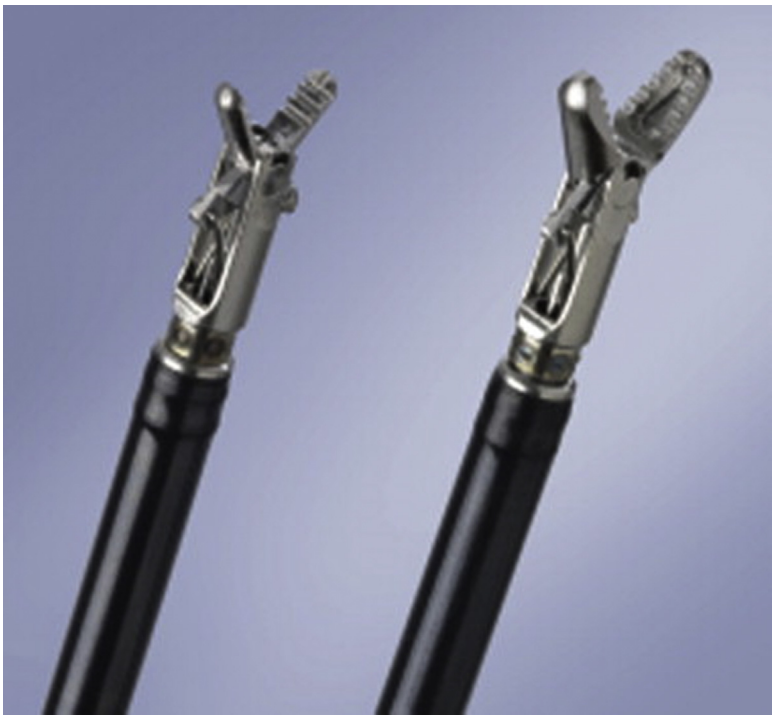

Figure 1. Colonic (*left*) and gastric (*right*) Coagrasper hemostatic forceps. (Image used with permission from Gastrointest Endosc 2015;81:1311-25.)

TTS clips were specifically developed for endoscopic hemostasis in the GI tract and have been in use for many years (Video 1, available online at www.VideoGIE.org). They are composed of 3 main components: a metallic double-pronged clip, a delivery catheter, and a handle used to operate and deploy the clip.[3] The orientation of some clips can be adjusted by rotating the handle itself or a component of the handle. Some clips can be reopened after initial closure before deployment. TTS clips of various sizes and lengths are commercially available (Table 4).

Cap-mounted clips were developed for endoscopic closure of GI perforations and fistulae, but they also have utility in hemostasis. Compared with TTS clips, cap-mounted clips are able to compress a larger amount of tissue.[14] Currently, 2 cap-mounted clip systems are commercially available; the over-the-scope clip system (OTSC, Ovesco Endoscopy AG, Tübingen, Germany) and the Padlock system (US Endoscopy) (Fig. 2). Both systems are cleared by the FDA for hemostatic indications.[15]

The OTSC system comprises an application cap with a preloaded nitinol clip that is mounted onto the distal tip of an endoscope. The mounted clip is attached to a rotating wheel installed on the handle of the scope by a string that runs through the instrument channel of the endoscope. Rotating the wheel on the handle releases the clip from the cap. The setup and deployment of these clips is similar to band ligators used to treat esophageal varices. Three variants of the clip are available, with differing configurations of the tissue-grasping teeth: type a (atraumatic), type t (traumatic), and type gc (gastric fistula closure).[14] The type a clip is marketed for hemostasis applications. The clips are available in 3 sizes, with the variation corresponding to different diameters of the application cap, which is necessary for compatibility with a range of endoscope outer diameters (8.5 mm to 14.5 mm). Two proprietary devices are available to further retract tissue into the cap if needed: a dual-arm forceps ("OTSC Twin Grasper") and a tissue anchoring tripod ("OTSC Anchor").[16]

The Padlock system consists of an application cap with a preloaded nitinol clip that is mounted onto the distal tip of an endoscope and is attached to a releasing mechanism installed on the handle of the scope by a linking cable. As opposed to the OTSC system, the linking cable runs outside the scope, not within the instrument channel.[15] This design theoretically may allow for more efficient suction of tissue into the cap.[15] The Padlock system is available in 2 options: "Padlock Clip" for endoscopes between 9.5 mm and 11 mm in outer diameter, and "Padlock Clip Pro-Select" for endoscopes between 11.5 mm and 14 mm in outer diameter.[17]

