Current endoscopic and pharmacological therapy of peptic ulcer bleeding

Lars Aabakken*
Chief of GI endoscopy
Rikshospitalet University Hospital, N-0027 Oslo, Norway

Peptic ulcer bleeding is the most significant complication of ulcer disease, remaining the most important reason for upper gastrointestinal bleeding even in the era of Helicobacter eradication. Endoscopic triage and management plays a vital role in the handling of these patients, albeit in close collaboration with radiological and surgical expertise.

Injection therapy, preferably with large volume epinephrine remains a core technology. Histoacryl and fibrin glue are more costly and less widely adopted alternatives.

Mechanical measures are attractive and clips offer an excellent solution, particularly in soft tissues, and in combination with initial injection. Thermal methods with coagulation and coaptive axial force have similar performance characteristics. Increasingly, the combination of injection therapy with either a mechanical or thermal method appears the best option to achieve permanent haemostasis. PPIs for potent acid inhibition improves the clotting regardless of other treatment modalities. In the setting of rebleeding, patient and ulcer factors determine whether repeat endoscopy should be attempted, but the surgeon should be close at hand in this situation.

Key words: APC; coagulation; endoscopic haemostasis; injection therapy; proton-pump inhibitor; recurrent bleeding; ulcer bleeding; haemoclips.

INTRODUCTION

Gastroduodenal ulcer disease is the commonest cause of upper gastrointestinal bleeding (Table 1). Ulcer disease is responsible for close to 50% of admissions caused by acute upper GI bleeding.1,2 Despite extensive eradication of Helicobacter pylori, the rate of ulcer bleeding appears almost unchanged, (40–60/100 000/year).1,3 However, the epidemiology is changing, with an increasing rate of HP-negative ulcers, particularly in Western countries. Partly, the rate of drug-induced ulcers, with a more malignant clinical course, is increasing, partly, it appears that the HP eradication era in particular...
has addressed the uncomplicated gastroduodenal ulcerations, leaving the rates of com-
plicated ulcers (bleedings and perforations) largely unchanged. Consequently, the mor-
tality has been almost constant at a rate of seven to 10%. Mortality from peptic ulcer
predominantly occurs in elderly patients with comorbidities.

In patients with ulcers presenting with ongoing bleeding or high risk features
(Forrest I, IIa, IIb), surgery was frequently required in the past to solve the situation.
However, endoscopic therapy has been well documented to treat these ulcers, obviating
the need for surgical therapy in all but the most dramatic situations.

It is, however, important to acknowledge the partial role of endoscopy in the situ-
aton of an acute upper GI bleeding. General care, endoscopy, surgery and radiological
service with selective embolisation all address specific critical needs that these patients
may present, and a multidisciplinary panel of expertise is required to offer the optimal
treatment. This is an important message, even though the rest of this chapter will
focus on the endoscopic options available.

INDICATIONS FOR ENDOSCOPY AND ENDOSCOPIC THERAPY

Along with initial resuscitation and monitoring of the patient with an acute upper GI
bleed, endoscopy plays an important role in the early handling. This comprises partly
triage to determine the subsequent level of care (out-patient, general ward, intensive
care), partly a precise diagnosis, and partly (optional) endoscopic therapy. These are all
vital elements in the initial endoscopy, usually integrated in a single endoscopic proce-
dure. Based on endoscopic findings and results of the therapy, the subsequent handling
can be precisely planned, and the prognosis can be more precisely conveyed to the
patient and the subsequent care-takers.

The timing of the initial endoscopy has been debated. In general, red hematemesis
indicates emergency upper endoscopy, while black hematemesis and/or melena with-
out haemodynamic instability can wait until normal working hours. However, from
a logistic point of view, early endoscopy has been advocated to ensure optimal utilisa-
tion of resources, since a normal upper endoscopy – or a clean ulcer base – in a stable
patient may justify prompt discharge of the patient. This type of early triage requires
access to prompt endoscopy around the clock, but may easily be economically justifi-
able as well as an excellent service to the patient. Lee et al were able to demonstrate
that a strict algorithm with discharge of the patient based on low risk endoscopic stig-
mata was associated with a significant lowering of hospital cost, without any adverse

