

Over-the-scope clip as first-line therapy for ulcers with high-risk bleeding stigmata is efficient compared to standard endoscopic therapy



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ABSTRACT

Background and study aims Ulcers with high-risk stigmata have significant rebleeding rates despite standard endoscopic therapy. Data on over-the-scope clip (OTSC) for recurrent bleeding is promising but data on first line therapy is lacking. We report comparative outcomes of OTSC as first-line therapy versus standard endoscopic therapy in ulcers with high-risk stigmata.

Patients and methods Consecutive adults who underwent endoscopic therapy for ulcers with high-risk stigmata between July 2019 to September 2020 were included. Patients were grouped into OTSC or standard therapy based on first-line therapy used on index endoscopy. Outcomes measured included: 1) intra-procedural hemostasis based on endoscopic documentation of adequate hemostasis; 2) 7-day rebleeding (>2 g/dL drop in hemoglobin, hematochezia or hemorrhagic shock); 3) cost of endoscopic interventions; and 4) procedure duration measured as endoscope insertion to removal time. Cost of tools used during the index endoscopy was included.

Results Sixty-eight patients were included, 47 were in standard therapy and 21 in the OTSC group. Hemostasis was achieved in 95.2% in the OTSC group compared to 83.0% in the standard therapy group ($P=0.256$, number needed to treat [NNT]: 9). Procedure time was shorter in the OTSC group (23 vs. 16 minutes, $P=0.002$). Cost of endoscopic interventions were comparable, $P=0.203$. Early rebleeding was less often in OTSC group, two (9.5%) compared to 10 (21.3%) in standard therapy group, NNT 9.

Conclusions Use of OTSCs as first-line treatment for ulcers bleed probably improves hemostasis and decreases early rebleeding. Use of OTSC as first-line therapy shortened procedure duration without increasing the cost of endoscopic interventions.

* Have contributed equally in this paper.

Introduction

Upper gastrointestinal bleeding (UGIB) accounts for approximately 200,000 hospitalizations annually in the United States although the incidence appears to be decreasing recently [1, 2]. Peptic ulcer disease is the most common cause of nonvariceal bleeding occurring in approximately 78 cases per 100,000 adults and in year 2009, led to a cost of \$7.6 billion dollars [1]. In-hospital mortality from non-variceal UGIB has also improved at a faster rate compared to incidence owing to improved adherence to resuscitation guidelines, improved access to endoscopy and almost universal use of intravenous proton pump therapy [1]. This is likely due to improved access to endoscopy, higher rate of endoscopy and endoscopic therapy alongside of proton pump inhibitor use.

Endoscopic therapy is primarily utilized in UGIB to decrease early rebleeding, which decreases mortality [3]. Despite increasing utilization of endoscopic therapy, early rebleeding rates remain high [4, 5]. Rebleeding risk in ulcers can be accurately assessed by the presence of high-risk stigmata for rebleeding which include active spurting, active oozing, non-bleeding visible vessel and adherent clot. Successful treatment of these high-risk lesions is an important determinant of rebleeding risk and mortality [6]. Current standard of endoscopic therapy consists of epinephrine injection followed by hemoclips or coaptive coagulation [7].

However, endoscopic intervention for high-risk stigmata can occasionally precipitate brisk bleeding necessitating emergent rescue therapy such as embolization or surgery especially in complicated lesions like fibrotic ulcers and in difficult locations. Over the last decade use of over-the-scope clip (OTSC) has emerged in treatment of recurrent ulcer bleeding with promising results [8]. Data on use of OTSC as first-line therapy are very limited [9]. Also, the cost of a new device will also have an impact on both availability and utilization. In this study we compared clinical outcomes and cost of endoscopic therapy with OTSC as first-line therapy to standard endoscopic therapy in UGIB from non-malignant ulcers.

Patients and methods

Study design and settings

Consecutive patients older than age 19 years who underwent endoscopic therapy for UGIB from non-malignant ulcer with high-risk stigmata were included. Patients were treated at three facilities located in a US Midwest metropolitan area between July 2019 and September 2020. Selection of first-line modality, OTSC versus standard therapy, was based on endoscopist preference. Procedures were performed by nine gastroenterologists, six of whom used OTSCs; gastroenterology fellows were involved in all the procedures. Patients were categorized into the OTSC group or standard treatment group based on the first-line therapy chosen on the index endoscopy. Subsequent endoscopies for recurrent bleeding were not included in the analysis. None of the patients were pregnant at the time of endoscopy or incarcerated. Sample size calculation was not

performed. This study was approved by the Institutional Review Board of Creighton University Medical Center.

