

Endoscopic clipping in non-variceal upper gastrointestinal bleeding treatment

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Since the earliest reports, advanced clipping systems have been developed, and it is possible to choose among many models with different structural and technical features. The main drawback of through-the-scope clips is their small size, which allows the compression of limited amounts of tissue needed for large-size vessel treatment. Therefore, the over-the-scope clip system was realized, allowing a larger and stronger mechanical compression of large tissue areas, with excellent results in achieving a definitive hemostasis in difficult cases. Many studies have analyzed the indications and efficacy of two-pronged endoclips and have shown good results for initial and permanent hemostasis. The aim of this review was to provide updated information on indications, positioning techniques, and results of clip application for endoscopic treatment of upper gastrointestinal non-variceal bleeding lesions.

Keywords: Clipping; Digestive endoscopy; Endoclips; Gastrointestinal bleeding; Over-the-scope clip

INTRODUCTION

Acute upper gastrointestinal (UGI) bleeding presents an incidence of approximately 40–150 new cases per 100,000 population/year, and it represents a common cause of hospital admission with a significantly associated morbidity and mortality rate, especially in elderly subjects.¹ The most frequent causes of acute UGI bleeding are non-variceal, including gastric and duodenal peptic ulcers (28%–59%); mucosal erosions of the

esophagus, stomach, or duodenum (1%–47%); Mallory-Weiss syndrome (MWS; 4%–7%); and malignancy (2%–4%).²

Despite the widespread use of proton pump inhibitors to reduce the incidence of UGI bleeding in the last 15 years, the rate of bleeding peptic ulcers caused by aspirin and non-steroidal anti-inflammatory drugs has increased.³ Moreover, the mortality rate has remained substantially unchanged over the last two decades, mainly due to population aging and the presence of comorbidities.^{4,5}

Although self-limiting in some cases, endoscopic treatment has been recommended as the first choice of treatment to reduce morbidity and mortality related to both acute bleeding and rebleeding episodes.⁶ Among the different therapeutic approaches used in endoscopy, clips can achieve immediate mechanical hemostasis without additional tissue damage.^{7,8} The earliest report on metal endoclips was published more than 40 years ago by a Japanese group,⁹ but the first experience with this endoscopic treatment of non-variceal bleeding was described in 1993.¹⁰ Thereafter Olympus Corporation (Tokyo, Japan) mar-

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keted the first model of through-the-scope (TTS) endoscopic hemoclip.

THROUGH-THE-SCOPE CLIPS

Apart from the device model, the mechanism of the clipping action is the compression of vessels by grasping the surrounding tissue of the lesion. Different TTS clips are currently available and diversified in terms of material (stainless steel, titanium, and nitinol), arm length, angle of closure, width of opening diameter, shape, and number of clip prongs. Moreover, preloaded and ready for use, the most recent clips are rotating and engineered to enable opening and closing more times prior to finalizing deployment, with a working length ranging between 225 and 250 cm. Furthermore, they are magnetic resonance imaging compatible with up to 3.0 Tesla. Clips have two closing arms, but a three-pronged arms model was introduced in 2003 (TriClip; Cook Medical, Bloomington, IN, USA). It allows easy grasping of a bleeding lesion, such as a polypectomy stalk, without the need for rotation, although it cannot be reopened. Unfortunately, this clip was marketed until 2015. Notably, multi-firing clip devices were developed, allowing the application of 3–4 preloaded, rotatable, and reopenable clips without changing the device. Data from a few studies in ex vivo or animal models showed no substantial differences that emerged in the efficacy among devices.¹¹⁻¹⁴ A recent study¹⁵ compared five commercially available TTS clips (Instinct, Cook Medical; Res-

olution, Boston Scientific, Marlborough, MA, USA; DuraClip, ConMed, Largo, FL, USA; SureClip, Micro-Tech, Ann Arbor, MI, USA; QuickClip Pro, Olympus, Center Valley, PA, USA). The open width, jaw length, global clip length, tail length, and functionality (rotatability, overshoot, precision of opening and closing, tensile strength, and closure strength) were evaluated. The clips were tested by using different models of gastroscope or duodenoscope in four configurations as follows: straight, duodenal sweep, full retroflexion, and across the duodenoscope elevator.

