

First-line endoscopic treatment with over-the-scope clips in patients with either upper or lower gastrointestinal bleeding: a multicenter study

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Raffaele Manta¹, Santi Mangiafico¹, Angelo Zullo², Helga Bertani¹, Angelo Caruso¹, Giuseppe Grande¹, Francesco Paolo Zito¹, Benedetto Mangiavillano³, Luigi Pasquale⁴, Andrea Parodi⁵, Bastianello Germanà⁶, Gabrio Bassotti⁷, Fabio Monica⁸, Maurizio Zilli⁹, Antonio Pisani¹⁰, Massimiliano Mutignani¹¹, Rita Conigliaro¹, Giuseppe Galloro¹²

Institutions

- 1 Digestive Endoscopy Unit, S.Agostino-Estense Hospital, Modena, Italy
- 2 Gastroenterology Unit, Nuovo Regina Margherita Hospital, Rome, Italy
- 3 Digestive Endoscopy Unit, Humanitas – Mater Domini Hospital, Castellanza, Varese, Italy
- 4 Gastroenterology Unit, San Giuseppe Moscati Hospital, Avellino, Italy
- 5 Gastroenterology Unit, Galliera Hospital, Genova, Italy
- 6 Gastroenterology and Digestive Endoscopy Unit, Belluno Hospital, Belluno, Italy
- 7 Gastroenterology Unit, Department of Medicine, Perugia University, Perugia, Italy
- 8 Gastroenterology Unit, Azienda Sanitaria Universitaria Integrata, Trieste, Italy
- 9 Gastroenterology Unit, Azienda Sanitaria Universitaria Integrata, Udine, Italy
- 10 Gastroenterology Section, Department of Emergency and Organ Transplantation, Bari University, Bari, Italy
- 11 Digestive Endoscopy Unit, Niguarda Hospital, Milan, Italy
- 12 Surgical Digestive Endoscopy, Department of Clinical Medicine and Surgery, Federico II University, Naples, Italy

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Corresponding author

Raffaele Manta, MD, Gastroenterologia ed Endoscopia Digestiva, Azienda Ospedaliera Universitaria di Modena, Ospedale S.Agostino-Estense, Viale Giardini Nord 1355, Baggiovara, Modena, Italy

Fax: +0039 059 3961216

raffaelemanta4@gmail.com

ABSTRACT

Background and study aims Endoscopic treatment is the mainstay approach for gastrointestinal bleeding, in either upper (UGIB) or lower (LGIB) tract. The over-the-scope clip (OTSC) may overcome limitations of standard clips or thermocoagulation in high-risk bleeding lesions. We evaluate the main clinically relevant outcomes following endoscopic hemostasis with OTSC in high-risk lesions and/or patients.

Patients and methods This was a retrospective analysis of prospectively collected databases including all patients with UGIB and LGIB who underwent OTSC placement as first-line treatment in eleven tertiary endoscopic referral centers. Technical success, primary hemostasis, rebleeding, blood transfusion, hospital stay, and hemorrhage-related mortality rates were evaluated.

Results Data from 286 patients, with either UGIB (N=214) or LGIB (N=72) were available. Overall, 112 patients (39.2%) were receiving antithrombotic therapy. Technical success and primary hemostasis rates were 97.9% and 96.4%, respectively. Early rebleeding occurred in 4.4%, more frequently in those on antithrombotic therapy, and no late rebleeding was observed. Following a successful primary haemostasis, only 5.2% patients needed blood transfusions, and the median hospital stay was 4 days (range: 3–11). Eighteen patients with either technical failure (N=6) or rebleeding (N=12) underwent radiological or surgical approaches. Overall, bleeding-related deaths occurred in 5 (1.7%) patients, including 3 patients with technical procedural failure, and 2 in the rebleeding group.

Conclusions Data from our large, multicenter study show that OTSC placement is an effective first-line treatment for hemostasis in high-risk patients and/or lesions both in upper and lower gastrointestinal tract.

