



# New haemostatic techniques: histoacryl injection, banding/endoloop ligation and haemoclipping

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New endoscopic modalities for the haemostasis of upper gastrointestinal bleeding include cyanoacrylate tissue glue injection for oesophageal and gastric varices, ligation using bands and loops for variceal and non-variceal bleeding, and clips for non-variceal bleeding. These new modalities aim to improve primary and secondary haemostasis rates and the safety of endoscopic treatment. Preliminary experience using these modalities has been encouraging, but prospective randomized trials using adequate patient numbers are still needed to validate their efficacy and safety. The choice of treatment will depend on the clinical context and the anatomy of the bleeding lesion. Cyanoacrylate injection, which achieves rapid haemostasis and obliteration of the treated varix, is ideally suited to acute variceal bleeding and the obliteration of large gastric varices. Bands and loops are used in conjunction with a transparent cap attachment for the elective treatment of oesophageal varices. The clip is most effective when a vessel from a non-variceal bleeding source can be identified.

*Key words:* haemostasis; ulcer bleeding; variceal bleeding; cyanoacrylate; tissue glue; Histoacryl; endoscopic ligation; banding; loop; endoloop; miniloop; clip; haemoclip.

Several new endoscopic haemostatic modalities have been introduced over the past decade. These include Histoacryl injection, ligation therapy using rubber bands and endoloops, and haemoclips. These modalities aim to improve haemostasis rates and the safety of endoscopic treatment. Preliminary experience using these techniques has been encouraging. Prospective randomized trials with adequate sample sizes are needed to validate the efficacy and safety of these newer haemostatic methods. For each of the modalities, the instrument, technique, benefits and risks are discussed.

## HISTOACRYL

### Instrument

N-butyl-2-cyanoacrylate (Histoacryl, Braun Melsungen, Germany) is a unique watery substance that polymerizes and hardens within seconds of its contact with

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a physiological medium such as blood. This remarkable property makes it an attractive agent for achieving rapid haemostasis of bleeding lesions, especially varices. When instilled directly into the varix lumen using the standard method of intravariceal injection, Histoacryl solidifies and permanently occludes the vessel lumen. This not only arrests active bleeding, but also prevents rebleeding from the treated varix.

#### Technique

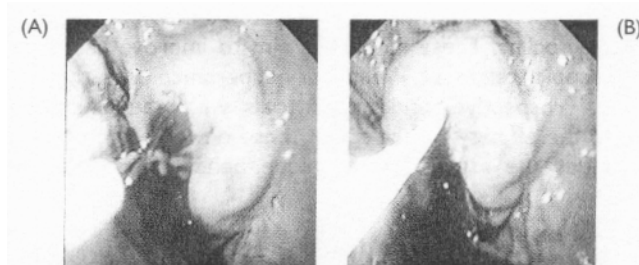
The technique of Histoacryl injection is essentially that of intravariceal sclerotherapy. Additional precautionary measures are required to prevent adherence of the glue to the endoscope or the working channel. The injection requires a well-co-ordinated team effort between endoscopist and nursing assistant.

Instrumental preparation begins with the endoscope. A therapeutic gastroscope with a large working channel is recommended to allow for suction after inserting the injection catheter. To prevent the liquid tissue adhesive from adhering to the endoscope, a few millilitres of silicone oil are smeared over the tip of the therapeutic gastroscope and sucked through the working channel.

To prevent premature solidification during injection, Histoacryl is diluted with the oily contrast agent Lipiodol (Byk Gulden, Konstanz, Germany). When Histoacryl is mixed in a ratio of 0.5 cm<sup>3</sup> (volume per tube of Histoacryl) to 0.8 cm<sup>3</sup> Lipiodol, hardening is delayed by approximately 20 seconds. The two components are drawn up together into a 2 ml syringe and then mixed by inverting the syringe several times. To help prevent Histoacryl from adhering to the catheter wall, several millilitres of Lipiodol are injected into the catheter.