Resolution was the fastest in terms of rotatability, with its primary rotation control ($p < 0.05$). Resolution, SureClip, and DuraClip allowed the rotation through the prescribed sequence across all scope configurations. SureClip and Resolution showed the least overshoot at 0% for the straight configuration, whereas all clips had overshoot at >75% for more strained configurations. SureClip and DuraClip had high precision for opening and closing movements, with the possibility to stopping at any point, unlike other clips that had an abrupt opening and a more controlled closure. The QuickClip Pro showed the highest peak force, which was comparable to the tensile strength required for lateral tissue manipulation. For closure strength, Instinct had the most gel compression, with 100% deployment success for all gel tissue thicknesses (up to 10 mm). Data from this study are clinically relevant, although they lack economic aspects. **Figure 1** reports the main features of the TTS clips, considering both the physical and the functional characteristics.








| TTS type | | Use | Disadvantage | Physical feature | | | Functional feature | | | | |
|---|----------------|--|---|--|--|--------------------------|--------------------|----------------|-------------------------|--|--------------------------------|
| | | | | Open width (mm)  | Jaw length (mm)  | Material | Rotatability | Overshoot/whip | Precision of open/close | Tensile strength of lateral manipulation | Strength of tissue compression |
|  | Resolution 360 | Preloaded and ready to use in spurting bleedings | Small size of clip arms not strong mechanical compression on large-size vessels | 11 | 9 | Stainless steel, cobalt | +++ | +++ | ++ | ++ | +++ |
|  | Instinct | | | 13, 5 | 9 | Stainless steel, nitinol | + | + | ++ | ++ | +++ |
|  | Quick clip pro | | | 11 | 10 | Elgiloy | + | + | + | +++ | + |
|  | Dura clip | | | 11 | 7 | Stainless steel | ++ | ++ | +++ | + | + |
|  | Sure clip | | | 14 | 11 | Stainless steel | ++ | +++ | +++ | ++ | ++ |

Fig. 1. Physical and functional features of through-the-scope (TTS) clips. +++, best performance; ++, good performance; +, medium performance.

OVER-THE-SCOPE CLIPS

Recently Ovesco (Tudbingen, Germany) has developed a nitinol over-the-scope clip (OTSC) that is mounted onto the distal tip of the endoscope, such as in rubber-band ligation devices. Owing to their structural features, OTSCs overcome the main limitations of TTS clipping devices, such as the small size of the clip arms, which limits their efficacy on large-sized vessels or lesions.¹⁶ Their performance in achieving definitive hemostasis is very high, mainly because of the larger and stronger mechanical compression of large tissue areas surrounding the vessels.¹⁷ However, reloading of the OTSC system requires removal of the instrument, which is a disadvantage.¹⁶⁻²⁰ OTSCs are particularly useful for endoscopic repair of digestive iatrogenic (postsurgical and postendoscopic resection) perforations and massive bleeding.¹⁸⁻²¹ The main technical characteristic of nitinol is that it applies a permanent closing force, which is necessary for sufficient tissue compression, as shown by phantom tests and in animal models.²² Two different configurations of OTSCs are available: the nontraumatic version with blunt teeth and the traumatic version with sharp teeth. The last developed clip is the Padlock (Aponos Medical Corporation, Kingston, NH, USA). It is a nitinol ring with six inner needles preassembled on an applicator cap, with a specific system to displace the thumb press. For the other OTSCs, this clip had a trigger wire placed near the shaft of the endoscope. The original form of the clip, that appears once it is deployed, is an 11 mm hexagonal ring that gathers, folds, and compresses the tissue.¹⁹ Padlock is equipped with a radial compression system that provides 360° tissue compression, and precise tissue controllers limit penetration and tissue-on-tissue pressure, maintaining blood flow to promote lesion healing.