Introduction

Gastrointestinal bleeding, with an estimated annual incidence ranging from 20 to 172 cases per 100 000, frequently occurs in clinical practice [1,2]. The bleeding may originate from either the upper gastrointestinal tract (UGIB) or lower gastrointestinal tract (LGIB), with acute UGIB occurring four to six times more frequently than LGIB [3,4]. Gastrointestinal bleedings frequently lead to hospital admission, and are associated with morbidity and mortality, especially in the elderly patients [1–4]. Moreover, some patients develop a rebleeding episode, which is associated with increased mortality [5]. Endoscopic therapy was proven to be effective in stopping active gastrointestinal bleeding, also reducing risk of rebleeding, need for surgery, the number of erythrocytes units for transfusion, and length of hospital stay [6].

Although endoscopic devices have been improved, achieving complete hemostasis still remains a challenge in those patients with complicated lesions, that is, severe bleeding from large vessels or large fibrotic ulcer. These patients, as well as those with endoscopic hemostasis failure, were generally treated with surgical or radiologic approaches [5]. For endoscopic hemostasis in these patients, use of over-the-scope clip (OTSC) was recently proposed. Indeed, emerging data support a role for such a device as both first-line and rescue endoscopic therapy in patients with non-variceal UGIB, and some data are available also for LGIB treatment [7].

This multicenter study aimed to evaluate data from patients who underwent emergency endoscopy for either UGIB or LGIB in whom the OTSC was used as first-line therapy. The main clinically relevant outcomes were evaluated.

Patients and methods

Study patients and procedures

Data from all patients with UGIB or LGIB who were treated with OTSC as first-line therapy in 11 Italian tertiary Hospitals between 2014 and July 2017 were prospectively maintained in a specific database and retrospectively analyzed. The endoscopic procedures were performed by skilled operators under either anesthesiology-assisted deep sedation or midazolam sedation, according to the clinical condition of the patient. The decision to use an OTSC (Ovesco Endoscopy AG, Tübingen, Germany) as first-line endoscopic treatment depended on the endoscopist's evaluation. Briefly, all high-risk patients and/or those with high-risk bleeding lesions were considered for such an approach. Patients on antithrombotic therapy and those with relevant comorbidities (heart, kidney, and hepatic impairment) were considered as high-risk. Bleeding lesions were classified as high-risk when at least one of the following conditions was present: lesion with bleeding artery or a vessel larger than 2 mm in diameter was visible; a lesion was deep penetrating, excavated or fibrotic in which presence of a microperforation could not completely be ruled out or thermal therapy could increase risk of perforation; and a lesion could not be safely treated by other endoscopic devices. Before the endoscopic procedure, written informed consent was obtained to the extent possible in emer-

gency situations from patients or their family members. Because this was a retrospective study, no patient identification was involved, and no study-driven clinical intervention was performed, our Investigational Review Boards waived formal review and approval, deeming the study to be an extension of existing procedures.

Study outcomes

The measured outcomes were: 1) technical success defined as correct deployment of the device on the bleeding lesion; 2) primary hemostasis, defined as bleeding stopping without additional endoscopic treatments; 3) early (within 24 hours) or delayed (within 30 days) rebleeding rate; 4) management with non-endoscopic procedures following endoscopic failure; 5) need for blood transfusion post-procedure; 6) length of hospital stay; and 7) procedure-related 30-day mortality rate. A rebleeding episode was considered when hematemesis, melena, hematochezia, shock or loss of hemoglobin higher than 2 g/dL occurred within 24 hours. A second-look endoscopy was planned on demand, according to the endoscopist's evaluation at the end of procedure.

Statistical analysis

Categorical variables are given as absolute and relative frequencies, and univariate analysis was performed by using the χ^2 test or the Fisher's exact test, as appropriate. The 95% confidence intervals (CI) were calculated. The Student's *t* test for unpaired data was used for comparing age between different subgroups. A *P* value <0.05 was considered statistically significant.