Although Histoacryl has a viscosity similar to that of water, the addition of Lipiodol increases the viscosity considerably. Rapid injection of the Histoacryl mixture may therefore require considerable injection pressure. The use of a large-bore sclerotherapy needle will make the injection easier. Attachment of the syringe to the injection catheter by a Luer lock will prevent the inadvertent spraying of Histoacryl during the injection.

Having localized the bleeding site, the bleeding varix is punctured at or in the vicinity of the rupture point in the usual manner for intravariceal injection (see Plate 18). Paravariceal injection must be avoided as this will lead to severe tissue ulceration. Because Lipiodol is radio-opaque, the intravariceal injection can be monitored fluoroscopically.



**Plate 18.** Endoscopic cyanoacrylate injection. (A) Actively bleeding fundal varix. The injection catheter is positioned in front of the bleeding varix. The needle is extended from the injection catheter. (B) Immediate haemostasis after a single (1 ml) intravariceal injection of Histoacryl. **Please see Appendix for colour figure.**

The Histoacryl-Lipiodol mixture is injected in small aliquots of between 0.5 ml (oesophageal varices) and 1.0 ml (gastric varices). This is followed immediately by an injection of distilled water to flush out any Histoacryl retained in the catheter. After injecting the tissue adhesive, the injection catheter is advanced several centimeters from the endoscope tip and flushed continuously with distilled water to keep it patent for further injections. As a precautionary measure to prevent endoscope damage, one should not aspirate through the suction channel of the endoscope during and for about 20 seconds after the injection of the tissue adhesive.

#### **Benefits**

The unique properties of Histoacryl address the limitations of sclerotherapy and band ligation in the treatment of variceal bleeding. These conventional modalities may fail to arrest acute variceal bleeding in up to one-third of patients, and variceal rebleeding may occur in 30-50% of patients (Infante et al, 1989). Furthermore, these modalities are not able adequately to eradicate gastric varices because of their large size and volume. Ulcers that form at the site of sclerotherapy or banding may result in massive variceal bleeding (Yassin and Eita, 1985; Trudeau and Prindiville, 1986).

Histoacryl has been used extensively in endoscopy centres in Europe, Canada, Asia and the Middle East to treat acute oesophageal and gastric variceal bleeding. At least 12 studies have been published to date that include close to 1000 patients (Binmoeller and Soehendra, 1995). The results of this treatment have been highly favourable in these studies. The control of active variceal bleeding was achieved in 93-100% of patients, and rebleeding rates were found to be less than 10% in most studies.

Two randomized controlled trials have been published comparing a combination of Histoacryl and sclerotherapy, and sclerotherapy alone for the treatment of bleeding oesophagogastric varices. In a study from Egypt, Thakeb et al (1993) randomized 114 patients to combined treatment or sclerotherapy using 5% ethanolamine. In the combined group, large oesophageal varices and gastric varices were treated with Histoacryl, and the remaining oesophageal varices were treated by sclerotherapy until eradication. The immediate haemostasis rates were 100% and 96% for the combined and sclerotherapy alone groups respectively. Combined therapy achieved variceal eradication quicker than sclerotherapy alone, and there was a lower rebleeding rate for the combined group (9% versus 25%). Liver failure was the major cause of death in the combined group, whereas bleeding was the major cause of death in the sclerotherapy-alone group.

Feretis et al (1990) from Greece randomized 126 patients with bleeding oesophageal varices to combined Histoacryl and sclerotherapy, and sclerotherapy alone. Among 38 patients with active bleeding, haemostasis was achieved with combined treatment in 95% and sclerotherapy alone in 78%. During a 30-day followup, the combined treatment group had a significantly lower rebleeding rate (10% versus 44%) and hospital mortality (11% versus 50%).

Lux et al (1997) performed a prospective study in which 44 patients with large (grade 4) oesophageal varices or varices with active bleeding refractory to sclerotherapy were treated by the intravariceal injection of a Histoacryl-Lipiodol mixture. The remaining smaller varices were treated by sclerotherapy (1% polidocanol) until eradication. There were eight early recurrent bleeds during hospitalization (18%), and

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the hospital mortality was 18.2%. Rebleeding during long-term follow-up occurred in 20 patients (56%). There were no serious complications attributable to cyanoacrylate injection.