### Table 1. Causes of gastrointestinal bleeding in the US (adapted from ref. 1).

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duodenal ulcer</td>
<td>24.3%</td>
</tr>
<tr>
<td>Gastric erosions</td>
<td>23.4%</td>
</tr>
<tr>
<td>Gastric ulcer</td>
<td>21.3%</td>
</tr>
<tr>
<td>Varicose</td>
<td>10.3%</td>
</tr>
<tr>
<td>Mallory–Weiss tear</td>
<td>7.2%</td>
</tr>
<tr>
<td>Oesophagitis</td>
<td>6.3%</td>
</tr>
<tr>
<td>Erosive duodenitis</td>
<td>5.8%</td>
</tr>
<tr>
<td>Neoplasm</td>
<td>2.9%</td>
</tr>
<tr>
<td>Misc</td>
<td>10.3%</td>
</tr>
</tbody>
</table>
events occurring in the discharged patients. Even if discharge is not always practical in the middle of the night, triage results may help choose the correct level of care within the hospital. However, a benefit from such triage requires strict adherence to the recommendations given – otherwise, ‘negative’ triage results does not help reducing the costs. Finally, as an added potential benefit, early endoscopy increases the chance to identify an intermittent haemorrhage from an obscure focus.

When the endoscopic procedure reveals a peptic ulceration as the likely source of bleeding, the subsequent handling is traditionally based on the Forrest classification of the lesion (Table 2). It has been shown convincingly that the risk of rebleeding is closely related to this classification. Active bleeding (Forrest Ia) carries a risk of recurrent bleeding of 55% and a mortality of 11%, while the corresponding numbers for an ulcer with a clean base is five and two percent, respectively (Figure 1).

More recent attempts on risk stratification have expanded the number of clinical parameters included in the calculations. Gugliemi and co-workers added information on liver cirrhosis, recent surgery, systolic blood pressure below 100 mmHg, hematemesis, and ulcer size to group the patients into four risk groups. The rebleeding rates of the four groups were zero percent, eight percent, 32% and 68% and the mortality six percent, nine percent, 14% and 36%, respectively. After 5 days, the residual risk of rebleeding was below four percent in all classes.

After deciding that the ulcer is likely to rebleed, but before initiating the endoscopic therapy, the surgeon on call should be notified. Sometimes, a stable situation can be acutely aggravated by manipulation of the ulcer, particularly in the distal duodenal bulb. If this happens, emergent access to the operating theatre is a prerequisite, in addition to ample intravenous access and cross-matched blood. Failure to consider these precautions prior to initiating endoscopic therapy can be fatal.

Selecting your tool for haemostasis is not trivial, as a host of different techniques are presently available (Table 3). Assessment and comparison of the various modalities is very difficult, and many of the available comparative studies are flawed by selective expertise and/or preferences. Taken together, it is very difficult to make out consistent ‘winners’ between the various methods. Thus, local preference, expertise and availability will be major determinants in the choice of method. It is becoming increasingly clear that combinations with a mechanical method may be preferable to injection therapy alone, otherwise, no clear recommendations can be given at this point. Accordingly, the following will describe the various methods available and comment on their utility and shortcomings, without focusing too much on head-to-head comparisons.

Common to all the methods of endoscopic haemostasis are some general principles: The stomach must be cleansed, and residual blood clots removed or flushed away. A large bore tube is often effective to accomplish this, and should be done if

<table>
<thead>
<tr>
<th>Grade</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>Arterial spurting</td>
</tr>
<tr>
<td>IB</td>
<td>Active oozing</td>
</tr>
<tr>
<td>IIA</td>
<td>Ulcer with non-bleeding visible vessel</td>
</tr>
<tr>
<td>IIB</td>
<td>Ulcer with adherent clot on surface</td>
</tr>
<tr>
<td>IIC</td>
<td>Ulcer with red or dark blue flat spot</td>
</tr>
<tr>
<td>III</td>
<td>Ulcer with clean base</td>
</tr>
</tbody>
</table>

Table 2. Forrest classification of peptic ulcer bleeding.
the initial endoscopic view shows substantial particular or coagulated gastric contents. Alternatively, a large channel (6 mm) endoscope can be used. Erythromycin 250 mg IV 20–40 min prior to the endoscopy may sometimes help evacuate gastric content as well and has been advocated as a routine measure in patients with hematemesis.11,12

Figure 1. Forrest classification of ulcer bleeding: (a) Ia – spurting, (b) Ib – oozing, (c) IIa – Visible vessel, (d) IIb – Adherent clot, (e) Iic – Flat spot, (f) III – clean ulcer base.
In our practice, this is only used in situations where the initial endoscopy failed due to non-removable gastric content before the procedure is repeated.

When the ulcer is covered with a clot, precise visualisation and targeting of therapy is difficult. Therefore, most experts advocate removal of such clots, ideally by flushing or catheter manipulation, but – if needed – with the use of forceps or a snare. Before such removal, the ulcer base should be injected through the clot with dilute epinephrine (1:10 000) (see below) to minimise the risk of initiating bleeding when the clot is removed.

