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Randomized Controlled Trial of Over-the-Scope Clip as Initial Treatment of Severe Non-Variceal Upper Gastrointestinal Bleeding

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Abstract

Background and Aims: No prior randomized controlled trial (RCT) has reported patient outcomes of large over-the-scope clip (OTSC) compared to standard hemostasis as initial endoscopic treatment of severe NVUGIB. This was our study aim.

Methods: Patients with bleeding ulcers or Dieulafoy's lesions and major stigmata of hemorrhage - SRH (active spurting bleeding, visible vessel, or clot) - or lesser SRH (oozing bleeding or flat spots – with arterial blood flow by Doppler probe) were randomized to OTSC or standard endoscopic hemostasis (with hemoclips or multipolar electrocoagulation – MPEC). Patients and their healthcare providers were blinded to treatments and made all post-randomization management decisions. Ulcer patients received high dose intravenous infusions of proton pump inhibitors (PPI) for 3 days, then 27 days of oral PPI. 30 day outcomes were prospectively recorded; data management was with SAS; and data analysis was by a statistician.

Results: 53 patients (25 OTSC, 28 Standard) were randomized, with similar baseline risk factors. However, there were significant differences in OTSC vs. Standard groups in rates of rebleeding (4% vs. 28.6%; p = 0.017; relative risk 0.10, 95% confidence intervals 0.01, 0.91; number needed

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to treat 4); severe complications (0 % vs. 14.3%); and post-randomization units of red cell transfusions (0.04 vs. 0.68). All rebleeds occurred in patients with major SRH and none with lesser SRH.

Conclusion: 1. OTSC significantly reduced rates of rebleeding, severe complications, and post-randomization red cell transfusions. 2. Patients with major stigmata benefited significantly from hemostasis with OTSC, but those with lesser stigmata did not.

Keywords

Non-variceal UGI hemorrhage; ulcer bleeding; Dieulafoy's lesion; hemoclips

www.ClinicalTrials.gov registration – NCT03065465

INTRODUCTION

Recurrent upper gastrointestinal (UGI) bleeding from peptic ulcers (PUB's) and Dieulafoy's lesions is common in high risk patients [1]. Further bleeding is also associated with complications and increased mortality of non-variceal upper GI (NVUGI) bleeding. [1,2,4] The current standard of care is to treat such patients with standard endoscopic hemostasis. [1, 2, 4]

However, in a recent randomized controlled trial (RCT), such patients treated with visually guided standard hemostasis techniques for severe NVUGIB and stigmata of recent hemorrhage (SRH) had a 30 day rebleed rate of 26.3%. [1] When arterial blood flow was successfully obliterated with more endoscopic treatment as monitored by Doppler endoscopic probe (DEP), rebleeding did not occur. [1] When residual blood flow was detected after initial endoscopic visually guided treatment, sometimes there were concerns about possible perforation with application of more multipolar probe thermal coagulation (MPEC) treatment or replacement of hemoclips. [1,6] We concluded that a new type of initial endoscopic treatment was needed to potentially reduce rates of further bleeding in such patients.

A large over-the-endoscope clip (OTSC) was reported to be effective and safe for hemostasis of severe NVUGI hemorrhage.[7] Most reports are retrospective, cohort studies, or a meta-analysis of OTSC for treatment of severe or recurrent PUB hemorrhage. [7–11] However, in patients with recurrent peptic ulcer bleeding, Schmidt et al recently reported that OTSC was significantly more effective than standard treatment in reducing further rebleeding in an RCT. [12] There have been no RCT's reported of initial treatment with OTSC for severe NVUGI hemorrhage.

Our purpose was to perform a RCT of OTSC as primary, initial treatment compared to current standard visually guided endoscopic treatment for severe NVUGI hemorrhage in patients with peptic ulcers or Dieulafoy's lesions. Our hypothesis was that OTSC would reduce rebleeding compared to standard endoscopic hemostasis because it grasps more tissue and more effectively obliterates arterial blood flow underneath SRH.

METHODS:

Study Design

The primary outcome was clinically significant continued bleeding or rebleeding (e.g. “further bleeding”) from the index lesion within 30 days. This is described as **rebleeding** in this manuscript. Secondary outcomes were additional treatment for rebleeding (endoscopic, angiographic or surgery), severe complications related to rebleeding, death, transfusions and hospital and intensive care unit (ICU) days. We also evaluated whether there were differences in subgroup analyses by treatment for patients with PUB’s and also for patients with major vs. lesser SRH, in accordance with recent CURE and international studies and the Forrest classification. [1, 6,13,14]

Study Sites and Patient Inclusion and Exclusion Criteria

This RCT was conducted at 2 academic medical centers (Ronald Reagan UCLA and Veterans Administration West Los Angeles Medical Centers) after IRB approvals and Clinicaltrials.gov registration (NCT03065465).