#### **Risks and drawbacks**

Since their discovery in 1949, cyanoacrylates have been applied as a tissue adhesive, embolization agent and haemostatic agent in a broad range of medical specialities including orthopaedics, plastic and facial surgery, vascular surgery and interventional radiology. The tissue reactivity and toxicity of the early short-chain cyanoacrylate monomers led to the synthesis of less histotoxic long-chain monomers, of which Histoacryl is the least histotoxic.

The overall clinical safety record of cyanoacrylates for the treatment of variceal bleeding has been excellent. The embolization of hardened Histoacryl—a serious complication—has been reported in rare cases: the estimated risk of embolization is less than 1%. Adhesion of the needle to the varix has been reported in one study in which Histoacryl was injected undiluted (D'Imperio et al, 1996). Minor complications, including dysphagia with and without stenosis, bacteraemia and pyrexia, have been reported in the literature. Because Histoacryl is ulcerogenic if injected into tissue, the strict intravariceal injection of Histoacryl will limit the risk of focal ulceration or stricture.

#### **Histoacryl for non-variceal bleeding**

Experience with Histoacryl for the treatment of arterial bleeding is limited to case reports and small series. Kok et al (1996) reported on successful haemostasis after the intralesional injection of Histoacryl in five patients with acute upper gastrointestinal bleeding who had failed on conventional endoscopic therapy. In a randomized study by Choudari and Palmer (1994), Histoacryl mixed with Lipiodol was not found to be superior to diluted adrenaline in achieving haemostasis in 32 cases of ulcer bleeding. The intravascular injection of Histoacryl into a major artery such as the gastroduodenal or splenic artery may lead to embolization and thus cause ischaemic complications. Vallieres et al (1989) reported a case of duodenal ulcer bleeding from the gastroduodenal artery that was controlled by injecting Histoacryl. The patient subsequently developed a severe pancreaticoduodenal necrosis that required pancreaticoduodenectomy.

## **BAND AND ENDOLOOP LIGATION**

The technique of rubber band ligation using a flexible endoscope was introduced by Stiegmann and Goff (Stiegmann, 1988) in 1988 for the treatment of variceal bleeding. The varix is sucked into a transparent cap mounted on the tip of the endoscope, and the band is applied at the base of the varix, thereby strangulating the variceal lumen. This modality offered a mechanical approach to achieving the eradication of visible varices and quickly gained popularity as an easier and safer alternative to sclerotherapy. Using the same basic principle of mechanical ligation, miniloops (Olympus Optical Co., Tokyo, Japan) have recently been developed as an alternative to rubber bands to achieve similar or possibly better results than rubber bands.

### **Technique of band ligation**

Band ligation is performed with a ligation device, of which there are now two designs: a single-shot ligator (Stiegmann-Goff ligation kit, Bard Medical, Tewksberry, MA, USA) and a multiple ligator (Multi-shooter, Wilson-Cook Medical Inc., Winston-Salem, USA, and other manufacturers). The Stiegmann-Goff set consists of an inner cylinder that fits into an outer cylinder. The outer cylinder is attached to the tip of the endoscope; the inner cylinder is loaded with the rubber band. A trip wire is inserted through the endoscope working channel and attached to the inner cylinder. The multiple ligator set consists of a single transparent plastic cylinder loaded with the bands, which is mounted on the tip of the endoscope. A drawstring that extends from the cylinder is backloaded through the working channel and connected to the spool of the cranking handle at the channel inlet port. The bands are individually released by pulling the string into the handle.

Using the Stiegman-Goff ligator device, only one band can be placed at a time. Thus the endoscope has to be removed after each ligation for the reloading of a rubber band. To facilitate repeat intubations of the oesophagus, a short overtube is inserted into the oesophagus to aid insertion of the endoscope. The overtube can be inserted over a Savary bougie that serves as an obturator to prevent injury to the oesophagus during insertion of the overtube. The multiple banding devices permit the application of several bands without having to remove the endoscope before every application. Placement of an overtube is therefore not necessary, making the procedure quicker and safer.