Outcomes

Primary outcomes measured were: (1) intra-procedural hemostasis based on endoscopic documentation of adequate treatment of high-risk stigmata without requiring rescue therapy with OTSC, emergent embolization or surgery; (2) 7-day rebleeding, defined by clinical evidence of ongoing bleeding (>2 g/dL drop in hemoglobin after initial stabilization, development of hematochezia or hemorrhagic shock); (3) procedure duration measured from endoscope insertion to final removal time; and (4) cost of endoscopic interventions. Cost was calculated based on the total cost of hemostatic clips, bipolar probe, injection needle, epinephrine vial, and OTSC during the index endoscopy. Cost was based on the amount charged to the hospital by the device manufacturer. Secondary outcomes measured were: (1) need for repeat endoscopy during hospitalization; (2) endoscopic intervention performed during repeat endoscopy; and (3) 30-day readmission for rebleeding, hospital length of stay and inpatient mortality.

Interventions

After resuscitation and administration of intravenous proton pump inhibitors, endoscopies were performed using an adult gastroscope with forward water jet system. Once the lesion was identified and examined for high-risk stigmata, the treatment modality was selected based on endoscopist preference. Standard therapy included deployment of 360-degree rotatable hemoclips or coaptive thermocoagulation using a bipolar probe at 15 to 20 watts for 8 to 10 seconds or in combination with or without epinephrine 1:10,000 dilution injection. For OTSC placement, the endoscope was withdrawn, an 11-mm OTSC with tooth and small spikes was loaded on the gastroscope, followed by reinsertion and deployment of OTSC over the high-risk stigmata while maintaining continuous suction. The whole ulcer was not always covered by the OTSC. Patients were observed in the hospital for 48 to 72 hours after the endoscopic therapy and all were treated with a continuous proton pump inhibitor infusion for 72 hours.

Data collection

Two gastroenterology fellows with more than 1 year of endoscopy training performed the retrospective chart review from the electronic medical record. All inpatient endoscopies performed during the study period were reviewed manually to ensure they were endoscopies done for UGIB. Patients who underwent endoscopic therapy during the index endoscopy for non-malignant ulcers with high-risk stigmata were included in this study. Data collection on eligible patients was performed using a predefined data collection sheet using Microsoft Excel. Data points included are key demographics and clinical characteristics. The reviewers were not blinded to the intervention and outcomes.

► **Table 1** Demographics and clinical characteristics in the two groups.

Characteristics	Standard therapy (n=47)	OTSC (n=21)	P value
Age, median (IQR), in years	67 (55–78)	58 (52–70)	0.137
Sex, men (%)	34 (72.3)	14 (66.7)	0.635
GBS, median (IQR),	11 (8–13)	10 (5–13)	0.526
Anticoagulation or antiplatelet use, n (%)	15 (32)	12 (57)	0.063
Reversal of anticoagulation, n (%)	1 (2.1)	1 (4.8)	
Endotracheal intubation for endoscopy, n (%)	11 (23.4)	4 (19.0)	0.763
Etiology n (%)			0.096
Peptic ulcer	41 (87.2)	15 (71.4)	
Anastomotic ulcer	4 (8.5)	6 (28.6)	
Mallory Weiss tear	2 (4.3)	0 (0.0)	
High-risk stigmata			0.194
Non-bleeding visible vessel	25 (53.2)	15 (71.4)	
Adherent clot	12 (25.5)	5 (23.8)	
Oozing ulcer with vessel	10 (21.3)	1 (4.8)	
Ulcer location			0.053
Stomach	11 (23.4)	4 (19.5)	
Esophagus or gastroesophageal junction	8 (17.0)	0 (0)	
Duodenum	24 (51.0)	11 (52.4)	
Gastrojejunal anastomosis	4 (8.5)	6 (28.6)	
Endoscopic tools used			
Bipolar probe	37 (78.7)	–	–
Hemoclips	24 (51.1)	–	–
Epinephrine	36 (76.6)	6 (28.6)	<.001
Rescue OTSCs	5 (10.6)	–	–

GBS, Glasgow-Blatchford bleeding score; IQR, interquartile range; OTSC, over-the-scope clip.

Statistical analysis

All descriptive statistics are stratified by treatment group. Continuous variables are presented as median and interquartile range, compared using the Mann-Whitney test. Categorical variables are presented as frequency and percent, compared using the chi-square or Fisher's exact test. Number needed to treat or harm was calculated, as appropriate. To account for censoring resulting from in-hospital mortality, the difference in length of hospital stay was evaluated using the Kaplan-Meier method and log-rank test. All analyses were conducted using SAS v. 9.4 with $P < 0.05$ used to indicate statistical significance.