All patients hospitalized with severe UGI bleeding were screened by clinical and laboratory criteria. For those lacking screen exclusions, written informed consent was obtained prior to urgent EGD. The following inclusion and exclusion criteria were utilized.

Inclusion Criteria:

1. Severe UGI bleeding by clinical parameters (hypotension, shock, syncope, tachycardia, melena, hematemesis, and/or hematochezia), laboratory evidence (hemoglobin Hgb ≤ 9 grams; or Hgb decrease of ≥ 2 grams from baseline), and 1 or more units RBC transfusion (All 3 were required).
2. Life expectancy of at least 30 days as determined by their ICU attending
3. ≥ 18 years of age
4. Written informed consent from the patient or a legal surrogate
5. NVUGI lesion on endoscopy - EGD (DU, GU, anastomotic ulcer or Dieulafoy’s lesion) with stigmata of recent hemorrhage (SRH) including major SRH (active spurting or pulsatile arterial bleeding, non-bleeding visible vessel -NBVV, or adherent clot); and lesser stigmata (oozing bleeding without clot or visible vessel or a flat spot with arterial blood flow underneath, detected by DEP as previously described [1, 6]).

Exclusion Criteria:

1. Do Not Resuscitate (DNR) that cannot be reversed; uncooperative patient or unable to consent
2. Active GI or other malignancy with survival expected < 30 days
3. American Society of Anesthesiology (ASA) score of ≥ 5
4. Shock, unresponsive to vasoactive drugs and/transfusion of ≥ 6 units RBC’s

5. Severe coagulopathy unresponsive to blood products transfusions: platelets < 20,000; International Normalized Ratio (INR) > 3.0; partial thromboplastin time (PTT) > 2x normal
6. Absolute contraindication to urgent EGD, such as GI perforation
7. Stricture of the esophagus, stomach, or pylorus that could not be dilated to allow passage of a 11 mm endoscope or an 11 mm OTSC
8. Cirrhosis of the liver with a history of recent GI bleeding from varices; recent band ligation with possible bleeding post banding ulcers; or recent bleeding from a nasopharyngeal (ENT) source, a Mallory Weiss tear, or portal hypertensive gastropathy
9. Recent UGI bleeding from a diffuse lesion such as esophagitis, Cameron ulcers, an angioma syndrome, or a UGI neoplasm.

Standardization and Training

All GI investigators were experienced clinical researchers and members of the CURE GI Hemostasis Research Group. Prior to the current RCT, we had an investigator meeting to standardize the classification of endoscopic SRH, discuss the study protocol, inclusion and exclusion criteria, IRB consents, study forms, randomization processes, blinding of patients and health care providers, and follow up procedures. For endoscopic training with OTSC devices and deployment, workshops with gastric bleeding models of ulcers and OTSC video cases were conducted for each investigator by the study PI (DJ).

Interventions and Randomization

When they met clinical and endoscopic criteria for PUB's or UGI Dieulafoy's lesions, patients were randomized in a 1:1 allocation during the endoscopy to either standard treatment or OTSC. The endoscopy attending randomized patients by opening an opaque, sealed envelope from a notebook previously prepared by the biostatistician in permuted blocks of four. The card designated the treatment as Standard or OTSC,

DEP was utilized for risk stratification in ulcers with flat spots to detect whether arterial flow was underneath this SRH, as previously described. [1, 6] Only spot patients with arterial flow detected were randomized onto this study.

A therapeutic panendoscope (Olympus or Pentax with 3.8 mm suction channel and a separate port for irrigation) was first utilized with target jet irrigation, suctioning fresh blood, and pre-injection of epinephrine prior to randomization. Endoscopic hemostasis was performed by a member of the CURE Hemostasis GI Attending group. Dilute epinephrine (1:20,000 in saline) in 3–4 aliquots of 1 ml was first injected next to active arterial bleeding to control the bleeding or into the pedicle of the adherent clot prior to cold guillotining it off, as previously described. [1, 15] For Standard treatments either through-the-endoscope hemoclips or MPEC were utilized (both from Boston Scientific Corp, Marborough, MA), at the discretion of the hemostasis attending. For softer, compliant lesions, hemoclips were utilized with or without MPEC pre-treatment, at a low power (12–15 watts setting) with long duration pulses (for 8–10 seconds) and firm tamponade on the SRH and a 10 French probe.