An endoscopic examination is first performed to assess the size, number and location of varices present. Ligation is begun at the most distal point of the variceal column, which may be at or below the gastro-oesophageal junction. Having targeted the varix, the tip of the endoscope is angulated toward the varix, and suction is applied continuously until the varix is sucked completely into the cylinder. Additional bands are placed in a helical formation in order to place only one band at a given level.

### **Technique of miniloop ligation**

Miniloop ligation differs from band ligation in two fundamental ways. First miniloops are made of non-elastic nylon, whereas bands are made of elastic rubber. Second, miniloops are actively tightened around the varix, whereas bands passively contract to a predefined diameter.

The cap for miniloop ligation contains an inner ridge that captures the opened loop (Figure 1). The loops are applied with a special delivery catheter that is inserted through the working channel of the endoscope. Any number of miniloops can be applied without having to remove the endoscope for reloading.

The miniloop, attached to the applicator catheter, is inserted through the working channel and opened inside the outer cylinder. The inner rim at the end of the cylinder captures the miniloop as it is opened. After the opened loop is aligned along the cylinder rim, the varix is aspirated into the cylinder. The miniloop is tightened around the base of the varix to the desired level of ligating force, and then released from the applicator device. The ligated varix thromboses and sloughs off over a period of 1-2 weeks, with subsequent scarring of the ligated site (see Plate 19).

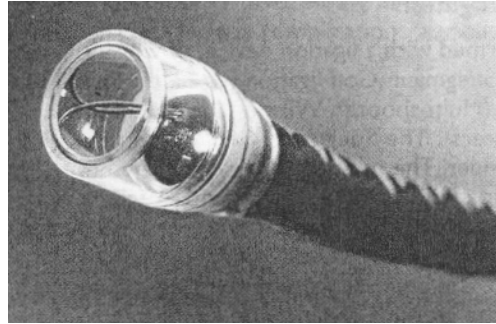
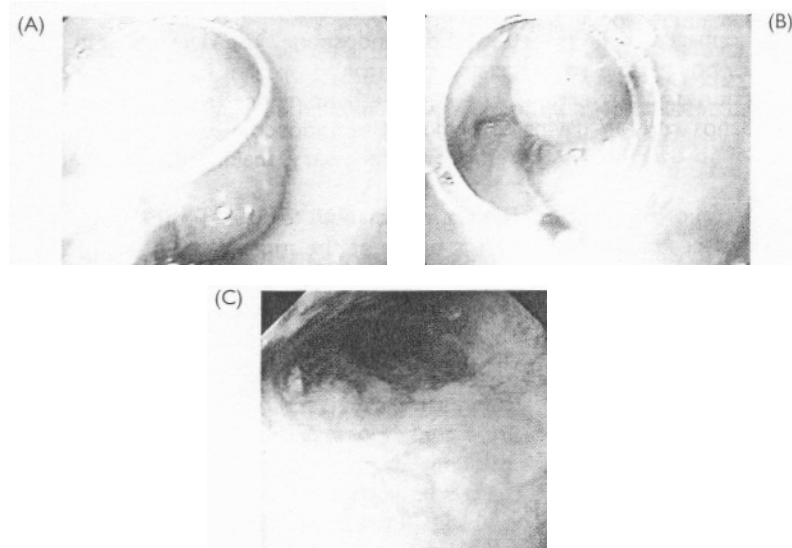


Figure 1. Transparent cap for loop ligation attached to the tip of the endoscope. The loop is aligned along the inner ridge of the cap and is ready for deployment.



**Plate 19.** Technique of endoloop ligation. (A) The varix is aspirated into the transparent cap, and the loop is manoeuvred around the base of the varix. (B) Appearance of the ligated varix after loop application. (C) Appearance 1 month later, showing varix eradication and scarring at the ligation site. **Please see Appendix for colour figure.**

### Benefits

Several randomized trials that have directly compared endoscopic variceal ligation with sclerotherapy have found ligation to be significantly better in terms of fewer complications (Stiegmann et al, 1992; Gimson et al, 1993; Laine et al, 1993; Hou et al, 1995), a quicker eradication of the varices (Gimson et al, 1993; Laine et al, 1993), a lower rebleeding rate (Gimson et al, 1993) and improved survival (Laine et al, 1993). A recent meta-analysis of published randomized trials concluded that variceal band ligation is superior to sclerotherapy in reducing oesophageal variceal rebleeding, mortality, and death due to bleeding (Laine and Cook, 1995).