Endoscopic suturing devices. An endoscopic suturing device (OverStitch, Apollo Endosurgery, Austin, Tex, USA) is currently available for clinical use. The primary applications of this device are perforation closure and bariatric treatment.[15] It is FDA cleared for soft tissue approximation.[15] Use of this device for attaining hemostasis in bleeding gastric and anastomotic ulcers has been described.[18,19]

TABLE 4. Mechanical hemostatic devices

Manufacturer	Device name	Sheath diameter (French)	Sheath length (cm)	Jaw opening width (mm)	List price	Special features
Boston Scientific (Natick, Mass, USA)	•Resolution Clip	•7	•155, 235	•11	•$330/each	•Open/close jaw up to 5 times •MR conditional up to 3 Tesla
	•Resolution 360 Clip	•7	•155, 235	•11	•$370/each	•Open/close jaw up to 5 times •MR conditional up to 3 Tesla •Controlled rotation in tortuous anatomy •Can be rotated by technician or endoscopist
Olympus America (Center Valley, Pa, USA)	•QuickClip2	•7	•165, 230	•9	•$713/box of 5 •$2726/box of 20	
	•QuickClip2 long	•7	•165, 230	•11		
	•QuickClip Pro	•7	•165, 230	•11	•$3714/box of 10	•Precise rotation •MR conditional up to 3 Tesla
Cook Medical (Winston-Salem, NC, USA)	•Instinct	•7	•207	•16	•$2621/box of 10	•Open/close jaw up to 5 times •MR conditional up to 3 Tesla
ConMed (Utica, NY, USA)	•Dura Clip	•7	•165, 235	•11	•$3000/box of 10	•Shorter clip design, closer proximity to tissue defect •Unlimited open/close before deployment •MR conditional up to 3 Tesla
Micro-Tech Endoscopy USA (Ann Arbor, Mich, USA)	•SureClip	•7	•165, 235	•11	•$1250/box of 10	•Shorter clip design •Unlimited open/close before deployment •MR conditional up to 3 Tesla
	•SureClip plus	•7	•235	•16		
Ovesco Endoscopy USA Inc (Carey, NC, USA)	•Over-the-scope-clip (OTSC)	•8.5 to 11 mm*	•165	•3, 6†	•$438	•Blunt or pointed teeth
		•10.5 to 12 mm*	•165, 220	•3, 6†	•$543 (3 mm) •$589 (6 mm)	•Blunt or pointed teeth
		•11.5 to 14 mm*	•220	•3, 6†	•$610	•Blunt or pointed teeth
US endoscopy (Mentor, Ohio, USA)	•Padlock Clip	•9.5 to 11 mm*	•165	•10‡	•$599	
	•Padlock Clip Pro-Select	•11.5 to 14 mm*	•165	•4 to 14‡	•$599	

*Endoscopy size.
†Endoscope cap depth.
‡Tissue chamber depth.

The OverStitch device requires a double-channel endoscope (compatible only with Olympus scopes GIF-2T160 or GIF-2T180; Olympus Corporation, Tokyo, Japan) and consists of a suture anchor with a detachable needle tip carrying absorbable (2-0 or 3-0 polydioxanone) or nonabsorbable (2-0 or 3-0 polypropylene) sutures.[15,20,21] This device is described in detail in an ASGE technology assessment titled Endoscopic Closure Devices.[22]

Banding Devices. Endoscopic band ligation (EBL) is a well-established therapy for bleeding esophageal varices, but it also has utility in the treatment of nonvariceal bleeding.[23] Endoscopic banding devices consist of a transparent cap, a connecting wire or string, and a handle. The cap is mounted on the distal end of the endoscope and carries 4 to 10 preloaded bands.[24] The cap is connected to the handle by a connecting wire or string that runs through the instrument channel of the endoscope. Once the bleeding lesion is suctioned into the cap, rotation of the handle pulls the connecting wire, leading to deployment of a band.[25] Placement of a band