Results

A total of 68 patients with UGIB underwent endoscopic therapy for ulcer with high-risk stigmata were included. Of them, 47 had standard therapy as first line and 21 patients received OTSC as first-line therapy. The two groups were similar in age, sex, anticoagulant or antiplatelet agent use, admission Glasgow-Blatchford bleeding score, etiology of ulcer, location of ulcer, and type of high-risk stigmata (► **Table 1**).

Hemostasis during endoscopy was achieved in 95.2% in the OTSC group compared to 83.0% in the standard therapy group ($P = 0.256$, number needed to treat: 9) (► **Table 2**). Five patients in the standard therapy groups needed OTSC as rescue therapy to achieve hemostasis during the index endoscopy. Technical success in OTSC group was 100%.

Index endoscopy procedure time was significantly shorter in the OTSC group (23 vs. 16 minutes, $P = 0.002$). We observed

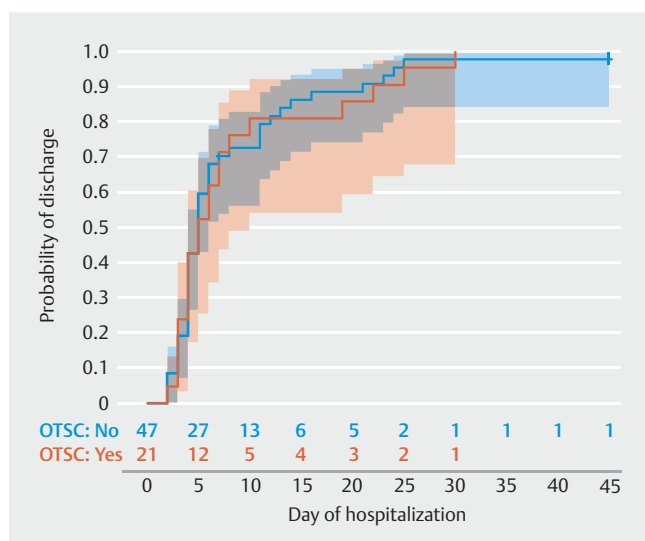
► **Table 2** Outcomes of conventional treatment versus over-the-scope clip (OTSC) as first-line treatment.

	Standard therapy group (n = 47)	OTSC group (n = 21)	NNT/NNH	P value
Intra-procedural hemostasis	39 (83.0)	20 (95.2)	NNT: 9	0.256
7-day rebleeding	10 (21.3)	2 (9.5)	NNT: 9	0.317
Repeat endoscopy	7 (14.9)	4 (19.1)	NNH: 25	0.727
Endoscopic intervention on repeat endoscopy	5 (10.6)	1 (4.8)	–	0.658
Vascular embolization performed	6 (12.8)	3 (14.3)	–	1.000
Procedure duration	23 [14–32]	16 [14–21]	–	0.002
Cost ¹	398 [242–596]	438 [438–482]	–	0.203
Length of hospital stay	5 [4–11]	5 [4–8]	–	0.864
In-hospital mortality	2 (4.3)	0 (0.0)	NNT: 23	1.000
30-day readmission ²	2 (4.4)	0 (0.0)	NNT: 24	1.000

OTSC, over-the-scope clip; NNT, number needed to treat; NNH, number needed to harm.

¹ Costs epinephrine vial \$15, bipolar probe \$198, injection needle \$29, through-the-scope clip \$199, and OTSC \$438.

² Analysis only includes patient discharged alive.



► **Fig. 1** Hospital length of stay shown as probability of discharge. Shaded areas represent 95% confidence intervals.

comparable cost of endoscopic intervention during the index endoscopy, median cost of \$398 (IQR \$242 to \$596) in standard therapy group vs \$438 (IQR \$438 to \$482) in OTSC groups, $P=0.203$). The average hospital length of stay was similar in both the groups ($P=0.864$) (► **Fig. 1**).

Early rebleeding occurred less often in the OTSC group, two (9.5%) compared to 10 (21.3%) in the standard therapy group, number needed to treat (NNT) nine. None of the patients from the OTSC group had 30-day rebleeding or related readmission whereas two patients (4.4%) in the standard therapy group had readmissions from rebleeding.

Discussion

Our comparative study results demonstrate a high rate of success in attaining hemostasis with OTSC as first-line endoscopic therapy for ulcers with high-risk stigmata compared to the standard endoscopic therapy, but this difference did not reach statistical significance, likely due to smaller sample size. The hemostasis achieved with OTSC therapy was probably more durable based on the numerically but not statistically lower 7-day and 30-day rebleeding rate. The cost of endoscopic interventions with OTSC use is comparable to standard endoscopic therapy. The procedure duration was shorter with OTSC use as first-line therapy. The NNT for additional patients to achieve hemostasis and to decrease early rebleeding was nine.

