REVIEW

New and emerging endoscopic haemostasis techniques

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ABSTRACT

Endoscopic treatment has been accepted as first-line treatment of upper gastrointestinal bleeding, both for variceal as well as for non-variceal haemorrhage. Dual modality treatment including injection therapy with mechanical or thermal haemostatic techniques has shown superior outcome compared with injection monotherapy in non-variceal bleeding. During recent years, new endoscopic devices have been developed and existing endoscopic techniques have been adapted to facilitate primary control of bleeding or achieve haemostasis in refractory haemorrhage. For mechanical haemostasis, larger, rotatable and repositionable clips have been developed; multiple-preloaded clips are also available now. Over the scope clips allow to ligate larger vessels and can close ulcer defects up to 20 mm. Topical, easily applied substances withdraw fluid from the blood and thereby initiate blood clotting. This can be helpful in diffuse oozing bleeding, for example, from tumour or hypertensive gastropathy and has also shown promising results in variceal and arterial bleeding as bridging before definitive treatment is available. Radiofrequency ablation and multiband ligation have emerged as new tools in the endoscopic management of gastric antral vascular ectasia. In acute refractory variceal bleeding, a covered and removable oesophagus stent can provide tamponade and gain time for transport to an interventional endoscopic centre or for radiological intervention such as TIPS.

INTRODUCTION

Despite all advances in endoscopic and clinical management, acute upper gastrointestinal bleeding (AUGIB) is still associated with a mortality around 10%.¹ NICE² and international guidelines³ recommend early risk stratification for AUGIB followed by endoscopic treatment of high-risk patients within 24 h. The Glasgow–Blatchford Score proved superior to the Rockall Score in predicting the

necessity of endoscopic or surgical intervention.⁴

Common endoscopic haemostasis techniques for AUGIB include injection, mechanical, thermal and ligation methods. Dual modality therapy combining injection therapy with clip application or thermal modalities (eg, heater probe and gold probe) is recommended as it has superior outcome compared with injection monotherapy. Adrenaline injection alone is not sufficient as it has often only a temporary effect.⁵

Despite all the technical advances, the limitations of endoscopic methods also need consideration before treating an individual case. Apart from age >70 years, Hb <8 g/dL and a serum albumin <3.3 g/dL, bleeding from arterial vessels with more than 2 mm diameter and the presence of haemorrhagic shock has the strongest association with endoscopic failure⁶ and should lead to early multidisciplinary discussion including interventional radiologists and surgeons. Comorbidities and intake of anticoagulation affecting medication have also a strong negative influence on the prognosis.⁷

In this review, new endoscopic devices and emerging endoscopic haemostasis techniques will be addressed.

THERMAL THERAPY

Coagulation forceps

In recent years, soft coagulation using haemostatic forceps has proven safe and efficient to control bleeding occurring during endoscopic submucosal dissection. This monopolar electrocoagulation system works by producing a temperature rise just below boiling point, causing protein denaturation, tissue dehydration and degeneration but without tissue carbonisation, so the grasped vessel is effectively sealed. This method has been reported also to successfully stop ulcer bleeding.^{8–10} Recently, a randomised controlled study

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showed superiority of soft coagulation using the haemostatic forceps compared with heater probe in achieving haemostasis in peptic ulcer bleeding.¹¹

CLIPS

Mechanical haemostasis allows the safe and permanent occlusion of bleeding vessels. Precondition, however, is the exact positioning on the vessel and the persistence of the clips until clotting and natural healing processes have occurred. If the bleeding source is in a suitable location and the endoscopy staff is experienced with the technique, mechanical haemostasis should be preferred due to the lower perforation rate. Duodenal ulcers at the posterior wall or bleeding sources, which are accessible only in retroflexion close to the cardia, can be challenging for clip application as the release mechanism can be jammed if the applicator is not straight. Often it is easier to advance the clip from the scope and open it before going into retroflexion. Deployment of a clip on hard ulcer base can also be difficult.

Through the scope clips

Through the scope clips (TTS) are produced from various companies and are available with different length of the branches. The newly developed Instinct Clip (Cook Medical, Ireland) provides rotatable branches with a wide opening angle. The clip can also be re-opened and closed again until the desired positioning is achieved. This means the clip can be redeployed if it is initially inaccurately placed. Each clip comes with a new applicator. In experimental studies, the handling in retroflexion and persistence of tissue occlusion were favourable.¹²

The new clip models from Olympus, Quick clip 2 and Quick Clip 2 long, are also rotatable and have reusable applicators. Often the application of multiple clips is required for safe ligation of the vessel. The Clipmaster 3 (Medwork) has three preloaded clips in one applicator, which can be positioned one after the other without the need to remove the applicator from the instrument channel.