The lower complication rates of endoscopic ligation compared with sclerotherapy can be explained by the inherent differences in the potential of these techniques for inducing tissue injury. Using the ligation technique, the extent and depth of tissue injury is limited by the instrument itself. It has been demonstrated in animal studies that only the mucosal and submucosal layers are aspirated into the cylinder. In contrast, sclerotherapy can induce variable degrees of tissue injury depending upon the type and amount of sclerosant used and the technique of injection employed.

Recent randomized studies suggest that ligation therapy may be associated with a higher rate of variceal recurrence than is sclerotherapy (Sakai et al, 1994; Baroncini et al, 1997; Sarin et al, 1997). In the Italian study by Baroncini et al (1997), the rate of recurrent varices was found to be significantly higher in the ligation group compared with the sclerotherapy group (30% versus 13%;  $P=0.03$ ). More long-term data are required to determine whether a higher incidence of variceal recurrence results in more rebleeding.

Using miniloops, an adjustable ligating force employing nylon material may produce results superior to those of band ligation. Furthermore, miniloop ligation may be more cost-effective and better tolerated by patients as there is no upper limit to the number of miniloops that can be applied after oesophageal intubation. Preliminary pilot experience with miniloops has shown this method to be effective and safe in patients with oesophageal varices. Rey and Marek (1996) used endoloops in 34 patients with acute or recent variceal bleeding and eradicated the varices in 27 out of 34 patients. The only complication was fever in two cases. There have been no published trials that have compared the efficacy and safety of miniloop and band ligation.

#### **Ligation for non-variceal bleeding**

Band and miniloop ligation has been used to treat non-variceal bleeding sources, such as Dieulafoy's lesion or bleeding arteriovenous malformations. Tseng et al (1991) first described band ligation for the treatment of non-variceal bleeding in an abstract. Subsequently, Delis and colleagues (Hou et al, 1995; Delis et al, 1996) reported on nine patients who underwent band ligation of gastric angiodysplasias. A total of 14 lesions were ligated in the gastric antrum and/or body using a multiple ligator in two patients and a single ligator in seven. Endoscopic controls were performed after 2, 4 and 15 days. After 2 days, all the bands had dropped off, and the ulcers had healed. No complications were observed. Matsui et al (1996) used band ligation in 10 patients with active bleeding from a Dieulafoy's ulcer ( $N = 4$ ), a Mallory-Weiss tear ( $N = 4$ ), a gastric ulcer ( $N = 1$ ) or gastric angiodysplasia ( $N = 1$ ). Haemostasis was achieved in all patients and was definitive in 9 out of 10 patients (with rebleeding only in one case of Dieulafoy's ulcer). There were no complications. Koutsomanis (1996) compared band ligation with adrenaline injection in 20 patients with bleeding ulcers. Haemostasis was successful in all patients, and no rebleeding was reported in the band ligation group. Two patients in the adrenaline group had rebleeding within one week.

#### **Risks and drawbacks**

Severe complications with ligation have been primarily related to the use of an overtube. Severe bleeding and perforation have been reported, resulting from pinching of

the oesophageal wall between the overtube and the endoscope (Goldschmiedt et al, 1992; Berkelhammer et al, 1993; Johnson et al, 1993). Passing the overtube over a bougie reduces the risk of overtube injury, but the elimination of an overtube altogether using a multiple ligation device is probably the safest approach.

Ligation-induced ulcers are usually shallow, but they can occasionally acquire significant depth and result in severe bleeding. Sakai et al (1994) reported massive, uncontrollable early rebleeding following the ligation of oesophageal varices in patients with Child-Pugh class C cirrhosis, leading these authors to question whether endoscopic variceal ligation (EVL) should be contraindicated in this patient subgroup. Transmural oesophageal necrosis after ligation has been reported (Schoonbroodt et al, 1994), the risk of which may be increased in immunosuppressed patients.