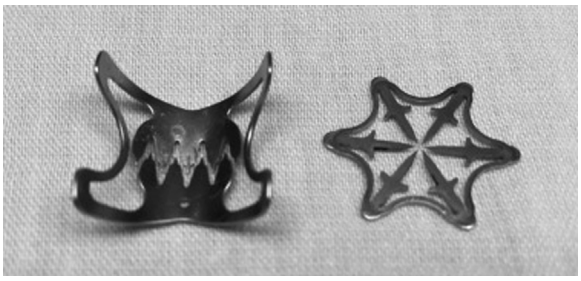

Figure 2. Over-the-scope (*left*) and Padlock (*right*) clips in deployed configuration. (Image used with permission form Gastrointest Endosc 2017;85:1087-92.)

at the base of the bleeding tissue causes mechanical compression that leads to hemostasis and subsequent thrombosis, necrosis, and sloughing.[23]

Covered self-expandable metallic stents. Covered self-expandable metallic stents (CSEMSs) have been used for the treatment of biliary and esophageal strictures for many years.[26] The use of CSEMSs as a salvage technique for hemostasis has been described.[15] CSEMSs induce hemostasis by mechanical tamponade of the bleeding vessel/lesion.

Topical hemostatic agents

Topical hemostatic agents are sprayed on the bleeding site to achieve hemostasis. Three different topical hemostatic agents are commercially available, but only Hemospray (also known as TC-325; Cook Medical, Winston-Salem, NC, USA) is currently FDA cleared for use in the United States.

Hemospray. Hemospray is an inorganic hemostatic powder that was used by the military for bleeding control before its introduction as an endoscopic hemostatic agent for use in the GI tract.[15,27] The Hemospray system consists of a cartridge with an integrated handle connected to a delivery catheter. The handle houses the hemostatic powder, a CO_2 cartridge, a knob to activate the CO_2 cartridge, a valve to control the flow of the powder, and a trigger button. The powder is sprayed toward the source of bleeding through a 7F or 10F dedicated catheter, which is advanced through the instrument channel of the endoscope.[28] The CO_2 cartridge in the handle of the device is activated by turning the activation knob. After a valve on the device is opened, the trigger button allows the pressure generated from the CO_2 cartridge to propel the powder through the catheter and onto the desired surface.[29] Hemospray is thought to cause hemostasis by sealing injured blood vessels and activating platelets and the intrinsic coagulation pathway.[28,30,31] Use of the Hemospray device is demonstrated in Video 2 (available online at www.VideoGIE.org).

Ankaferd blood stopper

Ankaferd blood stopper (ABS) (Ankaferd Health Products Ltd, Istanbul, Turkey) is a medical plant extract that has historically been used as a hemostatic agent in Turkish traditional medicine.[32] It is in liquid form and is delivered to the site of bleeding by a catheter, which is advanced through the instrument channel of an endoscope.[32] Various catheters can be used for this purpose. The mechanism of action is not well understood, but it may involve formation of an encapsulated protein mesh that acts as an anchor for rapid erythrocyte aggregation.[31,33,34] It may also influence angiogenesis and cellular proliferation.[31]

EndoClot

EndoClot (EndoClot Plus Inc, Santa Clara, Calif, USA) is an absorbable hemostatic polysaccharide powder derived from plant starch.[35] It is delivered to the site of bleeding with an applicator system, which includes a delivery catheter and a specially designed powder/air mixing chamber that is connected to the powder container and an air compressor. The delivery catheter is inserted into the instrument channel of the endoscope and positioned toward the bleeding lesion. Pressure from the air compressor propels the powder through the catheter directly onto the bleeding area.[36] The mechanism of action is thought to relate to formation of a gelled matrix that adheres to and seals the bleeding tissue, along with absorption of water from the blood, causing an increased concentration of platelets, red blood cells, and coagulation proteins at the bleeding site, with subsequent acceleration of the physiologic clotting cascade.[35]

Endoscopic Doppler probe

Endoscopic Doppler probe (EDP) does not directly provide hemostasis, but it may assist the endoscopist in assessing the success or failure of endoscopic therapy.[37] It may also guide treatment and help predict the risk of recurrent bleeding.[38] EDP systems consist of a control unit and a through-the-scope probe.[39] Two EDP systems are currently available for use in GI endoscopy: VTI Endoscopic Doppler system (Vascular Technology Inc, Lowell, Mass, USA), and the Endo-DOP system (DWL GmbH, Singen, Germany).[15] The VTI system uses a disposable 20-MHz probe with a diameter of 1.5 mm and lengths of 209 cm or 335 cm.[40] The Endo-Dop system uses a reusable 16-MHz probe with a diameter of 1.8 mm and a length of 250 cm.[41]

