ORIGINAL ARTICLE

The use of Cap-Mounted Clips as primary hemostatic modality in Nonvariceal Upper Gastrointestinal Bleeding: Current role and future perspectives

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Abstract

Nonvariceal upper gastrointestinal bleeding (NVUGIB) is an important condition that continues to exert a significant burden on healthcare systems. Despite improvement in the medical and endoscopic therapies for NVUGIB, the morbidity and mortality of this condition remain unchanged, largely related to the increasing age and comorbidities of the affected population. Several endoscopic modalities are available to manage bleeding lesions, but a significant proportion of patients suffer from primary failure in achieving hemostasis or rebleed after initial successful hemostasis, which carry worsened outcomes for patients

. Recently, the management of NVUGIB has seen significant evolution with the introduction of several novel endoscopic tools including cap-mounted clips. These clips have been utilized in managing patients with NVUGIB as a primary or rescue therapy with promising results. Several randomized controlled studies have been published in recent years addressing the role of such clips yielding overall favorable outcomes. In this article, we will review the recent updates in the role of cap-mounted clips in the management of NVUGIB, while identifying current limitations in the evidence that are pertinent to the adoption of this hemostatic modality by clinicians in routine practice.

Background

Nonvariceal upper gastrointestinal bleeding (NVUGIB) is an important gastrointestinal emergency that carries significant morbidity and mortality. NVUGIB, especially peptic ulcer disease, is a common cause for emergency room visits and hospitalization, accounting for more than 250,000 admissions annually in the United States alone, with a readmission rate of approximately 15% [1,2]. Despite the advances in the therapy of NVUGIB, including the use of proton pump inhibitors (PPI) and improvement in resuscitative measures, the mortality of NVUGIB has remained significant over the last 2 decades [3]. This is thought to be related to the increasing age of the affected population and the corresponding expanding underlying medical comorbidities burden. The cornerstone of NVUGIB treatment remains early patient triage using a validated risk assessment tool (most commonly the Glasgow Blatchford score), the performance of adequate resuscitative measures including the use of a restrictive blood transfusion strategy, an appropriate management of antithrombotics, and PPI administration [4]. Timely or so-called "early endoscopy" (within 24 hours from presentation) plays important diagnostic and therapeutic roles and continues to be an essential component in managing patients with NVUGIB but should only be performed once the patient is adequately resuscitated.

Traditional endoscopic hemostatic modalities

The endoscopic management of NVUIGB has improved over the years with the availability of several highly effective hemostatic tools including injection therapy (typically dilute epinephrine), through-the-scope (TTS) clips, and thermal therapies (e.g. bipolar electrocoagulation). Recent societal guidelines recommend the use of TTS clips or thermal therapies with or without epinephrine injection (i.e. combination therapy) for patients with high-risk lesions identified during endoscopy [5-7]. Despite the effectiveness of those therapies in controlling bleeding, conventional endoscopic therapy fails to achieve initial hemostasis in approximately 15% at the index endoscopy, while approximately 25% experience rebleeding after initial successful endoscopic treatment [8]. Patients who fail initial endoscopic therapy or experience rebleeding are at increased risk of complications and mortality [9]. Endoscopic predictors of rebleeding include active bleeding, large ulcer size (larger than 2cm), and a peptic ulcer located in the posterior duodenal bulb or high on the lesser gastric curvature [10]. These lesions are particularly challenging to manage using conventional endoscopic modalities, which highlights the limitations of currently available endoscopic tools in some patients exhibiting certain bleeding lesions.