**INJECTION THERAPY**

The principle of injection therapy is to create a combination of hydrostatic pressure, tissue oedema, vasoconstriction and inflammatory changes in the region of the ulcer, with acute as well as more long-lasting effects. It is technically by far the easiest method to learn and implement, and although injections must be precise, direct visualisation at the time of injection and angulation/position of the endoscope are less critical factors. Acute angulation of the tip of the endoscope also don’t affect the efficacy of the injection, and one injection rarely reduces the feasibility to make another.

However, standard injection therapy with saline or epinephrine offers only ‘relative’ haemostasis, with most of the effects disappearing rather rapidly, as the fluid dissipates from the region of interest. Also, injection is notoriously difficult in a firm fibrinous ulcer base, and injections must instead be placed at the anticipated location of the feeding vessel going into the ulcer.

**Epinephrine**

Diluted epinephrine (1:10 000) is the most widely available and used injection substance. Administration is done by a normal sclerotherapy needle, and the effect is thought to be exerted through a combination of tamponade and vasoconstriction. Large volumes are often needed to achieve haemostasis, and in one study, Park et al. documented that injection of 35–45 mL of a 1:10 000 solution of epinephrine

<table>
<thead>
<tr>
<th>Table 3. Endoscopic modalities for treating bleeding peptic ulcers.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection therapy</td>
</tr>
<tr>
<td>• Saline/sterile water</td>
</tr>
<tr>
<td>• Epinephrine</td>
</tr>
<tr>
<td>• Hypertonic solutions</td>
</tr>
<tr>
<td>• Sclerosants (polidocanol, absolute ethanol)</td>
</tr>
<tr>
<td>• Cyanoacrylate</td>
</tr>
<tr>
<td>• Fibrin glue</td>
</tr>
<tr>
<td>Mechanical treatment</td>
</tr>
<tr>
<td>• Clipping</td>
</tr>
<tr>
<td>• Suturing</td>
</tr>
<tr>
<td>Thermal treatment</td>
</tr>
<tr>
<td>• Bipolar electrocoagulation</td>
</tr>
<tr>
<td>• Heater probe thermal coagulation</td>
</tr>
<tr>
<td>• APC</td>
</tr>
</tbody>
</table>

In our practice, this is only used in situations where the initial endoscopy failed due to non-removable gastric content before the procedure is repeated.

When the ulcer is covered with a clot, precise visualisation and targeting of therapy is difficult. Therefore, most experts advocate removal of such clots, ideally by flushing or catheter manipulation, but – if needed – with the use of forceps or a snare. Before such removal, the ulcer base should be injected through the clot with dilute epinephrine (1:10 000) (see below) to minimise the risk of initiating bleeding when the clot is removed.

**INJECTION THERAPY**

The principle of injection therapy is to create a combination of hydrostatic pressure, tissue oedema, vasoconstriction and inflammatory changes in the region of the ulcer, with acute as well as more long-lasting effects. It is technically by far the easiest method to learn and implement, and although injections must be precise, direct visualisation at the time of injection and angulation/position of the endoscope are less critical factors. Acute angulation of the tip of the endoscope also don’t affect the efficacy of the injection, and one injection rarely reduces the feasibility to make another.

However, standard injection therapy with saline or epinephrine offers only ‘relative’ haemostasis, with most of the effects disappearing rather rapidly, as the fluid dissipates from the region of interest. Also, injection is notoriously difficult in a firm fibrinous ulcer base, and injections must instead be placed at the anticipated location of the feeding vessel going into the ulcer.

**Epinephrine**

Diluted epinephrine (1:10 000) is the most widely available and used injection substance. Administration is done by a normal sclerotherapy needle, and the effect is thought to be exerted through a combination of tamponade and vasoconstriction. Large volumes are often needed to achieve haemostasis, and in one study, Park et al. documented that injection of 35–45 mL of a 1:10 000 solution of epinephrine
was more effective than injection of 15–25 mL of the same solution, with fewer re-bleedings, although initial haemostasis was achieved in almost all patients, a surprisingly good result with injection therapy alone. For bleedings in the antrum, the rebleeding rate was zero percent versus 32% \( (p = 0.003) \). All patients received proton pump inhibitors throughout the observation period and \textit{Helicobacter pylori} was eradicated when documented. They observed no cardiological side effects from the large volume of epinephrine, speaking against this as a risk to be considered.