The probe is advanced through the instrument channel of the endoscope and applied to the bleeding site with light-to-moderate pressure at multiple points, including those immediately adjacent to any stigmata of bleeding.[39] The auditory Doppler signal helps identify the presence and course of bleeding vessels, which may not be visible. Disappearance of the Doppler signal after treatment indicates successful treatment of the bleeding lesion. Bleeding lesions that remain Doppler positive after treatment may be at increased risk of recurrent hemorrhage.[39,42]

EUS-guided hemostasis

EUS-guided hemostasis is an emerging modality for control of bleeding lesions that are not readily accessible or are refractory to standard endoscopic or interventional radiologic techniques.[43] In those settings, EUS has been used to inject various substances, deliver embolization coils, or mark the location of the bleeding vessel.[44] Most studies assessing EUS for bleeding control in the GI tract involve gastric variceal bleeding.[15,44] Studies assessing the utility of EUS for nonvariceal bleeding control are limited to small case series and case reports.

OUTCOMES DATA

Injection therapy

Diluted epinephrine is the most commonly studied injectate for endoscopic treatment of nonvariceal GI bleeding.[45] Epinephrine injection therapy promotes initial hemostasis, but this effect attenuates over time, with subsequent risk of recurrent bleeding.[46] In a meta-analysis of 19 RCTs in which epinephrine alone was compared with combination therapy for control of upper-GI bleeding (11 studies used a second injected agent, 5 used clips, and 3 used a thermal method), the risk of recurrent bleeding was significantly lower in the combination therapy groups than in the epinephrine-alone group, regardless of which second modality was applied (relative risk 0.53, 95% confidence interval 0.35 to 0.81).[47] Another meta-analysis of 16 studies reported similar findings.[48]

In contrast to upper-GI bleeding (UGIB), randomized comparative studies and meta-analyses evaluating injection therapy in acute lower-GI bleeding (LGIB) are lacking.[45] However, although data are limited, guidelines have discouraged epinephrine monotherapy in LGIB.[45] Although epinephrine injection can be used to gain initial control of active bleeding and improve visualization in nonvariceal upper- and lower-GI bleeding, it should be combined with another method to decrease the risk of recurrent bleeding.[45,49]

Thermal therapy

Multipolar electrocoagulation probe. In an RCT, patients with peptic ulcer bleeding were assigned to epinephrine injection followed by MPEC (n = 58) or MPEC alone (n = 56).[50] The rate of initial hemostasis was significantly higher and the required units of blood significantly lower in the combination therapy group.[50] There was no significant difference between the 2 treatment groups with respect to recurrent bleeding, need for surgical intervention, or length of hospital stay. In another RCT, patients with UGIB were randomized to combination therapy with epinephrine injection and MPEC (n = 21), or monotherapy with clip placement (n = 26).[51] Successful initial hemostasis, rate of recurrent bleeding, length of hospital stay, units of blood transfused, surgery rates, and mortality were not different between the 2 groups.[51]

In the lower-GI tract, a randomized study of 30 patients with bleeding radiation proctopathy compared the effectiveness of MPEC (n = 15) with APC (n = 15).[52] Although both modalities were equally effective for treatment of the bleeding, the overall adverse event rate including stenosis and pain was higher in the MPEC group.[52]

Heater probe. Two RCTs have compared treatment with heater probe to clip placement for nonvariceal UGIB, with somewhat conflicting results.[53,54] In 1 study, 113 patients were randomly assigned to receive treatment with either heater probe (n = 57) or clip (n = 56) application.[53] Initial hemostasis, 30-day mortality, and emergency surgery rates were similar for both groups. However, recurrent bleeding was significantly higher in the heater probe group (21% vs 1.8%; $P < .05$). Length of hospital stay and transfusion requirements were significantly lower in the clip group.[53] In the other RCT, 80 patients with peptic ulcer bleeding were randomized to treatment with either heater probe (n = 40) or clip placement (n = 40).[54] The rate of initial hemostasis was significantly higher in the heater probe group than in the clip group (100% vs 85%; $P = .01$), whereas recurrent bleeding rates were similar between the 2 groups.[54]