Cap-mounted clips

The cap-mounted clips, especially the Over-The-Scope clip™ (with the majority of published evidence addressing the OTSC®, Ovesco Endoscopy AG, Tubingen Germany) was originally designed for gastrointestinal defect closure. However, these clips have been increasingly used to manage NVUGIB. Since these clips are able to grasp deeper tissue than the traditional TTS-clips, they are able to control bleeding from a feeding submucosal vessel more effectively. Several studies and meta-analyses have concluded that the OTSC system is more effective than standard endoscopic approaches at controlling bleeding during index endoscopy and reducing the risk of rebleeding [11,12]. However, until recently, most of these studies, including the ones included in meta-analyses, were retrospective non-comparative studies, limiting the quality of such data. However, over the last 5 years, several randomized controlled trials (RCTs) have been published that have assessed the role of cap-mounted clips in the management of NVUGIB as a primary or rescue therapy. The first of these RCTs was the study conducted by Schmidt et al. which found OTSC to be superior to standard endoscopic therapy among patients with recurrent NVUGIB [13]. This led societal guidelines to recommend cap-mounted clips as rescue therapy for patients who experience rebleeding after initial successful endoscopic therapy [6,7].

However, the role of cap-mounted clips as primary therapy for NVUGIB has been gaining more attention recently after the publication of several RCTs comparing this modality to conventional endoscopic tools [14]; these are summarized in Table 1.

Table 1: Randomized controlled studies comparing OTSC with conventional endoscopic therapy as a primary modality for NVUGIB.

Study	Intervention Control	Lesion Type	Outcomes
Jensen et al. 2021 USA NCT03065465	OTSC (N=25) Standard therapy (N=28) Through-the-scope (TTS) hemoclips Multipolar probe thermal coagulation (MPEC)	**OTSC** Duodenal ulcer= 52% Gastric ulcer= 36% Anastomotic ulcer= 4% Dieulafoy's lesion= 8% **Standard therapy** Duodenal ulcer= 39.3% Gastric ulcer= 35.7% Anastomotic ulcer= 14.3% Dieulafoy's lesion= 10.7%	**Hemostasis** OTSC= 100% Standard = 100% **30-day rebleeding** OTSC= 4% Standard= 28.6%
Meier et al., 2022 Germany NCT03331224	OTSC (N=48) Standard therapy (N=52) TTS hemoclips	**OTSC** Peptic ulcer= 87.5% Anastomotic ulcer= 6.2% Dieulafoy's lesion= 4.2% Reflux esophagitis= 2.1%	**Hemostasis** OTSC= 100% Standard = 88.5% **30-day rebleeding** OTSC= 8.3%

	Thermal modality	Mallory-Weiss tear= 0% **Standard therapy** Peptic ulcer= 80.7% Anastomotic ulcer= 5.8% Dieulafoy's lesion= 5.8% Reflux esophagitis= 5.8% Mallory-Weiss tear= 1.9%	Standard= 15.4%
Chan et al., 2022 Hong Kong NCT031 60911	OTSC (N=50) Standard therapy (N=50) TTS hemoclips Thermal modality	**OTSC** Duodenal ulcer= 62% Gastric ulcer= 38% **Standard therapy** Duodenal ulcer= 52% Gastric ulcer= 48%	**Hemostasis** OTSC= 92% Standard= 95% **30-day rebleeding** OTSC= 10% Standard= 18%
Lau et al., 2023 Hong Kong NCT032 16395	OTSC (N=93) Standard therapy (N=97) TTS hemoclips Thermal modality	**OTSC** Peptic ulcer= 92.5% Dieulafoy's lesion= 4.3% Angiodysplasia= 0% Duodenal diverticulum=0% Gastrointestinal stromal cancer=2.2% Mallory-Weiss tear=1.1% **Standard therapy** Peptic ulcer= 89.7% Dieulafoy's lesion= 4.1% Angiodysplasia= 2.1% Duodenal diverticulum=1.0 % Gastrointestinal stromal cancer=1.0% Mallory-Weiss tear=2.1%	**Hemostasis** OTSC= 98.9% Standard= 93.8% **30-day rebleeding** OTSC= 2.2% Standard= 8.8%
Soriani et al, 2023 Italy (abstract) NCT035 51262	OTSC (N=61) Through-the-scope (TTS) hemoclips (N=51)	Not reported	**Hemostasis** OTSC= 98.4% Standard= 78.4% **30-day rebleeding** OTSC= 1.7% Standard= 5%

TTS: Through the scope

NVUGIB: Non-variceal upper gastrointestinal bleeding

OTSC: over-the-scope-clip

MPEC: Multipolar probe thermal coagulation.