Several technical drawbacks of both band and miniloop ligation therapy deserve mention. The endoscopic field of vision is restricted by approximately 30% because of the cylinder attached to the end of the endoscope. The cylinder also has the disadvantage that it impedes the selective aspiration of blood and saliva since the area of suction is expanded to the cylinder circumference.

#### **HAEMOCLIP**

Metallic clips were introduced for endoscopic haemostasis nearly two decades ago in Japan by Hayashi et al (1997). Significant improvements in the design of the applicator device were made in 1988. The new clip was found to be easier to place, to have a better grasping capability and to cause less trauma than the older model (Hachisu, 1988). Clips have been used primarily for non-variceal bleeding, but there are anecdotal reports from Japan describing the use of haemoclips for variceal bleeding.

#### **Technique**

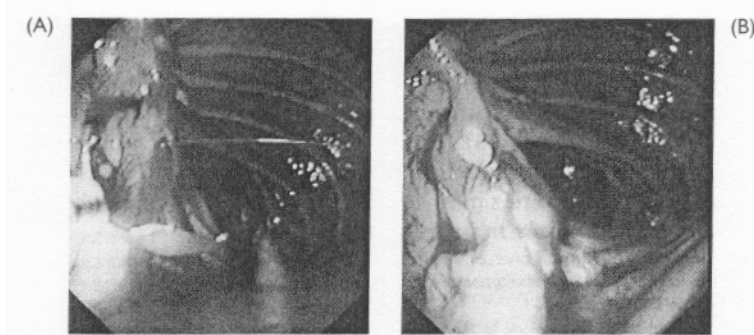
Haemoclips (MD 850, Olympus Optical Corp.) are made of stainless steel and have prongs that measure 6 mm in length and 1.2 mm in width. When fully open, the distance between the clip prongs is 12 mm. The haemoclip is loaded onto a clip application device (HX3L, Olympus Optical Corp.).

The retraction and extension of the clip from the applicator device is performed by sliding the teflon sheath forwards and backwards using the handle. Immediately prior to applying the opened clip, the prongs are maximally opened by retracting the clip approximately 1 mm. The orientation of the clip prongs is adjusted by rotating the handle clockwise.

A diagnostic endoscopy is performed to determine the bleeding site and activity. If visualization of the bleeding site is impaired by active bleeding, diluted epinephrine is injected around the bleeding site to reduce bleeding activity. Water jet irrigation of the bleeding site may also need to be performed. Haemoclips are applied after the bleeding vessel has been identified. If the vessel is large, the haemoclip can be applied directly to the vessel; small vessels are ligated by grasping the mucosa on both sides of the vessel and closing the clip around the vessel (Plate 20).

#### **Benefits**

The conventional endoscopic methods that have been widely used for the treatment of non-variceal bleeding are thermal application using the laser, heater probe, or



**Plate 20.** Clip ligation of a spurting bleed from an anastomotic ulcer. (A) The prongs of the clip are open and positioned for deployment. (B) Immediate haemostasis after placement of a single clip. The vessel is sandwiched between the adjacent mucosal folds. **Please see Appendix for colour figure.**

bipolar circumactive probe (BICAP), and local injection of adrenaline and/or a sclerosing agent. A drawback of all thermal and most injection haemostatic methods is treatment-induced tissue injury. Several clinical reports have described extensive necrosis and perforation following injection and thermal haemostasis (Chester and Hurley, 1990; Loperfido et al, 1990; Levy et al, 1991; Bedford et al, 1992). There is also an increased risk of perforation associated with the retreatment of bleeding lesions (Chung et al, 1991). In addition to local tissue injury, systemic side-effects following injection therapy may occur (Raoul et al, 1991). Mechanical haemostasis by the application of a metal haemoclip to a bleeding vessel is a conceptually appealing alternative to the currently available thermal and injection techniques. Injury to the surrounding tissue should be minimal owing to the targeted application of the clip to the bleeding vessel.