OTSCs were initially introduced for gastric perforations and fistula closures by tissue approximation. Over the last 5 years, however, their use has become more widespread, including for treatment of nonvariceal UGIB. Initial reports describe OTSC use as rescue therapy for recurrent ulcer bleeding but recent studies have reported promising results for first line therapy [8, 9]. These clips have the ability to grasp a large amount of tissue due to its wide jaw and higher degree of tension between two cusps helps to achieve good mechanical tamponade, ability to grip larger fibrotic, bleeding vessels, thus enabling its use in challenging lesions where standard treatment can be difficult. Also, because OTSC application is based on suction, they can be used for lesions in difficult locations in which holding a thermal coaptation probe for 8 to 10 seconds can be challenging. In our study, OTSC was not a preferred first-line tool for gastroesophageal junction or esophageal lesions. If an associated peptic stricture is present, OTSC is hard to use based on a narrow lumen, which limits reach with a clip (outer diameter is 16.5 mm) and maneuverability. We have used OTSCs for rebleeding with good success in one patient.

A recursive review of the literature identified only two studies comparing efficacy of OTSC as first-line therapy vs standard endoscopic therapy in non-variceal UGIB. A randomized controlled trial by Jensen et al. comparing ulcers or Dieulafoy lesions with high-risk stigmata and confirmed arterial flow with Doppler probe included 25 patients in the OTSC group and 28 patients in the standard endoscopic therapy group [10]. Intra-procedural hemostasis was 100% in both groups but early rebleeding was lower in the OTSC group (4% vs. 28.6%) and the NNT was four [10]. Another study that compared OTSC with standard endoscopic therapy as first-line use is from Italy, where 112 patients in the OTSC and 215 patients in the standard therapy group were identified using propensity score match analysis and had combination of ulcers, angioectasia and Dieulafoy lesions [11]. The early rebleeding rate in the OTSC group was 8% vs 20% in the standard therapy group. The early rebleeding rate in our study is comparable to the above-mentioned studies, with a frequency of 9.5% in the OTSC group vs 21.5% in the standard therapy group. In addition, our patients were more homogenous as we did not include patients with Dieulafoy's lesion or angioectasia. These vascular lesions are easier to treat due to absence of confounding factors such as fibrosis or granulation which can negatively affect endoscopic therapy. A high rate of success in intra-procedure hemostasis or successful treatment of high-risk stigmata with OTSC in non-variceal ulcer is reported to range between 88% and 100% [9,11–13]. In our study, successful treatment was achieved in 96% of patients when OTSC was used as first-line therapy for ulcer bleeding.

Use of OTSC for recurrent peptic ulcer bleeding was previously reported to be cost effective in the STING trial from Germany [14]. Our study demonstrates cost effectiveness of endoscopic intervention in the index endoscopy when OTSC is used as primary therapy. Our analysis did not include data on cost savings from the low rate of rebleeding and readmission to the hospital but demonstrated shorter procedure duration with OTSC as first-line therapy compared standard therapy with or without OTSC as rescue therapy. This leads to downstream patient care and cost benefits, such as reduced anesthesia time, more efficient operational use of the endoscopy suite, and reduced need for further invasive procedures. In addition to higher cost per OTSC clip, lack of training with use of OTSC is another concern among some gastroenterologists, anecdotally. One solution is to use simulation-based learning, which has shown to achieve mastery in use of OTSC and increase the rate of adoption in clinical practice, in both novice and experienced gastroenterologists [15].

A major limitation of our study was the retrospective study design. The choice of first-line therapy assignment could not be controlled in a retrospective study. In the majority of cases, first-line therapy assignment was dependent on the endoscopist on call for that particular day who performed the procedure. Therefore, there was some degree of randomness in intervention allocation. Another limitation is lack of standardization of endoscopic therapy training, in contrast to the study by Jensen et al, adding operator dependence on measured outcomes [9]. Based on the encouraging results in multiple stud-

ies, we aim to train the rest of our providers with OTSC, likely using a simulation model. Follow-up data were based on return to our hospital system and are limited by the fact that other healthcare systems in our metropolitan area could have been utilized by the patients. Cost estimation in our study was based on the hospital's contract with the device supplier, which most likely differs hospital to hospital.

Conclusions

The use of OTSC as first-line therapy for ulcers with high-risk stigmata probably improves rates of hemostasis and reduces risk of early rebleeding compared to standard endoscopic therapy. These observations need to be confirmed in a large sample. Although the cost of the individual OTSC is higher than other endoscopic hemostasis devices, the overall cost of endoscopic interventions during the index endoscopy does not increase significantly. This is because multiple devices are often needed in standard endoscopic therapy. Use of OTSC as first-line therapy shortened total procedure duration, thereby improving endoscopist efficiency in management of ulcer bleeds.

Competing interests

The authors declare that they have no conflict of interest.

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