The resolution clip (Boston Scientific) can be re-opened and results in effective tissue pressure, the maximal pressure in a vessel >200 mm Hg could be achieved in 10% in a training model.¹³ Compared with other clips (not including the Instinct clip), the resolution clip stays longer at the deployment site.¹⁴

Magnetic resonance imagining can be safely performed with all commercially available clips.¹⁵

Over the scope clip

The over the scope clip (OTSC) from OVESCO (Tübingen, Germany) has been designed to close resection defects and fistulae and it has also been added to the endoscopic haemostasis toolbox. Its mechanism resembles a bear trap with two opposite claws snapping to tightly close around tissue and

vessels. The deployment mechanism with the metal claws preloaded on a transparent cap, which has to be attached to the tip of the scope, is similar to the loading and handling of a varix band ligation device. The endoscopic target is sucked into the cap or pulled with a special anchor or forceps tool. Then, by rotating the hand wheel at the instrument channel the thread fed through the scope is pulled which deploys the forceful OTS clip (figure 1).

The force applied on the tissue and the diameter of tissue enclosed by the claws is much higher than with the TTS clips. In the Erlangen training model the maximal vessel compression >200 mm Hg could be achieved in 59%.¹³

A case series reported the successful use of the OTS clip in nine otherwise therapy refractory upper gastrointestinal bleeding.¹⁶ The largest series so far reported primary haemostasis using the OTS clip in 97% of 30 patients with previously failed conventional endoscopic therapy.¹⁷ The OTS clip is made from biocompatible nitinol and designed to act as a durable implant, but in special situations such as misplacement or inadvertent luminal obstruction, it can become necessary to remove it. Recently, a method for removal of the device by a bipolar cutting device has been described.¹⁸

Another, recently developed OTS clip (Padlock from Diamed) has a different deployment mechanism. The star-shaped clip is loaded onto a cap that has to be attached to the tip of the endoscope but the deployment cable remains parallel to the endoscope during intubation with the endoscope thereby leaving the working channel unoccupied.

Different TTS and OTS clip models are listed in table 1.

LIGATION

Detachable snares

Detachable snares (Endoloop, Olympus) are best suited for polyp-like lesions projecting into the lumen.

Figure 1 Deployment of the OVESCO clip: The endoscopic target is sucked into the cap, which is attached to the tip of the endoscope and preloaded with the clip. Rotating the hand wheel releases the clip which closes around the targeted tissue.

Table 1 Different clip models

Clip	Company	Opening (mm)	Characteristics
Through the scope clips (TTS)			
Resolution	Boston Scientific	11	Long retention
Quick Clip 2	Olympus	9	Rotatable
Clipmaster 2	Medwork	12	3 clips in a row
Instinct	Cook Medical	16	Rotatable, strong closing
Over the scope clips (OTSC)			
OTSC	Ovesco	11,12,14	Release mechanism through working channel
Padlock	Diagmed	11	Deployment cable parallel to scope, free working channel

They are mostly used for post-polypectomy bleedings in the colon and also for ligation of oesophageal varices, but they are rather unhelpful for flat or excavated lesions such as ulcers. However, recently, a combination of haemoclipping followed by placing a detachable snare has been reported as rescue therapy for difficult-to-control non-variceal bleeding (recurrence or primary endoscopic failure).¹⁹ Therefore, clips were positioned around the bleeding lesion and the endoloop used to contract the clips and the enclosed tissue in a purse-string fashion.

Band ligation

Endoscopic variceal band ligation is the standard-of-care method for the endoscopic management of acute oesophageal variceal bleeding and prevention of primary or secondary bleeding. In randomised controlled studies, oesophageal variceal band ligation has been shown to have fewer side effects than sclerotherapy and to achieve better bleeding control and lower re-bleeding rates.²⁰

In non-variceal bleeding, band ligation can also stop the haemorrhage in some cases; successful applications of endoscopic band ligation in cases of bleeding from angiodysplasia, Dieulafoy or Mallory–Weiss lesions have been reported.^{21–23}

More recently, endoscopic band ligation has also emerged for treatment of gastric antral vascular ectasia (GAVE).²⁴ In retrospective and prospective comparisons of patients with GAVE treated with endoscopic band ligation or argon plasma coagulation,

the ligation technique proved safe and slightly more efficient in bleeding control.^{25–27} Figure 2 illustrates a case of successful endoscopic band ligation treatment of a patient who repeatedly required blood transfusions for bleeding from GAVE.

TOPICAL SUBSTANCES

Diffuse bleeding is often difficult to treat with the established endoscopic techniques. Injection techniques have often only a temporary effect and argon-plasma-coagulation is cumbersome to apply for larger areas.

Especially in surgery, developments are aimed at topical substances for haemostasis. Topical application of thrombin, fibrin, clotting factors and also sucralfate has been reported also in endoscopic series in the past.²⁸ Now, two new topical substances, Hemospray (Cook Medical, Limerik, Ireland) and Endoclot (EPI, Santa Clara, California, USA) have been licensed for endoscopic treatment of non-variceal bleeding in Europe. Although the evidence on topical treatment using these powders is limited to prospective series while randomised controlled trials are missing, these topical substances seem to be effective for haemostasis in various types of bleeding, including difficult locations (posterior duodenal wall or lesser gastric curvature) and diffuse bleeding. The side effects and safety profile seem very favourable. The handling is very simple and does not require highly skilled endoscopic expertise, rendering the new substances very helpful also for emergency situations out of hours when skilled endoscopists may not be available.