Results

Descriptive analysis

A total of 286 patients (mean age: 68 years, range: 28–89 years; M/F: 154/132) were treated during the study period. Overall, 112 patients (39.2%) were receiving an antithrombotic (anticoagulant or antiplatelets) therapy. There were 214 (74.8%) patients presenting with UGIB and 72 with LGIB. As compared to UGIB, patients with LGIB were significantly older (Mean age: 76 ± 11.7 vs 66 ± 10.2 years; $P=0.04$), and were receiving more frequently antithrombotic therapy (52, 72.2% vs 60, 28.1%; $P<0.001$), while no difference emerged in gender distribution (males: 56.9% vs 53.8%). Indications for OTSC treatment are reported in ► **Table 1**. Peptic ulcers (gastric or duodenal) were the most frequent (131/214; 61.2%) cause of bleeding in the UGIB patients, while post-endoscopic mucosal resection (EMR) or post-endoscopic submucosal dissection (ESD) bleeding was the main (47/72; 65.3%) cause of LGIB. Overall, traumatic and non-traumatic OTSC clips were employed in 168 (58.7%) and 118 (41.3%) patients, respectively.

Technical and clinical outcomes

Correct positioning of OTSC was successful in 280 cases, accounting for a technical success of 97.9% (95% CI=96.2–99.6), while it failed in six patients with ulcers in either gastric body-fundus (3 cases) or posterior wall duodenal bulb (3 cases). Primary hemostasis was achieved in 270 patients

► **Table 1** Indications for endoscopic treatment in either upper (UGIB) or lower (LGIB) gastrointestinal bleeding patients.

	F1a	F1b	Spurting	Oozing	Patients
UGIB (N = 214)					
Duodenal ulcer	34	40			74
Gastric ulcer	24	33			57
Mallory-Weiss lesion			7	22	29
Post-gastric ESD			11	13	24
Anastomosis			10	9	19
Dieulafoy lesion			11		11
LGIB (N = 72)					
Post-EMR			9	16	25
Post-ESD			9	13	22
Anastomosis			8	11	19
Diverticula				4	4
Rectal ulcer	1	1			2

ESD, endoscopic submucosal dissection; EMR, endoscopic mucosal resection

(96.4%; 95% CI = 94.2–98.6) with a successful OTSC placement, while it failed in 10 patients treated for peptic ulcer (6 cases), post-mucosectomy bleeding (3 cases), and anastomotic bleeding (1 case). Early rebleeding occurred in 12 (4.4%) patients who achieved primary hemostasis, and no late rebleeding was observed. Of note, patients with rebleeding were on antithrombotic therapy more frequently than those without it (12/12, 100% vs 100/258, 38.8%; $P < 0.0001$). Overall 14 (5.2%) patients needed blood transfusions following a successful primary hemostasis, including 12 (100%) and 2 (0.8%) patients with or without rebleeding, respectively ($P < 0.001$). These patients received median packed red cell units of 2 (range: 1–3). Median length of hospital stay was 4 days (3–11 days). All results are summarized in ► **Fig. 1** and ► **Table 2**.