Another study\(^{14}\) looked at two smaller volumes (5–10 ml vs 13–20 ml). Although it is difficult to compare across studies, the rebleeding rates in this study (31% for 8 ml vs 15% for 16 ml) still indicates that lower volumes were less likely to offer acceptable permanent haemostasis. It is likely that with injection of ‘inert’, non-inflammatory substances as single treatment, large volumes are preferable. Normal saline, distilled water and glucose have all been advocated as viable alternatives to adrenalin, assuming that the haemostatic effect primarily is related to the tamponade effect. Furthermore, one might argue that the vasoconstrictor component of the adrenalin is short-lived and could mask a potential for rebleeding. In a recent comparative study, Liou et al\(^{15}\) studied saline versus adrenalin and a combination of the two for actively bleeding ulcers. Initial haemostasis was significantly lower in the normal saline group (88% vs 99%), and larger volumes of fluid were needed when saline was used, causing a more lengthy procedure. They found, however, that the rate of rebleeding was similar in the three groups, and recommended that combination injection of large volumes (40 ml) with initial epinephrine for haemostasis followed by normal saline be the preferable option, offering rebleeding rates of \(<5\%\) without noticeable side effects or technical complications.

\textbf{Polidocanol and sclerosing agents}

The use of sclerosants for non-variceal bleeding is declining, but should still be considered a valuable method, offer a cheap, easy and well documented means of treating bleeding lesions. With increasing access to mechanical of thermal methods, however, the use will probably be limited further. Polidocanol is a sclerosing agent, inducing inflammatory changes at the injection site. This feature is shared by other substances including ethanolamin-oleat, high-concentration alcohol and hypertonic glucose, but polidocanol is most widely applied, though primarily in the context of oesophageal varices.

The technique of injecting sclerosing agents is relatively straightforward. For non-bleeding vessels, the sclerosing solution is injected in small increments, usually 0.1–0.3 ml per injection at 3–4 sites around the visible vessel. Then, the vessel itself may also be injected. A total of two millilitres of fluid should rarely be exceeded.

Most clinical studies, particularly in the treatment of actively bleeding vessels, apply the sclerosant in combination with epinephrine, either as a subsequent injection, or as a mixture of the two. In theory, this would ensure sustained haemostasis through inflammation, thrombosis and scarring of the bleeding vessel. On the other hand, sclerosants are known to cause transmural necrosis, and injections in the upper half of the stomach is contraindicated in several countries due to the risk of late perforations at the injection site\(^{16}\) cited to be one percent\(^{17}\) with polidocanol, as well as with ethanol as sclerosing agent. There are few randomised comparative studies demonstrating the added utility of mixing or finishing off the injection therapy with a small volume of a sclerosing agent, but Lin et al compared prospectively the effect of endoscopic
injection with normal saline, three percent NaCl solution, 50% glucose/water solution, and pure alcohol during a period of 2 years. They were unable to detect any difference in initial haemostasis, rebleeding rate, emergency surgery or hospital stay. Nevertheless, this practice is widely adopted, in particular in situations where injection therapy is used without the addition of any mechanical modality. In the antrum and prepyloric region, as well as in the duodenal bulb, the risk of transmural necrosis is probably smaller than in the fundus of the stomach, and small volumes of a sclerosant (1–2 ml) are unlikely to cause significant complications.

**Cyanoacrylate**

N-butyl-2-cyanoacrylate (Histoacryl) is a tissue adhesive with a variety of medical applications. It is regularly used for the treatment of gastric varices, at least in Europe, while its role in bleeding peptic ulcers is more undetermined. Technically, the 0.5 ml of the Histoacryl glue is mixed with e.g. 0.8 ml Lipiodol contrast medium, and injected in small boluses directly into the bleeding vessel, after pre-filling the lumen of the needle with sterile water. After injecting the glue, subsequent sterile water boluses are used to empty the residual glue in the needle. The substance hardens very rapidly, and there is an inherent risk of damage to the endoscope, as well as to the operator and patient, if the glue is inadvertently dispersed. Moreover, the glue/lipiodol mixture is viscous, offering considerable resistance to injection. Care must be taken to screw the injection cannula securely onto the injection needle before application. Also, the procedure must be done quickly to avoid premature solidification of the glue.

In a study comparing Histoacryl to saline/epinephrine injections, 126 patients with bleeding or non-bleeding visible vessels were randomised. Initial haemostasis was achieved in 92% and 95% of patients, with marginally more rebleeding in the epinephrine group. In actively bleeding ulcers, the benefit of Histoacryl was more undisputable. Two cases of arterial embolisation did, however, occur in the Histoacryl group, with fatal outcome in one. Because of this rare but feared complication, most authors advocate the use of this substance only as a last resort before surgery. The substance is unavailable in several countries, including the US, for the same reason.

**Fibrin glue**

Injecting a two-component solution converting itself to fibrin in the injected tissue has been an available method for more then 15 years. Theoretically, it is an attractive principle, offering a 'physiological' haemostasis with minimal side effects. The substance is injected by a special dual-channel needle, where fibrinogen and activator is mixed on its way into the tissue. The technique is simple in principle, but because of the quick solidification of the fibrin and the complex design of the needle, there are still practical caveats to the method. Moreover, the substance is relatively expensive.