MPEC was also utilized for treatment of large (≥ 15 mm), firm based fibrotic ulcers where hemoclips could not be embed. Visually guided end points were control of active bleeding and flattening or cavitation of SRH and coaptive coagulation with MPEC or obliteration of the SRH with hemoclip, as previously described. [1, 6, 15,16,]

For OTSC treatment, the therapeutic endoscope was withdrawn and a diagnostic sized panendoscope with an OTSC 11, 3 a type attached at the tip was used to re-endoscope the patient, find the lesion, and center the OTSC over the SRH. With high grade suctioning applied and firm pressure to maintain the SRH centered, the OTSC was deployed.

Outcomes after Randomization and Criterion for Rebleeding

During and after randomization, patients and their healthcare teams (GI, medicine, surgery, ICU and primary care) were blinded as to the type of endoscopic treatment. However, lesion type, SRH, and success of initial hemostasis were reported to them. The latter physicians made all management decisions after randomization about medical-surgical treatments, diagnosing and managing complications, blood product transfusions, and ordering repeat EGD, angiography (IR), or surgery for treatment of further GI bleeding.

Further bleeding was defined with the same clinical and laboratory parameters as inclusion criterion #1 for severe UGI bleeding.

After randomization all patients received high dose proton pump inhibitors (PPI) infusions (80 mg and 8 mg/hour) for 72 hours followed by twice daily oral PPI for 30 days in patients with PUB's. Anti-thrombotic drugs necessary for chronic cardiovascular, stroke or thromboembolism prevention were restarted within 3–5 days of randomization. Clinical outcomes data were prospectively collected for 30 days on standard forms, de-identified, and entered onto computer files.

All authors had access to the study data and reviewed and approved the final manuscript.

Statistical Methods including Same Size Estimates:

SAS 9.4 (SAS, Inc, Cary, NC) was used for data management and statistical analyses. Data analysis compared background characteristics, endoscopic findings, and 30-day outcomes according to the 2 treatments. Data were later analyzed on an intention-to-treat basis with the assistance of a biostatistician (JG). [1] The cut-off p value for statistical significant was 0.05 in 2 sided testing. Fisher exact tests were used to compare binary variables. Continuous or ordinal variables were compared with non-parametric methods (Wilcoxon rank sum test). Computations were performed using StatXact 8.0 (Cytel Inc, Cambridge Mass) and SAS 9.4. All data analyses were performed according to an intension to treat basis and included all 53 RCT patients. Kaplan-Meier curves were created and time to lesion rebleeding was determined and compared by log rank test.

We estimated the rebleeding rate as 40% for the standard group and 5% for the OTSC group. These rates were based upon our cohort results in high risk patients with severe NVUGIH prior to start of this RCT and reports of the Schmidt RCT.[12] For the 35% difference a α = 0.05, β = 0.20 and two-tailed analysis, 27 patients/treatment group was sample size.

RESULTS:

The study was conducted between January 2016 and December 2019. It ended when projected enrollment was completed and funding finished. 346 patients with severe UGI bleeding were screened for possible enrollment; 200 were not consented because they had exclusions or lacked clinical or laboratory inclusion criteria; and 93 other patients were consented but excluded during urgent endoscopy because they lacked endoscopic criteria. All 53 patients who met both clinical and endoscopic entry criteria were randomized and treated, 28 to Standard endoscopic hemostasis and 25 to OTSC. All 53 patients completed 30 days of follow-up. 91 % of RCT patients had ulcers (DU 24, GU 19, anastomotic 5) and 5 patients (9%) had Dieulafoy's lesions. Patients had either active arterial bleeding (9), a NBVV in (24), adherent clot (7), oozing bleeding (4) or flat spots with arterial blood flow detected by DEP (9).[6] Refer to the Supplement for a CONSORT diagram of all patients assessed and excluded; consented but excluded on EGD; and randomized for this study.

There were no significant differences in patient baseline characteristics or endoscopic findings, except for a higher mean PTT in the OTSC group. See Table 1 for specific risk factors of Standard vs. OTSC patients. The mean sizes of ulcers was similar, with standard vs. OTSC having similar proportions of ulcers greater than or equal to 15 mm (42.9% vs 44%). [3] All additional baseline data were also well matched with randomization.

All patients with active bleeding or oozing had hemorrhage controlled and those with other SRH had cavitation (with MPEC) or clipping of non-bleeding SRH. However, there was a significant difference in the rate of further bleeding after randomization with 28.6% in standard patients (8/28) vs. 4% in OTSC patients (1/25). See Table 2. The risk of further bleeding was 90% lower for OTSC than Standard treatment with relative risk of 0.10 and 95% confidence intervals of 0.01, 0.91. The number of patients needed to treat (NNT) was 4. On a Kaplan-Meier plot (Figure 1), most of the patients had further bleeding within 4 days. The difference was significant by log rank test - $p = 0.016$.