Figure 2 shows the main features of OTSCs, considering both physical and functional characteristics. The cost of devices in

Italy is reported in Table 1, but they may vary in different countries.

LESIONS CLIPPING

Hemostasis is defined from both technical and clinical points of view. Technically, hemostasis is defined as a bleeding interruption for at least 1 minute after endoscopic treatment. Clinically, hemostasis is achieved when no further decrease in hemoglobin level occurs following endoscopic treatment and shock correction. Clips can be used for both therapeutic and preventive purposes.

Therapeutic use of clips

Several studies have reported that clips are particularly helpful and effective when acute active bleeding is encountered and a hemorrhagic source is identified. Indications for clipping include gastric ulcer, duodenal ulcer, MWS, Dieulafoy lesion, post-operative anastomosis bleeding, post-polypectomy and mucosectomy bleeding, angiodysplasias, and post-sphincterotomy bleeding.^{7,14,22-31}

Table 1. Cost for single clip of different models currently marketed in Italy

| Model | Cost (€) |
|-----------------------|----------|
| Instinct | 160 |
| Resolution | 140 |
| QuickClip Pro | 130 |
| DuraClip | 115 |
| SureClip | 90 |
| Ovesco ^{a)} | 500 |
| Padlock ^{a)} | 500 |

^{a)}Ovesco and Padlock clips are provided in a complete kit, with a distal transparent cap and release system.




| OTSC type | | Use | Disadvantage | Material |
|---|---|---|--|----------|
|  | No traumatic version (with blunt teeth) | Endoscopic repair of digestive iatrogenic (postsurgical and postendoscopic resection) perforations and massive bleeding | Reloading of the OTSC system needs removal of the instrument | Nitinol |
|  | Traumatic version (with sharp teeth) | | | Nitinol |
|  | Padlock | | | Nitinol |

Fig. 2. Main features of the over-the-scope clip (OTSC).

1) Bleeding peptic ulcer

Bleeding peptic ulcer is the main cause of UGI bleeding.³² Early endoscopic treatment should be performed within 24 hours upon admission to reduce the risk of rebleeding and the need for surgery.³³⁻³⁵ Endoscopic clipping is indicated for patients with active bleeding ulcers and for those with a non-bleeding visible vessel (Forrest classes Ia, Ib, and IIa). Ulcers corresponding to type IIb on the Forrest classification have specific management consisting of clot removal to evaluate whether the lesion is suitable for endoscopic hemostasis.⁸ Lau et al.³⁶ have reported endoscopic clipping as an effective treatment, similar to epinephrine injection and thermocoagulation in terms of efficacy. Moreover, other studies underlined that clipping as monotherapy reduces the rebleeding rate and requirement for surgery when compared to epinephrine injection alone, with an efficacy comparable to that of thermocoagulation.³⁷⁻³⁹ The European Society for Gastrointestinal Endoscopy (ESGE) guidelines recommend endoscopic clipping as the first choice of treatment for ulcers with no active bleeding, whereas epinephrine injection combined with a mechanical or thermal method is indicated for active bleeding ulcers.³³ The success rate of clipping with two-pronged clip treatment varies from 85% to 100%, and it is lower in patients with chronic ulcers.³⁴ Factors predicting clipping failure include ulcers >2 cm, brittle or callous lesions, localization of ulcers, such as the posterior duodenal wall, large non-bleeding vessel within the lesion, excessive blood in the stomach, presence of shock, or multiple comorbidities.⁸ In all these conditions, failure is mainly due to difficulty in clip placement; therefore, the skill of the endoscopist plays a pivotal role.