Song et al\(^\text{20}\) conducted a randomised comparison to epinephrine injections in 127 patients with bleeding ulcers or visible vessels. Although there was a tendency to better primary haemostasis and less rebleeding, there was no significant difference between the two groups.

Pescatore et al\(^\text{21}\) compared epinephrine with epinephrine plus fibrin glue in another trial of 135 patients, where the initial rate of haemostasis was 100% in both groups. Recurrence of bleeding did however occur in a little over 20% in both groups, with no added utility of the fibrin glue.
Finally, a large European multicentre study headed by Rutgeerts et al\textsuperscript{22} addressed the possibility of repeated fibrin glue injections, compared to single injections with fibrin glue or polidocanol. All patients were pre-treated with epinephrine. Injections were repeated until visible vessels disappeared. A total of 790 patients were randomised to the three groups. The rebleeding rate was 23\%, 19\% and 13\% in the polidocanol, single fibrin and repeated fibrin groups, respectively, a marginally significant benefit of repeated fibrin compared to polidocanol. However, final outcome did not differ in the three groups, and the added utility of an expensive and cumbersome scheme is questionable. Also, the relevant comparison between repeated polidocanol and repeated fibrin glue was not made.

At present, fibrin glue represents a safe and available option in difficult cases, but there is no solid evidence to justify widespread use of the substance for this indication.

**MECHANICAL THERAPY**

Mechanical measures to stop ulcer bleeding mimic surgical principles, and offer the most reassuring means to occlude a bleeding vessel. The current range of available technology is limited to variants of clips, but it is expected that the NOTES development will offer various endoscopic means of suturing which will eventually be applicable also to ulcer bleeding. At present, one of the technologies closest to realisation is the anchoring technique,\textsuperscript{23} which applies small metal anchors to either side of a lesion, then approximates the two with a thread lock tying the two anchored threads together. Surely, more ingenious solutions will emerge, replacing the initial cumbersome and less effective contraptions developed for anti-reflux procedures.

**Clips**

In the meantime, clips offer an excellent opportunity to provide instant mechanical clamping of bleeding or non-bleeding vessels. Various models are available, the latest development featuring the ‘Resolution clip’ (Microvasive Endoscopy, Boston Scientific Corp, Natick, Mass) which can be reopened and repositioned, much like a biopsy forceps (Figure 2), and the ‘InScope Multi-Clip Applier’ (IMCA) (InScope, a division of Ethicon Endo-Surgery, Cincinnati, OH), which can fire multiple clips, and also reopen

*Figure 2. The ‘Resolution clip’ allows reopening of the clip prior to release for more accurate positioning.*
and realign for better tissue approximation. Both are significant improvement on previous single attempt clips, although those are cheaper and quite often sufficient.

Clips are most easily placed on small, soft lesions, typically Dieulafoy-lesions, where the tissue can indeed be approximated by the clip (Figure 3). Conversely, the stiff, fibrinous base of a typical peptic ulcer is sometimes difficult to negotiate. Care must also be taken not to clip off a visible vessel stump, initiating bleeding during the procedure. To avoid this, it would be considered prudent to inject epinephrine into the ulcer base where subsequent clipping is planned.

Clipping is easiest when the endoscope can be kept in a straight position, with the possibility of axial push into the tissue. Tangential access to the lesions sometimes results in poor anchoring of the clip in the gastric wall. The fundic region can also be a challenge, because the firing mechanism is often weakened when the scope tip is retroflexed. Clips also work poorly through the working channel of a duodenoscope, and the elevator must be minimally engaged to allow release of the clip.

Most clips slough off within days or 1–2 weeks. However they can occasionally remain for months. From personal experience, clipping narrow regions (cardia, distal duodenal bulb) in haemophiliacs can sometimes induce subsequent mechanical trauma to the adjacent mucosa with secondary bleeding problems.

A Japanese group\(^2\) compared the performance of 1st generation clips to sclerosant treatment or a combination in a randomised study of 126 patients. An average of 3 clips were used in each treatment session. Initial haemostasis was achieved in all patients, and permanent haemostasis in 90% (clips only) and 93% (clips + injection). Clips compared favourably to ethanol injection alone in this study, although no difference in mortality was seen. Combining the two appeared to yield little additional benefit. In a comparison to distilled water injection, initial haemostasis was similar, but the rebleeding rate was higher with distilled water.\(^2\)\(^5\) Two more randomised studies\(^2\)\(^6\),\(^2\)\(^7\) verify the impression that rebleeding is less frequent with clips than with various injection methods alone although initial haemostasis is excellent with all methods.