Significantly more severe complications related to rebleeding occurred in the Standard than the OTSC treatment group (14.3% - 4/28- vs 0 % - 0/25 – $p = 0.049$). Refer to Table 3 for details. Also significantly more units of RBC's were transfused after randomization in the Standard treatment group than the OTSC group: 0.68 vs 0.04 Units ($p = 0.021$). There were no deaths nor surgeries. All other 30-day outcomes were arithmetically worse in the Standard treatment group than the OTSC group.

Refer to Figure 2 for Kaplan-Meier plot of more bleeding for patients with PUB's – no Dieulafoy's lesions included. There were also significant differences for Standard vs. OTSC PUB patient outcomes including 30 day rates of more bleeding – 28% (7/25) vs. 4.4% (1/23) - and units of RBC transfusion after randomization (0.48 vs. 0.04). For PUB's the NNT was 4.2.

No RCT patient with either oozing bleeding or a flat spot rebled during 30 days of follow-up after either treatment: 0/5 (0%) in the Standard group vs. 0/8 (0%) in the OTSC group. Only patients with major SRH (pulsatile arterial bleeding, NBVV, or adherent clot) had further bleeding. The rebleeding rate with these major SRH in the Standard group was 34.8% (8/23)

and with OTSC was 5.9% (1/17). Refer to Table 3 for details by SRH and treatment. For major SRH, the NNT was 3.5. For the Kaplan-Meier plot of time to more bleeding in the subgroup of PUB and Dieulafoy's lesions, see Figure 3 in the Supplement.

DISCUSSION:

This is the first RCT report of OTSC as initial treatment of severe NVUGIB. In contrast to earlier studies, [7–12] our RCT was for initial endoscopic treatment of clinically severe UGI hemorrhage from ulcers and Dieulafoy's lesions. Our new RCT results confirm the effectiveness and safety of OTSC reported in prior studies of patients with severe hemorrhage from ulcers. [7–12]

The most compelling clinical result of our RCT was the significantly reduced rate of further bleeding in the OTSC group compared to the standard treatment group: 4% vs. 28.6%. In recent DEP studies, OTSC more effectively obliterated arterial blood flow under SRH than standard hemostasis and this highly correlated with lower rebleeding rates in NVUGIB. [1,6,17] There was a relative risk reduction of 90% in further bleeding with OTSC. With the reduction in rebleeding of 24.6%, the number of patients needed to treat with the OTSC was only 4. A significant difference in rebleeding was also found in patients with PUB's and also those with major SRH.

For comparison to the Schmidt RCT, refer to Table 4. There are significant methodologic differences in these two RCT's. Unlike the Schmidt study[12], which reported 7-day results of rebleeding and was a crossover study, we did not crossover patients with rebleeding and therefore could report other clinically relevant 30-day outcomes. We also report significant differences in severe complications related to rebleeding and higher post-randomization RBC transfusions in the standard group compared to the OTSC treatment.

We addressed the question about who would benefit most from OTSC by comparing the rates of further bleeding in patients with major SRH to patients with lesser SRH, as previously reported. [1, 6,13] RCT patients with the major SRH accounted for all of the rebleeding – Standard group 34.8% (8/23) and the OTSC group 5.9% (1/17). Refer to Table 3 for each major SRH. In our recent DEP studies, these patients had high rates of residual blood flow after standard visually guided endoscopic hemostasis, which correlated with high rebleed rates of 26–35%. [1, 6] In contrast, prior RCT patients with oozing bleeding or flat spots did not have residual arterial blood flow after standard endoscopic treatments and they had very low rebleeding rates. [1, 6] Contrary to patients with major SRH (as classified here), those with oozing bleeding (Forrest IB) also were reported in a recent international study to have low rebleeding rates and not to benefit from high dose PPI infusions after successful endoscopic hemostasis. [13] In our current RCT, no patient with these lesser risk SRH (oozing or flat spots) had rebleeding in either treatment group. They are unlikely to benefit from OTSC since standard endoscopic hemostasis was effective, safe, and also resulted in no rebleeding.

Whether the analyses included all patients (ulcers and Dieulafoy's lesions) or only ulcer patients, the results were the same. There were significantly lower rates of rebleeding

and RBC's transfused after randomization in patients with major SRH (active spurting or pulsatile arterial bleeding, NBVV, or adherent clot) but not lesser SRH (oozing bleeding or flat spots with arterial blood flow beneath). For the OTSC vs. Standard treatments of patients with major SRH, the NNT's were low - ≤ 5.