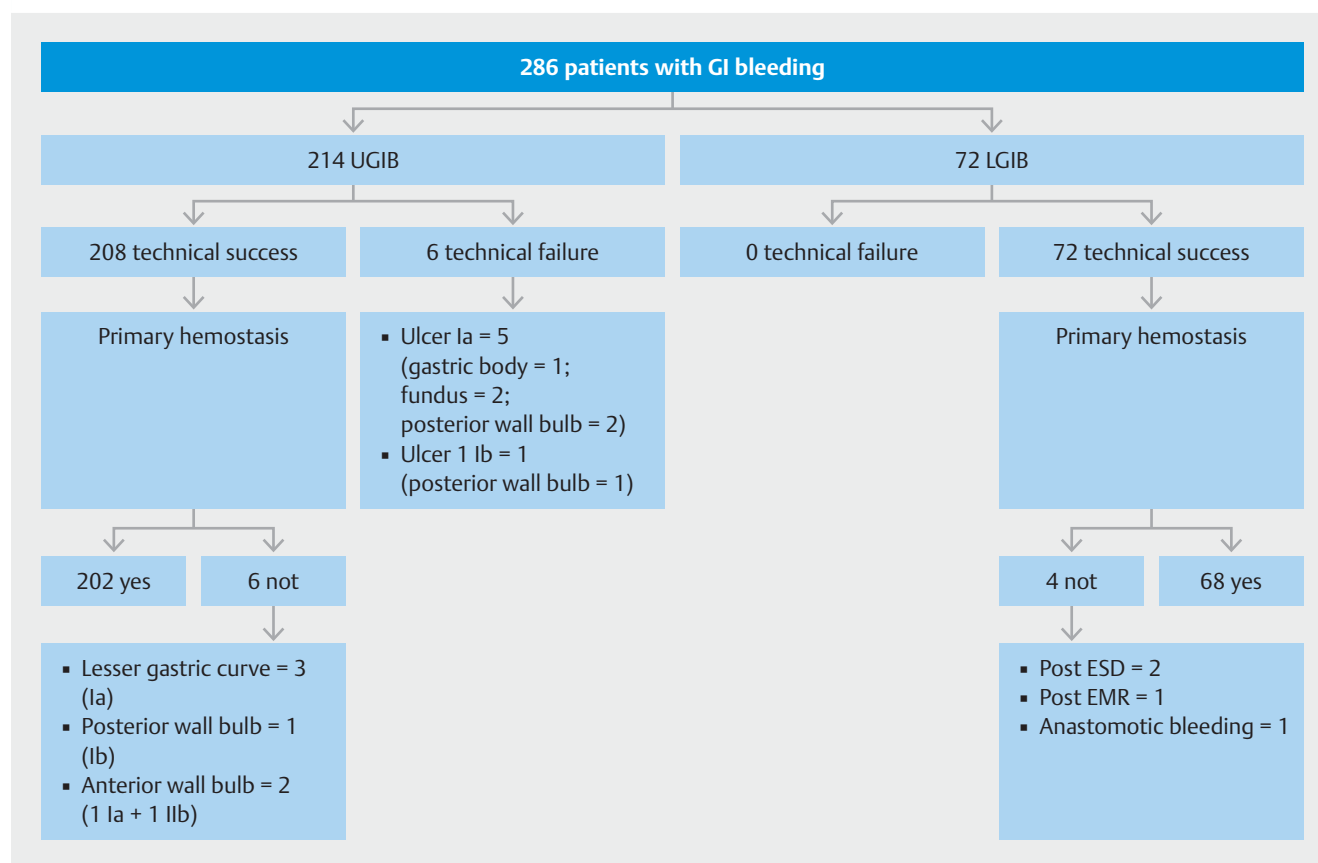
Management of failure patients

Of the six patients with technical failure, four were treated with radiological arterial embolization and two with surgery (1 laparoscopic ulcer closure; 1 Whipple intervention). Of them, one and two patients who underwent surgical or radiological approach, respectively, died within 30 days. In the 10 patients with primary hemostasis failure, hemorrhage was successfully stopped by using an additional endoscopic technique in the same session (N = 4), radiological vascular embolization (N = 5), or surgery (N = 1). Finally, the 12 patients with early rebleeding were managed with epinephrine injection and/or endoscopic clip (N = 8) or radiological vascular embolization (N = 4). In this group, one patient died 8 days following vascular embolization, and another patient 22 days following surgical treatment performed after vascular embolization failure. Thus, a total of 5 patients (1.7%; 95% CI = 0.22–3.26) died within 30 days from procedure for a bleeding-related cause, including three of six pa-

tients following technical failure, and two of 12 with early rebleeding.

Discussion

Gastrointestinal bleeding is often a dramatic and potentially life-threatening event, particularly in the elderly and in patients with relevant comorbidities in whom a definite mortality rate has been reported [1–4]. An effective endoscopic procedure at the first attempt is clinically relevant not only for achieving stable primary hemostasis, but also for preventing rebleeding [5]. Endoscopic hemostasis is currently performed with different approaches, by using diverse devices [8]. Unfortunately, endoscopic thermocoagulation is able to consistently seal only small bleeding arteries (<2 mm). On the other hand, application of standard hemostatic clips can be difficult in chronic ulcers with a fibrotic base or in lesions located in the posterior wall of the duodenal bulb or the lesser gastric curvature [9]. Moreover, these clips not infrequently dislodge, leading to recurrent bleeding. More than 10 years ago, the OTSC was introduced for endoscopic closure of gastrointestinal perforations, leaks, and fistulas by firmly approximating tissues [10, 11]. Recently, OTSC has been proven to be effective in reducing complications (perforation and bleeding) when preventively positioned after ESD in the duodenum [12]. Few case series highlighted the usefulness of OTSC application also in patients with gastrointestinal bleeding [13, 14], allowing simultaneous sealing of the blood vessel and closure of the ulcer by compressing the surrounding tissue around the lesion. In a recent German study, OTSC application achieved a high success rate (92.4%) in 118 patients with UGIB [15]. Our large, multicenter study found that OTSC is a valid hemostatic option as first-line therapy in both UGIB and LGIB patients. Indeed, it may be success-



► **Fig. 1** Main results of the study.