Comparisons to thermal methods are somewhat more mixed.\(^2\)\(^8\),\(^2\)\(^9\) Taken together, these two randomised series indicate equality between the procedures for all clinically relevant parameters.

An increasing body of evidence indicates that combining injection therapy with another modality, e.g. clipping, offers superior results. Lo et al\(^3\)\(^0\) randomised 105 patients

---

Figure 3. (a) Oozing bleeding from a small ulceration, (b) haemostasis after application of two haemoclips.
to epinephrine injection alone or a combination with clipping. Rebleeding occurred in 21% vs four percent ($p = 0.008$). Among the patients with rebleeding, repeated combination therapy was more effective than repeated injection therapy in achieving permanent haemostasis (100% vs 33%, $p = 0.02$). No patient required an emergency operation in the combination therapy group. However, 5 patients in the epinephrine injection group underwent emergency surgery to arrest bleeding (zero percent vs nine percent, $p = 0.023$). A recent Cochrane review confirms the results of this study.\(^\text{31}\) In their metaanalysis of 1763 patients, adding a second procedure reduced further bleeding rate from 18.8% to 10.4%; OR 0.51; 95% confidence interval (CI) 0.39–0.66, and emergency surgery from 10.8% to 7.1%; OR 0.63; 95% CI 0.45–0.89. Mortality fell from five percent to 2.5% OR 0.50; 95% CI 0.30–0.82. Subanalysis showed that the risk of further bleeding decreased regardless of which second procedure was applied. In addition, the risk was reduced in all subgroups.

Clipping high risk lesions that may eventually need angiographic treatment with embolisation offers the added utility of marking the lesion. The clip is easily seen on X-ray, guiding the radiologist in locating the offending vessel.\(^\text{32}\)

**THERMAL THERAPY**

Heating the bleeding tissue to coagulation, with or without the combination of appositional pressure, is another viable modality to treat bleeding peptic ulcer. This is to be regarded as another mechanical modality, that according to the Cochrane review should be combined with epinephrine injection to achieve the best end result.

**Heater probe**

The heater probe generates coagulating heat at the tip of a multiple use catheter connected to a simple heat-generating device (Olympus Optical, Tokyo, Japan). The combination of pressure to co-apt the vessel walls and heat to coagulate the tissue offers effective haemostasis in most ulcer bleedings. During therapy, the distal tip of the heater probe is applied directly to the bleeding site. Initially, four to five pulses of 30 J/pulse are given. If bleeding persists, the procedure is repeated. Finally, several pulses of 15–20 J/pulse are given surrounding the bleeding site (Figure 4).

The heater probe compared favourably with clipping in a randomised trial from Taiwan.\(^\text{29}\) Initial haemostasis was achieved in all 40 patients in the heater probe group, compared to 85% in the haemoclip group. However, rebleeding and other parameters were similar. This and several other studies primarily show good performance and comparable results for all the mechanical modalities for haemostasis. Personal preference and expertise probably affects results more than any minor differences between the methods.

**Gold probe**

The gold probe (Microvasive Endoscopy, Boston Scientific Corp, Natick, MA) is a combination catheter that includes an injection needle as well as a bipolar electrocoagulation device. Small bursts of diathermic energy is delivered through the tip coils of the catheter while the tip is pressed into the ulcer base, at the vessel, as well as in a circular fashion adjacent to the visible vessel or bleeding point. The added utility of this particular instrument is the possibility to inject with the same tool, obviating the need to switch catheters between the two components of the treatment. Lin looked at this
tool in comparison with epinephrine injection\textsuperscript{33} and found that the rebleeding rate was significantly less (seven percent vs 30\%) and transfusion requirements were lower in the gold probe group, although hospital stay duration and mortality did not differ. A similar study from Europe came to the same conclusion.\textsuperscript{34}

**APC**

Argon plasma coagulation has more recently been introduced as a modality even for bleeding peptic ulcers. It is traditionally being used for other gastrointestinal haemorrhages and thermal ablation of minor mucosal pathology, but it appears that the thermal energy, though superficial and not combined with mechanical pressure, still can be successfully utilised in the setting of ulcer bleeding. The advantage is the safety, ease of use and the availability in most endoscopy units.