There are some limitations and potential critiques of the current RCT. It was of moderate size with 53 patients. Different SRH had small numbers and therefore subgroups were categorized as major or lesser SRH. [1,2,4,6,13] The rebleeding rate in the standard treatment group was high but comparable to the Schmidt RCT. [12] That rate of rebleeding was quite high (28%), but is also very similar to patients with severe NVUGIB reported in our recent DEP RCT (26 %) in the standard group, treated by the same investigators.[1, 6] Another critique may be that well trained members of the CURE Hemostasis team performed the treatments, achieved initial hemostasis in all patients and our results may not be generalizable to community practice. We agree that extra training will be needed for successful deployment of OTSC. This type of training will be a challenge for both GI fellowship programs and GI post-graduate continuing education (CME) programs which aim to teach about best management of severe NVUGI bleeding.[18] Also, this study included patients with flat spots which most endoscopists do not treat with endoscopic hemostasis. We included them because PUB's with flat spots had arterial blood flow detected in about 45% in recent CURE studies and the rebleeding rate on medical management without endoscopic treatment was about 20%. [1, 6]

CONCLUSIONS:

1. In patients with severe UGI bleeding from ulcers or Dieulafoy's lesions, primary endoscopic treatment with OTSC significantly reduced post-randomization rates of rebleeding, severe complications, and RBC transfusions compared to standard endoscopic hemostasis. 2. In largest subgroup of PUB patients, OTSC also significantly reduced rebleeding and RBC transfusions compared to standard endoscopic hemostasis. 3. Patients with major SRH had high rates rebleeding after standard endoscopic hemostasis and benefited significantly from treatment with OTSC, but patients with lesser SRH (oozing or flat spots) had no significant extra benefit of OTSC. 4. Based upon our current RCT results as initial hemostasis and those of Schmidt for retreatment of PUB rebleeding[1,12], current guidelines for standard endoscopic hemostasis of severe NVUGI hemorrhage should be re-evaluated and updated.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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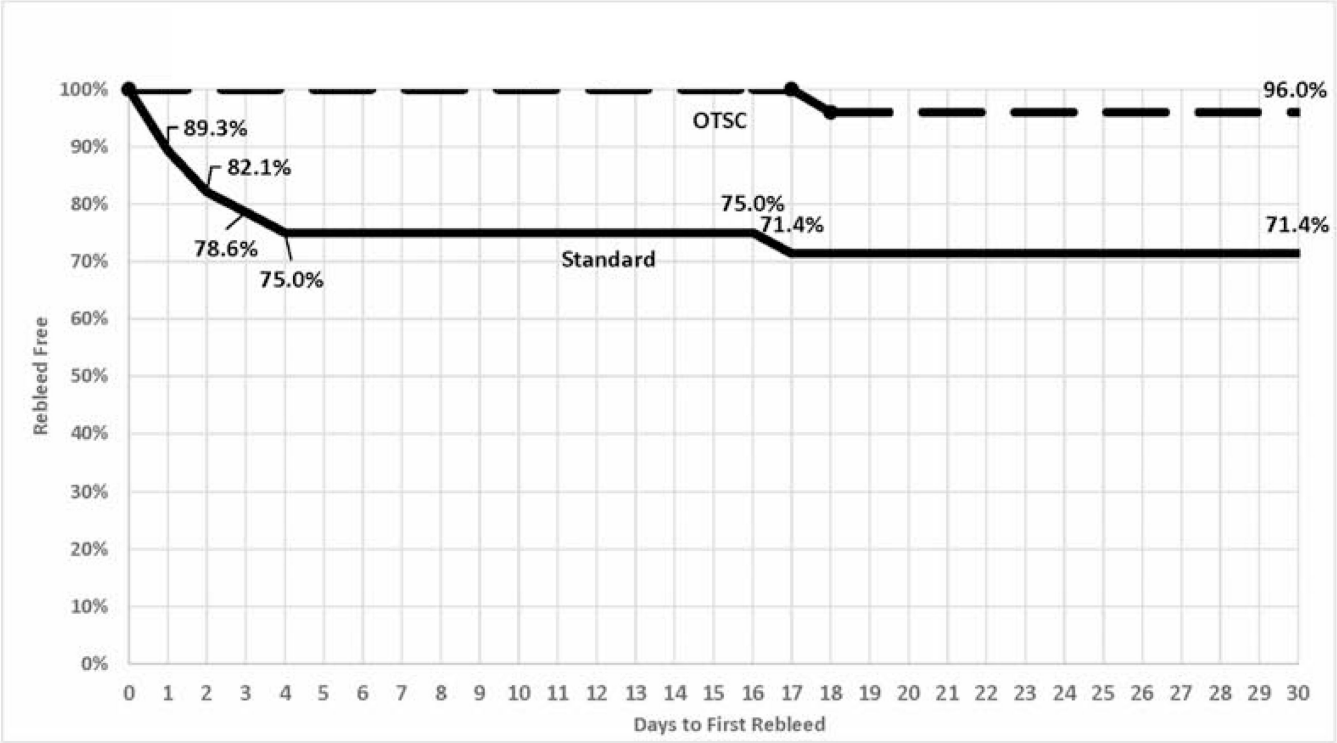