In a study of 93 patients with peptic ulcer bleeding, participants were randomized to receive either endoscopic clip placement (n = 46) or heater probe thermocoagulation plus epinephrine injection (n = 47).[55] Five patients were excluded because of clip placement failure. Initial hemostasis and recurrent bleeding rates were similar in both groups.[55] A meta-analysis of 15 RCTs (n = 1156) found thermocoagulation with MPEC or heater probe to be equally effective as clip placement for treatment of nonvariceal UGIB.[56]

Hemostatic forceps. In a retrospective study of 39 patients with peptic ulcer bleeding (29 gastric, 10 duodenal), initial hemostasis was achieved in 37 patients (95%) by use of a monopolar hemostatic forceps. Recurrent bleeding requiring treatment occurred in 2 patients.[11] In a prospective nonrandomized study, 50 patients with nonvariceal UGIB underwent treatment by a bipolar hemostatic forceps (27 patients) or clip placement (23 patients). Hemostasis was achieved in all patients who underwent hemostatic forceps treatment, compared with 78% (18 of 23) of patients treated with clip placement ($P < .05$).[12] In a prospective noninferiority study, patients with peptic ulcer bleeding were randomized to receive either epinephrine injection plus APC (n = 75) or epinephrine injection plus soft coagulation with monopolar hemostatic forceps (n = 76).[57] Hemostasis was achieved in 96% of patients in both groups, and there was no difference in the rate of recurrent bleeding at 30 days.[57]

Argon plasma coagulation. A meta-analysis of 2 RCTs (n = 121) comparing monotherapy with either APC or other endoscopic hemostatic interventions (heater probe, injection sclerotherapy) for treatment of peptic ulcer bleeding found no significant outcomes differences between the treatment modalities.[58] In an RCT of 116 patients with peptic ulcer bleeding, patients were randomized to combined therapy with distilled water injection plus APC (n = 58) or distilled water injection alone (n = 58).[59] Although initial hemostasis rates were similar (97% vs 95%), the recurrent bleeding rate was significantly lower in the combination therapy group (3.6% vs 16%, $P = .03$).[59]

Three RCTs of comparable size (n = 151 to n = 185) have evaluated the effectiveness of APC plus epinephrine versus other modalities (heater probe, clip, hemostatic forceps) plus epinephrine for treatment of peptic ulcer bleeding.[57,60,61] In all 3 trials, there were no significant differences between the 2 groups in terms of initial hemostasis (>95% in all treatment arms), recurrent bleeding, or other relevant clinical outcomes.

Serial APC treatments in patients with bleeding gastric antral vascular ectasia (GAVE) have been associated with reduced transfusion requirements and improved hemoglobin levels.[62-64] In an RCT of 88 cirrhotic patients with GAVE, participants were randomized to endoscopic treatment with either EBL (n = 44) or APC (n = 44).[65] The number of sessions required for complete obliteration of the lesions was lower with EBL therapy (2.98 sessions vs 3.48 sessions; $P < .05$). The EBL group also required significantly fewer blood transfusions. There were no significant differences in adverse event rates between the 2 groups.[65] APC has shown effectiveness for treatment of other types of UGIB including angioectasias, Dieulafoy lesions, portal hypertensive gastropathy, and tumor bleeding in small case series.[66-69] In a Korean retrospective series of 66 patients with obscure GI bleeding who underwent balloon enteroscopy and were found to have small-bowel angioectasias, 45 patients underwent endoscopic treatment (APC in 87%), and 21 did not receive any endoscopic treatment.[70] During a mean follow-up time of 24.5 months, the recurrent bleeding rates in the endoscopic-treatment arm and no-treatment arm were 15.6% and 38.2% ($P = .059$).

Multiple small studies and case series have reported a reduction in rectal bleeding and transfusion requirements and improvement in hemoglobin levels after serial treatments with APC for radiation proctopathy.[71-74] One RCT (n = 30) found APC to be equally effective as MPEC, with fewer adverse events for control of rectal bleeding associated with radiation proctopathy.[52] APC has also been reported to be an effective treatment for bleeding colonic angioectasias.[75]

Mechanical therapy

Through-the-scope clips. In a subgroup analysis from a large meta-analysis (20 studies, n = 2472) of patients with high-risk bleeding ulcers treated endoscopically, no combination of treatments was superior to mechanical therapy with hemostatic clips alone.[76] Another meta-analysis of 15 RCTs (n = 1156) suggested that successful application of clips is superior to injection therapy but comparable with thermocoagulation in producing definitive hemostasis in patients with nonvariceal UGIB.[56]