A randomised, controlled study comparing APC with heater-probe coagulation,\textsuperscript{35} suggested that APC is equally as safe and effective. In both groups of patients, epinephrine injection was administered before thermal treatment. Of 185 cases analysed, 97 were in the heater-probe group and 88 in the APC group. No significant differences

\textbf{Figure 4.} Heater probe treatment of a small ulcer bleeding: (a) before treatment, (b) approximation of the heater probe, (c) final result.
were detected in terms of initial haemostasis at index endoscopy, frequency of recurrent bleeding, requirement for emergency surgery, number of units of blood transfused, length of hospital stay, and mortality rate. Another comparison to sclerotherapy showed similar results, and a Cochrane review concluded that APC was similar to other endoscopic therapies for non-variceal upper GI bleeding.

PHARMACOLOGICAL THERAPY

Platelet aggregation is impaired in acidic environments, hence blood clots that form on the surface of peptic ulcers are unstable. In the stomach, an almost complete shutdown of gastric secretion is required to facilitate platelet aggregation and clot formation. Increasingly, the acid inhibition offered by H2-antagonists has been shown to be suboptimal in the context of acute upper gastrointestinal bleeding. Proton pump inhibitors are consistently more effective in keeping the gastric pH constantly below 4.0, and are increasingly advocated in all kinds of ulcer treatment, albeit as an adjunct to initial endoscopic therapy.

Proton pump inhibitors

Proton pump inhibitors (PPIs) can be given perorally or intravenously, but are usually administered intravenously in the setting of acute bleeding, obviating the need for peroral medication. Initial studies reported conflicting results in terms of the efficacy of this strategy, but increasingly, evidence suggests that potent acid inhibition is indeed an effective adjunct to endoscopic therapy.

In a material from India, Khuroo was able to show this in 220 patients, randomised to receive either oral omeprazole 40 mg twice daily or placebo for 5 days after endoscopic confirmation of a bleeding ulcer or visible vessel. Seventeen patients with non-bleeding visible vessel or a clot were less likely to have further bleeding. A reduction in recurrent bleeding was not evident in those patients with ulcers with spurting or oozing haemorrhage who were given oral omeprazole. In ulcers that stopped bleeding spontaneously, acid suppression again seemed to prevent recurrent bleeding.

More solid data were presented by Lau et al using intravenous omeprazole. After haemostasis had been achieved, 240 patients were randomly assigned in a double-blind fashion to receive omeprazole (given as a bolus intravenous injection of 80 mg followed by an infusion of 8 mg per hour for 72 h) or placebo. After the infusion, all patients were given 20 mg of omeprazole orally per day for eight weeks. The primary end point was recurrent bleeding within 30 days after endoscopy. Bleeding recurred within 30 days in 8 patients (6.7%) in the omeprazole group, as compared with 27 (22.5%) in the placebo group. Most episodes of recurrent bleeding occurred during the first three days, which made up the infusion period (5 in the omeprazole group and 24 in the placebo group, \( p < 0.001 \)).

The evidence concerning acid inhibition in the context of bleeding ulcers was collected in a recent Cochrane publication. A total of 24 randomised controlled trials comprising 4373 patients were included in their metaanalysis. All cause mortality was unaffected by the pharmacological intervention, but several other endpoints indicate an effect related to potent acid inhibition. PPIs significantly reduced rebleeding compared to control; pooled rates were 10.6% with PPI versus 17.3% with control treatment. The need for surgery was also significantly reduced, and for both parameters, PPIs were superior to H2-antagonists.
The timing of PPI co-therapy is still debated. Keyvani\textsuperscript{41} was able to show a benefit of pre-endoscopy acid inhibition on a variety of clinical parameters. However, a more recent Cochrane review on this topic\textsuperscript{42} concluded that PPI treatment initiated prior to endoscopy in patients with upper gastrointestinal bleeding significantly reduces the proportion of patients with stigmata of recent haemorrhage at index endoscopy, but without affecting important outcomes, namely mortality, rebleeding or need for surgery.

In our practice, except in known variceal bleeding, PPI treatment is initiated on admission of patients with acute upper gastrointestinal bleeding, alongside the clinical assessment and stabilisation of the patient. Verification of the offending lesion is not critical before starting the treatment, as all of them will benefit from stable clots. If other lesions than ulcers are found, e.g. Mallory–Weiss-lesions or haemorrhagic gastritis, PPIs would probably be beneficial even in lower doses, but no evidence exists for this option. For ulcers, healing is probably accelerated, and the odds of appropriate visualisation and exact targeting of the bleeding vessel are improved. However, evidence is still needed to support this strategy, and cost-effectiveness data are completely lacking.