Figure 1. Proportion of All Patients (with Ulcers or Dieulafoy's Lesions) Without Further Bleeding (Rebleed Free) During 30 Days After Randomization

All 53 patients are included – 25 OTSC and 28 Standard hemostasis. This is a Kaplan-Meier plot of time to further bleeding, with log rank test p = 0.016. The cumulative further bleeding rate to 30 days was 4.0% (1/25) in the OTSC group vs. 28.6% (8/28) in the Standard treatment group. The number needed to treat is 4.0.

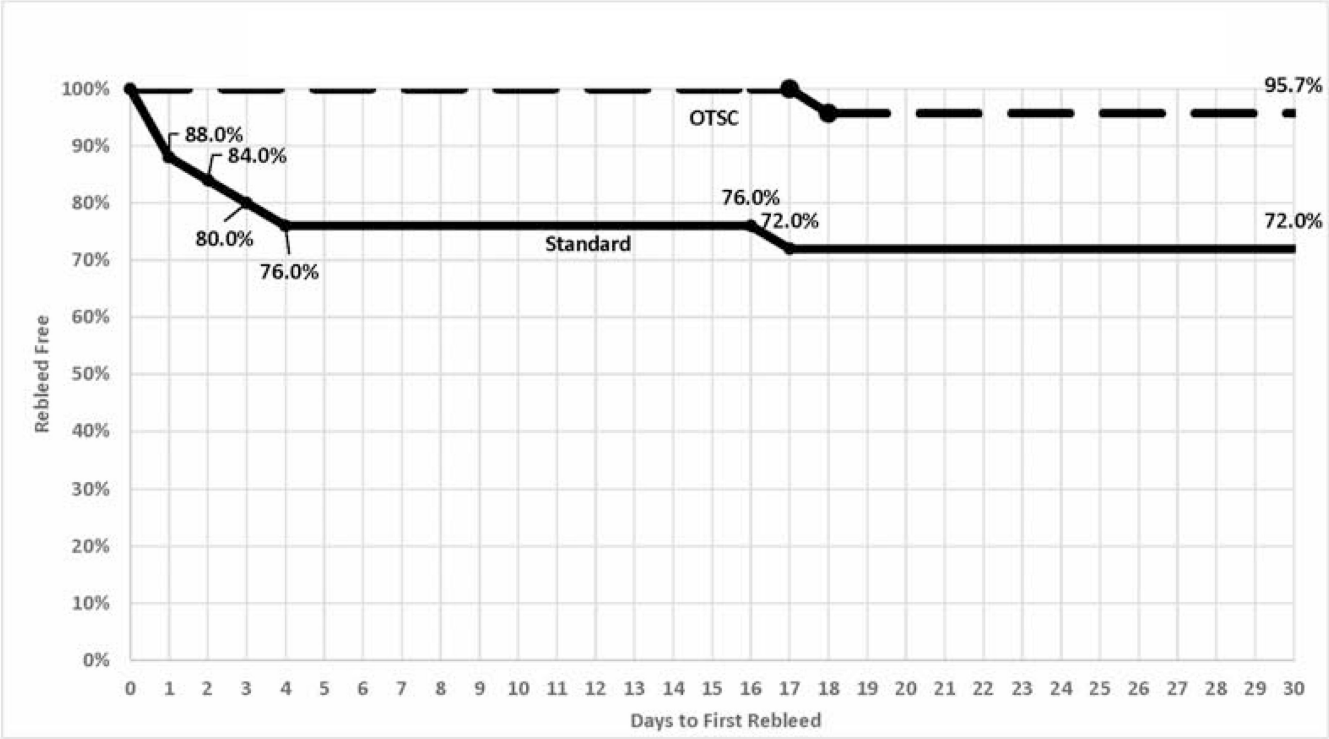

Figure 2. Proportion of Peptic Ulcer Patients without Further Bleeding (Rebleed free) During 30 Days of Follow-up After Randomization.