Most of these studies have concluded that despite the high successful hemostasis rates at index endoscopy achieved with both OTSC and conventional hemostatic tools, recurrent bleeding is significantly lower in the OTSC group.

Despite the promising results of these RCTs, several important methodological limitations may affect these observations. The study by Jensen et al. [15] suffered from several important limitations including failure to meet enrollment targets, imbalances between groups, and the higher rates of rebleeding in the control group compared to other published studies. The study by Meier et al. [16] focused mostly on elderly patients with NVUGIB and found significantly higher rates of initial hemostasis using OTSC compared to conventional hemostatic tools (mostly TTS clips). Again, despite the promising results, the study suffered from some methodological limitations including the inconsistent pre-injection of epinephrine in half of the OTSC group and the routine use of second-look endoscopy (which is not recommended by practice guidelines), that may have over-estimated the benefits of OTSC, as well as the inclusion of larger ulcers (larger than 20 mm) in the control arm which may have underestimated the efficacy of the standard endoscopic tools [17]. The third study by Chan et al. included patients with large ulcers (15mm or greater) and was the exception among all published RCTs as it failed to show a difference in the initial hemostasis or 30-day rebleeding between the 2 interventions [18]. This study also suffered from some limitations including the low statistical power and high technical failure in applying the OTSC. In fact, the technical aspect of applying the OTSC became more apparent in the trial by Lau et al. that also concluded that OTSC is more effective than conventional endoscopic tools, both at achieving hemostasis at index endoscopy and at reducing 30-day rebleeding [19]. However, patients who were deemed not suitable for OTSC application, purely from a technical aspect, were excluded from the study rather than being considered a failure of OTSC, which occurred in 5% of otherwise eligible patients [19]. This methodological characterization limits the generalizability of the results and may have favored the OTSC group. The final RCT by Soriani et al. also showed more favorable outcomes with OTSC but has only been published in abstract form to date, hence an adequate detailed assessment of the study methodology is not possible at the time of writing of this commentary [20].

An important aspect to consider when opting to use OTSCs is the expertise of the endoscopist applying this therapy. The published RCTs to date have only included highly experienced endoscopists trained in using OTSC, some of which underwent dedicated standardized teaching prior to using this technology in the trials. Even with appropriate training, failure to apply the OTSC (approximately 3-8%) [18,19] or misplacement occurred resulting in severe complications including perforation and obstruction from pseudopolyp formation (2%) [19].

Furthermore, if the OTSC is applied inappropriately to the bleeding lesion and it fails to control the bleeding, further salvage endoscopic interventions may become difficult if not

even impossible, which may result in higher utilization of rescue transarterial embolization [18]. Furthermore, the exact OTSC type to use in NVUGIB remains unclear but a recent retrospective study suggested the OTSC-a is preferred due to an associated lower risk of recurrent bleeding and blood transfusions compared to the OTSC-t [21]. In addition, the costs of such clips are significantly greater than other hemostatic modalities, even if the strategy of using OTSC as rescue therapy has been shown to be cost-effective [22]; the cost-effectiveness of this strategy as first-line therapy thus needs to be better characterized prior to its routine implementation in many jurisdictions.

What is the current role of OTSC in NVUGIB?

Should all these methodological issues deter us from using OTSC as a modality to manage NVUGIB? The answer is probably no, however, careful considerations must be taken into account before this technology is used, if ever, on a routine basis by endoscopists in routine practice.

These aspects include adequate technical training on using the OTSC, while understanding the limitations and risk associated with its use. The essential question is when should we use OTSC in patients with NVUGIB? The clear answer is among patients who failed conventional endoscopic therapy or have recurrent bleeding as suggested by societal guidelines. In addition, patients who are predicted to have higher risk of rebleeding with conventional endoscopic tools based on the bleeding lesion's endoscopic appearance may benefit the most from applying these clips as first-line therapy.

Immediate adoption of the OTSC in routine practice as primary hemostastic endoscopic modality for all patients with NVUGIB is probably not appropriate at this stage. Further analyses and additional data are needed to clarify the subset of patients who will benefit most from such an approach.

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