Although no randomized studies have assessed the use of TTS clips in LGIB, case series and reports have suggested the effectiveness of clips for this purpose.[45,77] For diverticular bleeding, endoscopic clips have been recommended to reduce the theoretic risk of transmural colonic injury associated with contact thermal therapy.[77] An RCT (n = 1499) did not find prophylactic clipping to affect the rate of postpolypectomy bleeding for polyps <2 cm in diameter.[78] A recent meta-analysis confirmed these results and suggested that the use of prophylactic clip placement after polypectomy should not be a routine practice.[79] However, prophylactic clip placement in certain high-risk patients (eg, requiring anticoagulation, large and/or right-sided lesions) may be beneficial, and this decision should be individualized.[80]

Cap-mounted clips. In a retrospective study of 93 patients with 100 episodes of severe upper- (n = 69) and lower- (n = 31) GI bleeding treated with the OTSC system, immediate hemostasis and absence of in-hospital recurrent bleeding were achieved in 88 of 100 (88%) and 78 of 100 (78%) patients, respectively.[81] Other smaller studies have shown similar results.[82-85] Successful use of the Padlock system to achieve hemostasis has been reported in 2 case series totaling 5 patients (1 bleeding rectal ulcer, 3 postpolypectomy bleeds, and 1 duodenal Dieulafoy lesion).[86,87]

Endoscopic suturing. Outcomes data on the use of the Overstitch device for hemostasis in the GI tract are limited to a small case series of 3 patients with gastric ulcer bleeding and a case report of bleeding anastomotic ulcer after gastric bypass surgery.[18,19] In all patients, bleeding was controlled with the suturing device.

Banding devices. In a study of 88 cirrhotic patients with GAVE who were randomized to EBL or APC, the number of sessions required for complete obliteration of the lesions and the number of required blood transfusions were significantly lower with EBL therapy.[65] In a retrospective analysis of a prospectively maintained endoscopic database, outcomes from 24 patients with bleeding duodenal Dieulafoy lesions were evaluated.[88] After treatment with EBL (n = 11) or endoscopic clip placement (n = 13), primary hemostasis was achieved in all patients. Recurrent bleeding was observed in 1 patient (9.1%) from the EBL group and in 5 patients (38.5%) from the clip group ($P = .166$). There were no differences in secondary outcomes between the 2 groups, including number of endoscopic sessions required, need for angiographic embolization or

emergent surgery, transfusion requirements, or length of hospital stay.[88] In a Japanese series of 53 patients with colonic diverticular bleeding, EBL provided effective hemostasis in 26 of 27 (96%) patients with active hemorrhage or a nonbleeding visible vessel.[89]

Covered self-expandable metallic stents. The use of CSEMSs for hemostasis in the GI tract has been studied in a randomized controlled fashion only in the setting of esophageal variceal bleeding.[90] In the biliary tract, successful use of CSEMSs for hemostasis has been reported in cases of uncontrolled bleeding after sphincterotomy, sphincteroplasty, intraductal biopsy, and anastomotic stricture dilatation in posttransplantation patients.[91-94] Successful use of CSEMSs for hemostasis in the esophagus, duodenum, and colon has also been described in small case series and case reports.[95-99]

Topical hemostatic agents

Hemospray. Hemospray treatment was evaluated in a French registry of 202 patients with UGIB of various causes across 20 centers.[100] Immediate hemostasis was achieved in 195 of 202 patients (96.5%), independently of whether it was used as first-line therapy (91/94; 96.8%) or salvage therapy (104/108; 96.3%). The type of lesion did not influence immediate hemostasis, which was achieved in 72 of 75 (96.0%) of ulcers, 58 of 61 (95.1%) of malignant lesions, 34 of 35 (97.1%) of postendoscopic bleeding, and 31 of 31 (100%) of bleeding from other causes.[100] Recurrent bleeding was noted at day 8 and day 30 in 26.7% and 33.5%, respectively. Other smaller studies have shown similar results.[101, 102] Use of Hemospray for control of LGIB, early postoperative anastomotic bleeding, and postsphincterotomy bleeding has shown promise in case series and case reports.[28,103-105]

Ankaferd blood stopper. In a retrospective case series of 26 patients with upper- and lower-GI bleeding of various causes (including Mallory-Weiss tear, Dieulafoy lesion, GAVE, radiation proctopathy, and postpolypectomy bleeding), application of ABS provided hemostasis in all patients.[32] Other case series and case reports have indicated the effectiveness of ABS in the treatment of variceal bleeding, tumor bleeding, postsphincterotomy bleeding, and diverticular bleeding.[106-109] Large prospective studies are lacking.