Regarding the use of OTSCs in the treatment of refractory bleeding from peptic ulcers, a large series showed a primary success rate of 100%, with a recurrence rate of only 3.7%.⁴⁰ Similar results were achieved in patients with severe bleeding unresponsive to other endoscopic treatments, recurrent bleeding, or high-risk lesions.^{16,41-43} By summarizing data of 1,517 cases, a recent review calculated an overall success rate of 85% with OTSC positioning in refractory bleeding ulcers.⁴⁴ The use of OTSCs as the first-line treatment in high-risk patients has been proposed,⁴⁵ but American Gastroenterological Association guidelines suggest that hemostasis by OTSCs should be considered only in selected patients who had undergone conventional electrosurgical coagulation and hemostatic clips that are unsuccessful or predicted to be ineffective.⁴⁶

2) Mallory-Weiss syndrome

MWS is typically treated conservatively. Endoscopic treatment with endoscopic clipping, as well as with epinephrine injection or thermocoagulation, is recommended in cases of active bleeding at the procedure time or deep mucosal lacerations⁴⁷ and provides less tissue damage, decreasing the risk for perforation and necrosis in patients with MWS.²¹ In their study, Cho et al.⁴⁸ and Park et al.⁴⁹ showed that endoscopic clipping and endoscopic band ligation were effective and safe treatment in cases of bleeding lesions, and achieved higher success rates in terms of prevention of rebleeding compared to injection therapy.

3) Dieulafoy lesion

Dieulafoy lesions are usually localized in the stomach and duodenum, and endoscopic clipping is considered superior to injection tools and is more effective for the management of acute bleeding than for reducing the rebleeding rate. In case of rebleeding, the placement of a metal clip at the site of the bleeding allows it to be recognized if endoscopic or surgical intervention is required.⁴⁶ For these reasons, mechanical hemostasis with endoclipping or band ligation, should be the first choice of treatment for this type of lesion, although there is no consensus regarding its superiority compared to thermocoagulation. In a meta-analysis by Barakat et al.,⁵⁰ treatment with endoscopic band ligation was compared with endoclipping in patients with UGI bleeding from a Dieulafoy lesion, and showed that the two treatments achieved similar results in terms of primary hemostasis. The ESGE guidelines recommend that endoscopic treatment of these lesions should be achieved with mechanical or thermal methods, such as monotherapy or in combination with epinephrine injection.^{33,51}

Preventive use of clips

Endoscopic clipping is frequently used to prevent complications, such as delayed bleeding (i.e., occurring within 30 days) after endoscopic mucosal resection (EMR). Although controversy exists regarding the cost-benefit ratio, guidelines have encouraged the use of endoclips in this setting as a preventive measure.⁵²

1) Esophageal or gastric endoscopic resections

Despite a lack of consistent data, clipping closure during esophageal or gastric EMR or endoscopic submucosal dissection to prevent delayed bleeding is often performed in clinical practice.

The use of endoclips in these situations has been suggested in patients with portal hypertension, patients on anticoagulation and antiplatelet therapy, and in cases of a non-bleeding visible vessel at the resection site.⁵³⁻⁵⁶

2) Duodenal endoscopic resections

Endoscopic resection of duodenal lesions is technically difficult, mainly due to the marked peristalsis, reduced lumen, and challenging endoscope and device positioning.⁴⁹ Moreover, the diffuse submucosal vascularization of the duodenum combined with the presence of Brunner's glands increases the risk for bleeding complications up to 14%, hindering the lifting of the target lesions.^{57,58} An et al.⁵⁹ showed that after endoscopic resection of nonampullary superficial tumors, preventive clipping of the site was associated with a reduced incidence of delayed bleeding (2.1% vs. 13.6%; $p=0.053$). The usefulness of preventive clipping has been confirmed in other studies,^{60,61} particularly for lesions that are >10 mm or with visible vessels of >2 mm⁶²⁻⁶⁴; however, randomized studies are still lacking. Moreover, clipping was found to be superior to other endoscopic treatments, such as epinephrine injection, with a significant reduction in rebleeding, fewer units of blood transfused, and a shorter hospital stay.⁶⁵⁻⁶⁷