**SOMATOSTATIN**

Somatostatin inhibits both acid and pepsin secretion and combines these effects with a reduction in gastroduodenal mucosal blood flow which seems to be important in the pathophysiology of peptic ulcer bleeding. Additionally, the inhibition of pepsin secretion might induce a decreased proteolytic activity preventing the dissolution of freshly formed clots at the site of bleeding.\textsuperscript{43} Thus, the drug offers a combination of physiological effects that should theoretically be highly beneficial in the setting of peptic ulcer bleeding. However, clinical data typically fail to support this concept, including a recent randomised comparison between somatostatin (250 mg/h for 48 h after a bolus of 250 mg) and pantoprazol (8 mg/h for 48 h after a bolus of 40 mg). In 164 patients, Tsibouris et al\textsuperscript{44} found a similar acid inhibition, but a higher rebleeding rate with somatostatin, although no difference was seen in mortality of need for surgery.

With the presently available data, there is no compelling evidence to replace PPI-based acid inhibition with somatostatin infusion in peptic ulcer bleeding.

**REBLEEDING AND REPEAT ENDOSCOPY**

Clinical recurrence of bleeding must be expected in 10–20% of patients regardless of initial success. In this situation, the endoscopist must decide whether to repeat endoscopic attempts or refer the patient to surgery or radiological intervention directly. It is difficult to find strong support in the literature for a fixed strategy, probably because the decision must be strongly related to the character of the ulcer, the technicalities of the first attempt, as well as the expertise of the endoscopist repeating the procedure. Lau et al.\textsuperscript{45} analysed the results in 48 patients who underwent endoscopic re-treatment, in comparison to 44 patients randomised to surgery directly. In their material, long-term haemostasis was achieved in 35 patients after a single repeat endoscopy procedure, while 13 required emergent surgery. Ulcer perforation occurred in two patients, in association with repeated thermal coagulation, both requiring surgery. Of 44 patients assigned to surgery, 22 underwent gastrectomy, which was associated with greater morbidity. The two groups did not, however, differ in regard to mortality rate. In a logistic regression analysis, ulcers larger than two centimetres in diameter and hypotension at the time of rebleeding were two independent factors that predicted failure of
endoscopic retreatment. The findings of Lau et al. suggest that, in the management of patients with recurrent bleeding after initial endoscopic control, a selective approach can be adopted based on the characteristics of the ulcer and the patient. Large ulcers, particularly in the distal duodenal bulb, should probably be treated by surgery if bleeding recurs. Those who are poor surgical candidates might benefit from repeated endoscopic treatment, but the strain on e.g. patients with cardiovascular co-morbidity of repeated severe hypotension and anaemia due to several failed endoscopies should also be considered. Some of these patients may still be better off with expedite surgery. A close collaboration with the surgeon in question is warranted, and he should be present during the endoscopy if at all possible. This way, the decision for further handling can be done in an even more qualified way and the subsequent surgery will be facilitated by hands-on knowledge of the anatomy of the ulcer. Along the same cross-disciplinary lines, the interventional radiologist should be on board in these discussions, to select the patients that would be available for embolisation therapy. This topic is discussed further by the chapter by Dr Gouma elsewhere in this issue.

**CLINICAL ALGORITHM**

The specific handling of a patient with a suspected bleeding peptic ulcer at the individual hospital is depending on the local expertise and facilities for this group of patients. The algorithm suggested in Figure 5 requires access to expert endoscopy treatment as

![Figure 5. Suggested flowchart for handling of acute upper gastrointestinal bleeding.](image_url)
needed. The utility of urgent surgery or radiology services again depends strongly on logistics, as well as expertise available within each field. The role of PPIs is still debated, thus, the pre-endoscopy initiation of such treatment can justifiably be delayed till the result of the endoscopy. HP treatment is relevant in all ulcers that are HP positive, but initiation of the eradication treatment usually awaits clinical stabilisation of the patient.

CONCLUSION

Endoscopy is a core method in the handling of peptic ulcer bleeding, for assessment and triage, as well as for treatment. A variety of methods have been established, all with clinical utility. Many methods merit similar success, and for the individual endoscopist it is reasonable to focus on a few. A combination of epinephrine injection therapy with one of the mechanical or thermal modalities appear to offer the best chance of permanent haemostasis. However, the options of radiologic or surgical treatment should be considered, in particular in the context of rebleeding.

Practice points

- Peptic ulcer bleeding is the most important cause of upper GI bleeding.
- Urgent endoscopy allows triage and assessment, as well as endoscopic treatment of peptic ulcer bleeding.
- Large volume epinephrine injection therapy should be attempted initially in most ulcer bleedings.
- Combinations of injection therapy with a mechanical and thermal methods are preferable to a single method approach.

Research agenda

- Optimal timing, duration, administration and dosage of acid inhibition should be determined.
- Utility of endoscopic re-treatment electively or on rebleeding needs clarification.
- Improved suturing devices should be developed and tested in the context of peptic ulcer bleeding.

REFERENCES