EndoClot. In a prospective multicenter study of 70 patients, hemostasis was achieved in 30 of 47 (64%) patients with UGIB treated with EndoClot as a first-line therapy, 11 of 11 (100%) patients with UGIB treated with EndoClot as a salvage therapy, and 10 of 12 (83%) patients with LGIB.[110] In another study, LGIB after EMR was successfully controlled with EndoClot in 18 of 20 (90%) lesions, with no procedure-related adverse events.[111]

Endoscopic Doppler probe. In an RCT for the assessment of hemostasis in UGIB, 148 patients (125 with peptic ulcers, 19 with Dieulafoy lesions, and 4 with Mallory Weiss tears) were assigned to either standard (visually guided) endoscopic hemostasis (n = 76) or hemostasis-assisted by Doppler monitoring of blood flow (n = 72).[39] The primary outcome (recurrent bleeding within 30 days of endoscopic hemostasis) occurred more frequently in the control group (26.3%) than in the Doppler group (11.1%; $P = .021$).[39] Other nonrandomized studies have also suggested that Doppler probes can be of use for risk stratification of patients with UGIB, inasmuch as lack of a Doppler signal after hemostasis indicates a reduced risk of recurrent bleeding, whereas a persistently positive signal is a marker for higher risk of recurrent bleeding.[38,112] Similar findings in a study of 38 patients with diverticular bleeding suggest a potential risk stratification role for EDP in LGIB as well.[113]

EUS-guided hemostasis. Use of EUS in the therapy of nonvariceal GI bleeding is limited to small case series and case reports. In a case series involving 17 patients with nonvariceal GI bleeding of diverse causes, EUS was used for either injection (eg, cyanoacrylate, ethanol), coil embolization, or tattooing the site of a subepithelial vessel for subsequent EBL. In this series, EUS-directed therapy was successful in 15 of 17 (88%) patients, with no further bleeding over a median follow-up duration of 12 months.[44] Other case series and reports have described similar results.[114-116]

EASE OF USE

Many hemostatic devices require an adequate view of the bleeding source and precise, en face positioning of the endoscope to facilitate direct contact with the bleeding lesion. In many cases, these conditions may not be easily achievable. Noncontact hemostatic devices such as APC and topical hemostatic agents obviate the need for some of these conditions and are generally easier to use. Heater probes and bipolar probes require adequate pressure on the tissue and sufficient duration of treatment to induce coaptive coagulation. Both excessive pressure and duration of treatment increase the risk of deep tissue injury and perforation, whereas inadequate pressure or treatment duration can exacerbate bleeding by unroofing the bleeding vessel.[117]

APC is a noncontact technique requiring an operative distance from the probe tip to the tissue that ranges from 2 to 8 mm.[3] Longer distances hamper ignition of the plasma, whereas probe contact with the tissue may potentially cause flow of argon gas into the submucosa, leading to pneumatosis and rarely extraintestinal gas.[118] Any liquid (eg, blood) between the probe tip and bleeding tissue can induce the development of a coagulation film that can prevent adequate treatment of the bleeding source.[118]

Deployment of TTS clips may be challenging through an angulated endoscope or over a duodenoscope elevator.[3] TTS clips also may be difficult to place on

bleeding vessels within a large fibrotic ulcer base because there may be inadequate tissue to anchor the clip.[3] Rotatable clips may permit easier alignment of the open jaws with the bleeding vessel. Differences in the jaw opening and the length of the tail of the clip may affect performance in different anatomic locations. Potential disadvantages of the cap-mounted clips include requirement for scope withdrawal to load the device, difficulty in traversing the cricopharyngeus or luminal stenoses with the mounted cap, and challenge in accessing certain areas of the GI tract.[21] In addition, cap-mounted clips are difficult to remove. Limitations of endoscopic suturing devices are lack of widespread availability, need for a double-channel endoscope, technical complexity, and restricted maneuverability, hindering access to some areas of the GI tract.[21]