TECHNICAL TIPS

The application of clips on bleeding lesions located in the proximal stomach, particularly along the lesser curvature, might be technically difficult; therefore, the experience of the operator plays a major role. Following the identification of the bleeding point, the typical two-pronged clip was exposed from the sheath, rotated to the desired axis, opened to its maximum width, and then pressed against the lesion. Partial suction should be applied, allowing the lumen to collapse, and the clip is then deployed. Indeed, the effect of clipping is stronger when the distance between the scope tip and the tissue is minimal, optimizing force translation.^{41,42} Moreover, it is fundamental to maintain the catheter as perpendicular as possible to the organ wall. Therefore, lesions in the lesser curvature of the gastric body, posterior duodenal bulb, or cardia are less amenable to clipping because of their relative tangential position in most situations.⁴⁴⁻⁴⁷ If needed, the procedure can be repeated, with a mean of three clip applications reported in the literature.^{1,5,7,8,16,21} After the first clip was placed at the bleeding point, subsequent clips were positioned around the lesion to occlude the submu-

cosal vessels.^{5,12,35-40}

In a retroflexed position, clip deployment can be very demanding. In such cases, it is better to expose the clip from the sheath or even partially open it before retroflexing the scope. Nevertheless, moving an open clip may be dangerous, and scraping the lesion or dislodging it precociously, and should be avoided. Chronic hardened ulcers represent another challenge because the callous tissue may hamper a correct clip application.^{5,8,56} Due to their location, there are lesions that are not fitting for clipping, such as those where the clip could snatch the vessel rather than clip it, resulting in a significant damage. In cases with difficult access, other techniques have been suggested (cautery, use of injection devices, argon plasma coagulation, and hemostatic powders).^{12,54-56}

The OTSC system was designed to overcome the limitations of traditional TTS clips (large ulcers of >2 cm, large visible vessels, or chronic ulcers) leading to a larger and stronger mechanical compression of large tissue areas surrounding the vessel without direct trauma, with a high compression force of 8–9 N. This reduced the need for the application of multiple clips and improved the initial success rate.⁶⁸ The correct, effective, and safe application of OTSCs depends on the fit between the cap and lesion. With the help of specific application devices, such as forceps or graspers, the lesion can be fixed and then pushed into the cap. Since visualization is impossible at the moment of application, the endoscopist must ensure the correct position. A disadvantage of this device in cases of active bleeding is the necessity to mount the OTSC system distally on the endoscope, which must be removed and reintroduced. A recent review pointed out some shortcomings of the OTSC deployment.⁶⁹ These include difficulty in introducing the probe in patients with stenosis of the UGI tract or intubated patients, incorrect location and shallow placement due to premature clip deployment, and mucosal damage during insertion. Moreover, after identifying the lesion with an endoscope, it is necessary to exit and return to the previously identified site for clip deployment. The Padlock clips, owing to a cup deeper than the OTSC, allow a more efficient suction that is sufficient to ensure tissue adhesion to the instrument tip into the cap, without requiring other grasping instruments. The retroflexed position, angulated digestive segments, large fibrotic ulcers, and complex postsurgical anatomy represent challenges in OTSC positioning. For these reasons, it is very important that the endoscopist using the OTSC system is skilled.

CONCLUSIONS

The possibility of choice among many endoclip models, with different physical and technical features, allows the endoscopic treatment of UGI bleeding caused by different diseases, such as bleeding peptic ulcers, MWS, Dieulafoy lesions, or bleedings after endoscopic resections, which also reduces the risk of re-bleeding compared to other endoscopic treatments. OTSCs are particularly indicated for the endoscopic treatment of massive bleedings owing to their stronger mechanical compression of large tissue areas, and they were designed to overcome the limitations of TTS clips, although there are some situations, such as retroflexed position, angulated digestive segments, large fibrotic ulcers, and complex postsurgical anatomy, which are challenging for OTSC positioning.

Conflicts of Interest

The authors have no potential conflicts of interest.

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Author Contributions

Conceptualization: GG; Formal analysis: RMan, AZ; Data curation: DAT, RMai, MP; Investigation: DAT, RMai, MP; Validation: GDDP; Supervision: GDDP; Resources: GL; Methodology: GL; Writing-original draft: GG; Writing-review & editing: AC. All authors have approved the final submitted draft.

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