This is a Kaplan-Meier plot of time to further bleeding, with log rank test p = 0.026. The cumulative 30-day further bleeding rate was 4.3% (1/23) in the OTSC group vs. 28% (7/25) in the Standard hemostasis group. The NNT is 4.2.

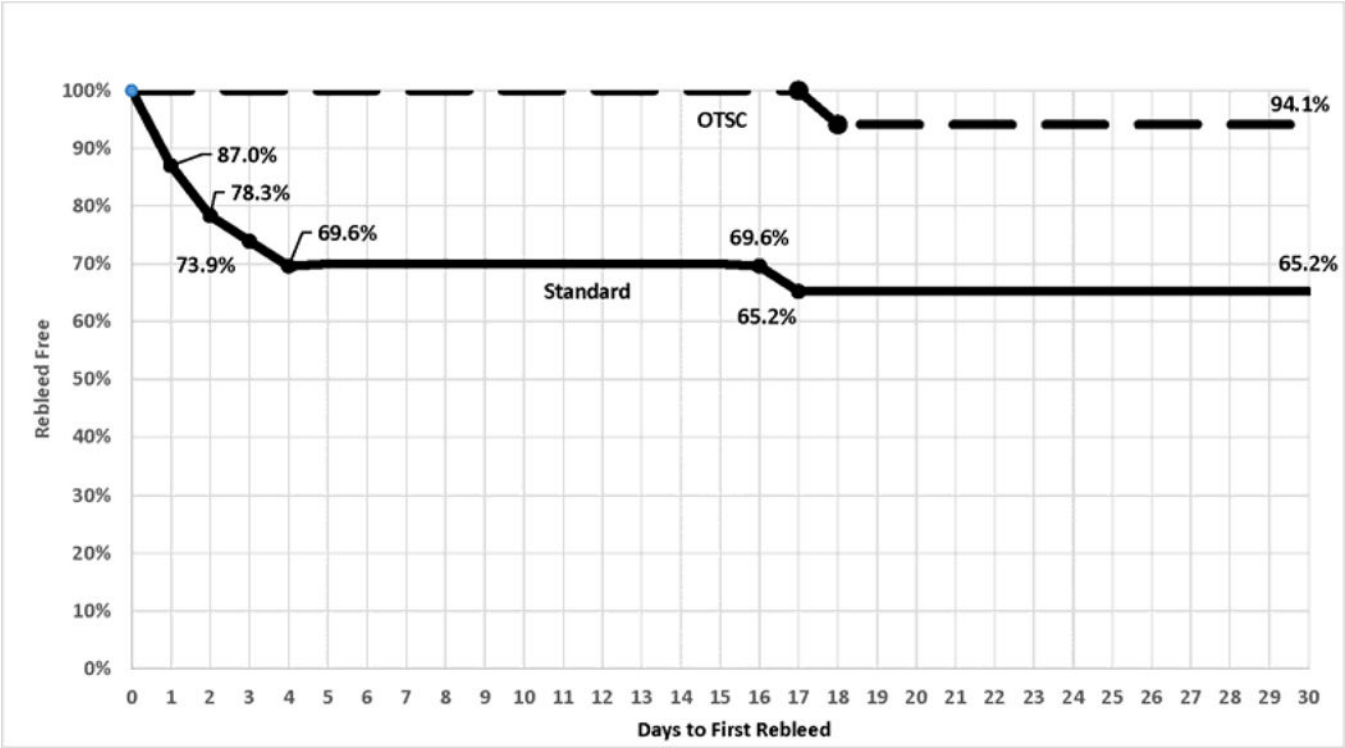

Figure 3. Proportion of Patients with Major Stigmata of Hemorrhage (SRH) without Further Bleeding (Rebleed Free) During 30 Days After Randomization

Legend: Proportion of patients with major stigmata of hemorrhage (active arterial bleeding, non-bleeding visible vessel, or adherent clot) without further bleeding during 30 days after randomization. There are 17 OTSCand 23 Standard treatment patients with these SRH. This is a Kaplan-Meier plot of time to further bleeding of these high risk patients. By log rank test, p = 0.029. The cumulative further bleeding rate was 5.9% (1/17) in the OTSC group vs. 34.8% (8/23) in the Standard treatment group. The number needed to treat is 3.S.

Table 1.