Figure 2 Multiple band ligation for treatment of transfusion-dependent gastric antral vascular ectasia. The right image demonstrates the gastric antrum 2 months after successful band ligation treatment.

Endoclot

Endoclot is a non-toxic haemostatic powder consisting of biocompatible modified polysaccharides derived from starch, which are absorbable and undergo fast degradation. It is designed as an adjunct haemostasis tool. The ultra-hydrophilic particles are sprayed via an application catheter through the instrument channel onto the bleeding source. An air compressor propels air down the catheter, preventing catheter occlusion. The polymers rapidly absorb water from blood, causing high concentration of platelets, red blood cells and clotting factors and thereby accelerating the

clotting cascade. In contact with blood, the powder forms a gel-like barrier adhering to the mucosa and sealing the wound as well as aiding clotting.

Publications on endoscopic application of Endoclot are very rare: Huang *et al*²⁹ report haemostatic control using Endoclot in all of their 20 cases of colorectal bleeding after endoscopic mucosal resection.

The substance is available in Australia and European countries.

Ankaferd blood stopper

Ankaferd blood stopper is a plant preparation used in the traditional Turkish medicine for wound healing. It is a standardised mixture of different dried plants (liquorice, thymia vulgaris, galgant brennnessel). The powder is supposed to initiate the clotting cascade and activate the plasmatic coagulation, but the exact mechanism of action is not completely understood. Endoscopic application of Ankaferd has been reported in anecdotal cases of Mallory Weiss lesions, GAVE syndrome, anastomotic ulcers and variceal bleeding, but controlled studies are lacking.^{30–33} Ankaferd is not licensed for endoscopic haemostasis in the UK.

Hemospray (TC-325)

Hemospray (Cook Medical, Limerik, Ireland) is an inert mineral powder which has been used in military surgery for haemostasis. The powder is sprayed through a catheter onto the bleeding source using a pistol-like device with a carbon dioxide cartouche in the handle (figure 3). The substance is effective only in contact with blood, so an active bleeding needs to be present.

So far, the largest experience with hemospray comes from an European multicentre survey which reported primary haemostasis using hemospray as monotherapy in 85% of 66 patients with various upper gastrointestinal non-variceal bleedings.³⁴ Successful application of the powder to stop variceal bleeding has also been published in case reports.^{35 36}

Interestingly, the powder seems to remain only briefly in the stomach, it could not be identified in a second-look endoscopy the next day in a study reporting a primary haemostasis rate of 98.5% in 60 patients with non-variceal bleeding.³⁷

Another interesting indication for hemospray might be the treatment of diffuse tumour bleeding. In various tumour entities, hemospray has been successful with lasting effect.³⁸

Table 2 summarises the characteristics and mode of action for the different haemostatic powders.

REMOVABLE STENT

The oesophageal placement of fully covered self-expandable metal stents (SEMS) is an interesting alternative treatment to the Sengstaken balloon tamponade in patients with acute bleeding from oesophageal varices refractory to medical and endoscopic treatment. The radial forces of the self-expandable nitinol stent covered with a plastic membrane provides a standardised compression of the varices, resulting in effective haemostasis (Ella, Hradec Kralove, Czech Republic).

The stent has radiopaque markers in the middle and at the ends but is usually placed endoscopically without fluoroscopy, over a placed guide wire.^{39–43} It even can be placed similarly to the Sengstaken tube without endoscopy by positioning with a gastric balloon,⁴⁴ but the endoscopic insertion over a guide wire is preferable.

Retrieval loops at both stent ends allow the endoscopic atraumatic stent removal after 1–2 weeks via a special extractor device.

Complications observed include oesophageal ulcerations, stent migration and bronchial compression.^{41 45}

Oesophageal tamponade using SEMS can offer effective and safe but temporary haemostasis as bridging to stabilise the patient for transport into interventional centres and to organise definitive treatment such as TIPS.

Figure 3 The hemospray uses an aerosol delivery system (A) to spray the haemostatic powder towards the source of the bleed, so it does not require the accuracy needed for conventional endoscopic methods. The powder covers the bleeding point (B), absorbs the water and forms a barrier.

Table 2 Haemostatic powders

Powder	Company	Substance	Mechanism of action	Absorption
Ankaferd Blood stopper	Ilac Kozmetik AS, Turkey	Mixture of plants	Protein agglutination activating erythrocyte and leucocyte aggregation	Degradable
Hemospray	Cook Medical, Ireland	Minerals	Water absorption Concentration of platelets and clotting factors Tamponade	Inert Non-degradable
EndClot	EPI	Polysaccharides	Water absorption Tamponade Concentration of platelets and clotting factors	Absorbable

In conclusion, many new haemostatic techniques are evolving. The topical application of haemostatic powders appears promising but larger controlled studies are needed to confirm the haemostatic efficacy of sprayed powders in AUGIB.

The optimal choice of the endoscopic technique for haemostasis depends on the type of the bleeding source, the endoscopist's skills, the available equipment, the patient's clinical condition and costs.

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