► **Table 2** Main outcomes following endoscopic treatment.

	Total (N = 286)	UGIB (N = 214)	LGIB (N = 72)
Technical success (%)	280 (97.9)	208 (97.2)	72 (100)
Primary hemostasis (%) ¹	270 (96.4)	202 (97.1)	68 (94.4)
Early rebleeding (%) ²	12 (4.4)	9 (4.5)	3 (4.4)
Post-treatment blood trasfusion (%)	14 (4.9)	8 (3.7)	6 (8.3)
Hospital stay, median (range); days	4 (3–11)	4 (2–10)	4 (3–11)
Mortality (%)	5 (1.9)	4 (2)	1 (1.5)

UGIB, upper gastrointestinal bleeding; LGIB, lower gastrointestinal bleeding

¹ Calculated in 280 patients who achieved technical success.

² Calculated in 270 patients who achieved primary hemostasis.

fully applied in the vast majority of patients, with a procedure-related failure rate as low as 2.1 %, mainly including lesions localized in the gastric fundus or in the posterior wall of the duodenal bulb. Similarly, clinical success was impressively high when considering that primary hemostasis was achieved in more than 96 % of patients in whom the OTSC was correctly positioned.

Another clinically relevant finding was that only 5.2 % of patients needed blood transfusions following a successful primary hemostasis with OTSC, and that it was possible to discharge pa-

tients within few days (median: 4 days). This would suggest a firm and definitive closure of bleeding source with such a device. Of note, the early rebleeding rate was acceptably low (< 5 %), and it mainly occurred in patients on antithrombotic therapy in our study. Such a finding is consistent with the rebleeding rate ranging from 0 % to 22 % reported in other studies [7], and with observation that rebleeding following OTSC placement occurs in up to 35 % of patients receiving antithrombotic therapy [16]. However, other studies failed to show that antith-

robotic therapy was an independent factor of rebleeding in these patients [14, 17].

To our knowledge, this the largest, multicenter study on OTSC use for first-line therapy in fitting patients with either UGIB or LGIB. Indeed, a recent overview of data from the last decade found a total of 14 case series, mainly focused on UGIB, with a median of only 8 patients (range: 1 to 44) enrolled [13]. Overall, in these studies, clinical success rates ranged from 77.7% to 100% when OTSC was used as first-line therapy, with a rebleeding rate of 7.4% to 13.6% in the few series including more than 20 patients. Similar data were found in the most recent multicenter study [15]. In addition, preliminary data from a randomized study found that OTSC application was more effective than standard hemostasis (through-the-scope clip or thermal plus adrenaline) as rescue therapy in patients with peptic ulcer rebleeding [18].

Data on OTSC as first-line treatment in LGIB patients are still scanty, with the largest series including only 22 cases [13]. Therefore, our data on 71 patients with LGIB could be regarded as particularly relevant. In our series, the most frequent causes of LGIB were those post-endoscopic or surgical procedures (EMR, ESD, and anastomosis). We observed that technical and clinical successes were similarly high in UGIB patients, suggesting that OTSC may also be used successfully in patients with lower gastrointestinal bleeding.

Finally, an overall bleeding-related mortality rate as low as 1.7% was observed in our case series. This would appear consistent with the zero mortality reported in another study enrolling patients receiving antithrombotic therapy who were managed with OTSC placement as first-line treatment [14]. In our series, death occurred only in patients in whom the OTSC placement was impossible or who experienced rebleeding. Unfortunately, the fatal event happened despite the interventional radiology or surgical approaches that were performed. These observations would suggest that further therapeutic improvement is required in these patient subgroups.

Conclusion

In conclusion, data from our large, multicenter study found that OTSC placement is an effective first-line treatment for hemostasis in high-risk patients and/or who have lesions both in the upper and lower gastrointestinal tract. Therefore, cost-effectiveness studies are urged to establish whether this approach is cost-effective as compared to other endoscopic treatments.

Competing interests

None

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