Patient Baseline Characteristics and Endoscopic Diagnoses

Variable	OTSC (N=25)	STANDARD (N=28)
Age *	67.6 ± 16.5	66.5 ± 14.8
Aspirin before bleed	15	15
Anticoagulant before	6	7
Hypotension or Shock	10	12
Syncope	2	3
Inpatient Bleed	5	5
Baseline Hemoglobin *	7.1 ± 1.5	7.7 ± 2.3
RBC's for resuscitation *	2.0 ± 1.8	2.2 ± 1.9
INR *	1.27 ± 0.29	1.19 ± 0.24
PTT (sec) *	31.1 ± 7.8	26.8 ± 4.2
Glasgow-Blatchford Score *	12.6 ± 3.0	12.6 ± 2.9
CURE Prognosis Score *	3.20 ± 0.96	3.29 ± 1.05
DU	13	11
GU	9	10
Anastomotic ulcer	1	4
Dieulafoy's lesion	2	3
[1] Ulcer Size (mm) *	11.4 ± 6.0	12.4 ± 6.4
[2] Ulcers ≥ 15 mm	11 (48%)	11 (44%)
Stigmata of Hemorrhage		
Major SRH		
Active Bleed	2	7
Non-bleeding visible vessel	12	12
Adherent Clot	3	4
Lessor SRH		
Oozing bleeding	2	2
Flat spot with arterial flow	6	3
Gender		
Female	6	4
Male	19	24
Smoking Hx	0	1
Drinking	1	2
NSAID Hx	9	8
Anti-Platelet Drug Hx	2	7
H. pylori status		
Positive	3	5

Variable	OTSC (N=25)	STANDARD (N=28)
Negative	15	8
Not done	7	15
ASA Score		
II	9	7
III	12	14
IV	4	7
Child's Class		
A	2	2
B	1	2

[*] Mean +/− Standard deviation.

[1] Ulcer size was diameter of PUB's. Dieulafoy's lesions were not included.

[2] Ulcers ≥ 15 mm – 23 total ulcer patients were in OTSC vs. 25 in Standard group.

Table 2.

30 Day Clinical Outcomes of Patients by Endoscopic Treatment

	OTSC (N=25)	STANDARD (N=28)	p-Values
Further Bleeding [1]	1 (4%)	8 (28.6%)	0.017
Severe Complications [1]	0 (0%)	4 (14.3%) [2]	0.049
Angiographic Embolization [1]	0 (0%)	2 (7.1%)	0.173
Surgery	0	0	---
Deaths	0	0	---
Units RBC's after Randomization [3]	0.04 ± 0.2	0.68 ± 1.56	0.030
Hospital Days [3]	7.56 ± 8.17	10.0 ± 16.19	0.227
ICU Days [3]	2.40 ± 3.48	11.11 ± 37.06	0.236

[1]Proportions compared by chi-square

[2]Severe complications related to further bleeding and requiring escalation of medical care were: 1 CVA, 1 CHF, 1 aspiration pneumonia and 1 bleeding ischemic ulcers after angiographic embolization

[3]Means ± standard deviation. Statistical comparison with Kruskal-Wallis test.

Table 3.

Patients with rebleeding within 30 days by Major Stigmata of Hemorrhage (SRH)*

	STANDARD TREATMENT	OTSC
Active Arterial bleeding (Forrest I A)	3/7 (42.9%)	0/2 (0%)
Non-bleeding Visible Vessel (F II A)	3/12 (25%)	1/12 (8.3%)
Adherent Clot (F II B)	2/4 (50%)	0/3 (0%)
TOTALS	8/23 (34.8%)	1/17 (5.9%)

F is Forrest classification.

*No patients with oozing bleeding (FIB) or flat spot (FIIC) and with positive arterial blood flow by Doppler probe had rebleeding and therefore are not included in this table of major SRH. As discussed in the manuscript, we consider FIB and FIIC to be lesser SRH.

Table 4.

Comparison of Two OTSC RCT's: Study Details and Design

	Schmidt et al RCT [12]	CURE Hemostasis RCT
Number of patients	66	53
Lesion types	PUB's	Ulcers and Dieulafoy's lesions
Initial vs. Re-treatment	Re-treatment of rebleeds	Initial treatment of bleeds
Blinding (of patients and healthcare providers)	No	Yes
Study centers - number	19	2
Pre-study Investigator Meetings for Standardization	No	Yes
Cross-Over for More Bleeding	Yes	No
PPI Infusion Standardized	No	Yes
Standard (Control) group treatment	Most had HC or injection; few had MPEC	Equal #'s of MPEC and/or HC with or without epinephrine pre-injection
Study funding	OVESCO Endoscopy	NIH CURE: DDRCC and ASGE
Outcomes reported	Further bleeding at 7 days and for cross overs	+ Further bleeding at 30 days + Other 30 day clinical outcomes

OTSC is over-the-scope-clip. RCT is randomized controlled trial. PUB's are peptic ulcer bleeding. HC is through the endoscope hemoclips. MPEC is multipolar electrocoagulation.