Advantages of topical hemostatic agents include ease of application in a variety of locations and the potential utility for treatment of many different bleeding lesions.[30,119] Disadvantages of these agents include a transient reduction in endoscopic visualization and possible interference with other treatment modalities if hemostasis should fail.[30,119]

SAFETY

Adverse events of injection therapy are usually related to the substance injected rather than to the needle itself.[3] Rare adverse events include tissue necrosis, ulceration, and perforation, and also hypertension and cardiac arrhythmia with epinephrine injection.[120,121] Serious adverse events of endoscopic thermal hemostasis include uncontrollable bleeding and perforation.[122] Pooled data from prospective controlled trials of bipolar electrocoagulation and heater-probe therapy for peptic ulcer hemostasis reported bleeding that required urgent surgery in 5 of 1684 cases (0.3%) and perforation in 8 of 1684 cases (0.5%) .[123] The risk of perforation may be increased with retreatment after initial thermal therapy.[124] A meta-analysis of RCTs reported similar results.[125] Adverse events from APC are rare and include distention of the GI tract with argon gas, submucosal emphysema, pneumomediastinum, pneumoperitoneum, and perforation.[3] Intracolonic gas explosion with inadequate colonic cleansing has been described; as such, complete colonic cleansing is recommended before use of APC in the colon.[118] Clip deployment failure has been described at certain locations in the GI tract, particularly the posterior wall of the duodenal bulb.[56] Perforation from clip placement has been reported but is exceedingly rare.[126] The reported adverse events associated with topical hemostatic agents are primarily technical in nature, including occlusion of the spray catheter or instrument channel.[126]

FINANCIAL CONSIDERATIONS

List prices of commonly used hemostatic devices in the United States are shown in Tables 1 through 4. Device costs for most clinical enterprises will be lower than list prices owing to purchasing agreements. Current Procedural Terminology (CPT) codes for endoscopic hemostasis, any method, include the following: 43227 (esophagoscopy), 43255 (EGD), 44366 (enteroscopy not including ileum), 44378 (enteroscopy including ileum), 44391 (colonoscopy through stoma), 45334 (flexible sigmoidoscopy), and 45382 (colonoscopy). When CPT codes are used for nonvariceal bleeding, additional codes for injection or EBL are not concomitantly reported.

AREAS FOR FUTURE RESEARCH

Topical hemostatic agents such as Hemospray are promising treatments for GI bleeding. Comparative studies between these agents and other conventional modalities would be useful to better define their clinical role. Cap-mounted clips may be particularly useful in refractory bleeding because they allow ligation of larger vessels and may be less hindered by fibrotic tissue than TTS clips. Further clinical experience will serve to better define the bleeding lesions and the anatomic locations that are best served by cap-mounted clips. The presently available endoscopic suturing system is restricted to use with a double-channel endoscope, but a suturing platform is in development for use with standard endoscopes and thus may potentially have broader applicability. Although hemostatic forceps have been used primarily for the prevention and treatment of bleeding during endoscopic resection, their use as therapy for noniatrogenic GI bleeding should be further evaluated.

SUMMARY

Endoscopic evaluation and treatment remain a cornerstone in the management of nonvariceal upper- and lower-GI bleeding. A variety of devices are available for hemostasis of bleeding lesions in the GI tract. Other than injection therapy, which should not be used as monotherapy, there are few compelling data that strongly favor any one device over another. For endoscopists, the choice of a hemostatic device should depend on the type and location of the bleeding lesion, the availability of equipment and expertise, and the cost of the device.

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Abbreviations: ABS, Ankaferd blood stopper; APC, argon plasma coagulation; ASGE, American Society for Gastrointestinal Endoscopy; CSEMS, covered self-expandable metallic stent; CPT, Current Procedural Terminology; EBL, endoscopic band ligation; EDP, endoscopic Doppler probe; U.S. FDA, United States Food and Drug Administration; GAVE, gastric antral vascular ectasia; HP, heater probe; LGIB, lower GI bleeding; MPEC, multipolar electrocoagulation; OTSC, over-the-scope clip; PTFE, polytetrafluoroethylene; RCT, randomized controlled trial; TTS, through-the-scope; UGIB, upper GI bleeding.

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