Ohta et al (1996) reported on the use of haemoclips in 10 critically ill patients with severe active bleeding from stress ulcers ( $N = 9$ ) and Mallory-Weiss tears ( $N = 1$ ). Haemostasis was successful in all 10 patients after the placement of between one and seven clips. There was no rebleeding and no complications occurred.

Expanding on previously published data (Binmoeller, 1993), we used haemoclips over a 37-month period to treat 114 consecutive patients with clinically significant non-variceal upper gastrointestinal bleeding. All patients had either active bleeding (spurting or oozing) or a non-bleeding visible vessel on gastroscopy. Fourteen patients were not candidates for haemoclip treatment at index endoscopy because of lesion inaccessibility ( $N = 4$ ), torrential bleeding ( $N = 8$ ) or diffuse bleeding ( $N = 2$ ). Haemoclip treatment in the remaining 100 patients arrested active bleeding in all but four cases (a 4% initial haemostasis rate). Active bleeding was precipitated in four patients with a non-bleeding visible vessel; however, the bleeding could be immediately arrested with haemoclip retreatment. An average of three haemoclips was placed per patient. Recurrent bleeding occurred after a mean of 3 days in seven patients (a 7.3% overall rebleeding rate). Follow-up endoscopy did not show any evidence of clip-induced tissue injury or impairment of healing. Haemoclips dislodged spontaneously with healing of the primary lesion, usually after 1-3 weeks of placement.

Randomized trials comparing haemoclips with other endoscopic haemostatic modalities are currently in progress. The final results of a randomized study from Barcelona were recently reported in abstract form (Sabat et al, 1998). Two hundred and fifty-one peptic ulcer patients were randomized to injection therapy with

adrenaline alone or injection combined with haemoclips (arterial bleeding:  $N = 73$ ; non-bleeding visible vessel:  $N = 178$ ). Of these, 128 patients received injection therapy (1 0-20 cm<sup>3</sup> adrenaline 1 : 10 000) followed by clipping of the visible vessel (1 -5 clips); 123 patients underwent injection therapy alone. In 20 cases, the clips could not be placed. Rebleeding occurred in 23% of the patients with haemoclips compared with 19% of those in the group with injection therapy alone. Transfusion requirements and the length of hospital stay were similar in the two groups. No differences in the need for emergency surgery and the mortality rate were found.

#### **Risks and drawbacks**

No serious complications have been reported using haemoclips. A technical drawback is that haemoclips need to be individually reloaded onto the applicator device. This poses a problem in the setting of active bleeding, where clips may need to be applied in rapid sequence. Having two applicator devices is helpful in this situation. Accessing the bleeding vessel with the haemoclip may be difficult, especially in the bulb of the duodenum where the manoeuvrability of the endoscope is more limited. Other locations that are difficult to access are the cardia and fundal regions, since these must be approached either tangentially or in the retroflexed position. Clips may not hold when applied to chronic ulcers with fibrotic bases. A manoeuvre that the authors have found to improve anchorage of the haemoclip is to apply constant forward pressure as the haemoclip is slowly closed by the endoscopy assistant. Finally, a prerequisite for haemostasis using clips is the precise identification of the bleeding vessel. This may be difficult in the setting of active bleeding, and the injection of diluted epinephrine may be required to reduce the activity of bleeding.

#### **CONCLUSION**

Several new haemostatic modalities have been introduced over the past decade. Faced with an expanding list of haemostatic modalities to choose from, which modality should the endoscopist choose to treat gastrointestinal bleeding? The only sensible recommendation that can be made at this time is that the endoscopist should acquire sufficient expertise in one or two methods of endoscopic haemostasis. If one modality fails to control the bleeding, a second should be available and attempted. A combination of modalities may be required in some cases. Most importantly, it is important to recognize which bleeding lesions are suited for endoscopic therapy, and what the limitations of endoscopic treatment are. If bleeding is massive from a major artery (e.g. gastroduodenal or splenic artery), immediate surgery is preferable. Poorly accessible and diffusely bleeding lesions are not likely to respond to endoscopic treatment and should be considered for surgical management.

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