Over-the-Scope Clips Are More Effective Than Standard Endoscopic Therapy for Patients With Recurrent Bleeding of Peptic Ulcers

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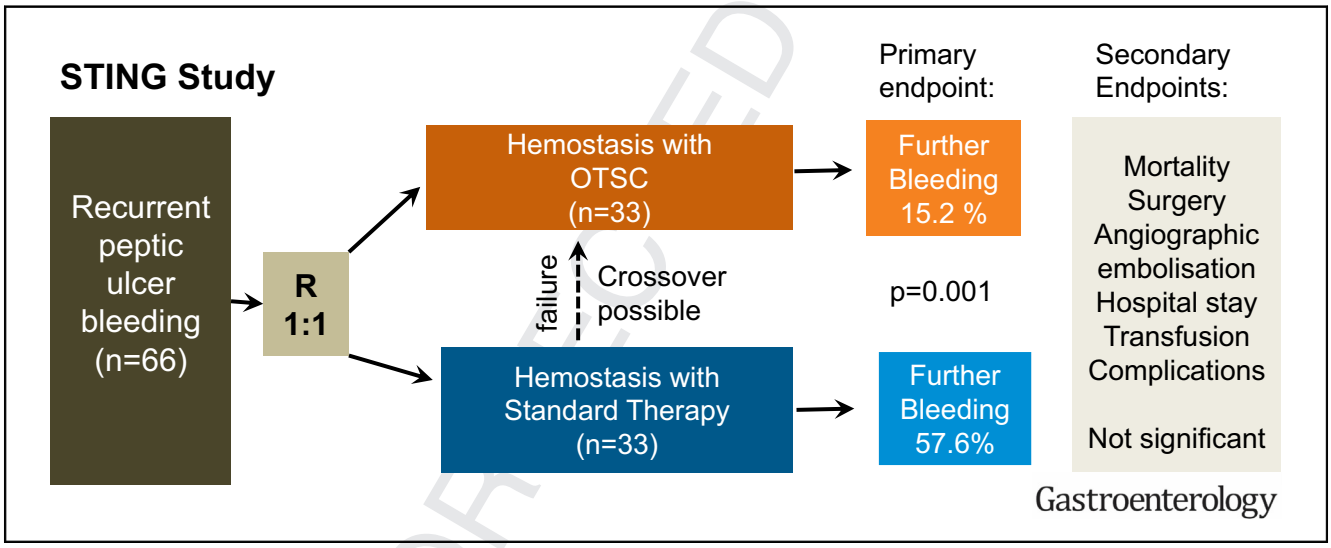

BACKGROUND & AIMS: Endoscopic hemostasis is effective in treatment of bleeding peptic ulcers. However, rebleeding is difficult to treat and associated with substantial morbidity and mortality. We performed a prospective randomized trial to determine whether over-the-scope clips (OTSCs) are more effective than standard treatment of severe recurrent upper gastrointestinal bleeding. **METHODS:** We performed our study at 9 academic referral centers (in Germany, Switzerland, and Hong Kong) from March 2013 through September 2016. Adult patients with recurrent peptic ulcer bleeding following initially successful hemostasis (66 patients in the intent-to-treat analysis) were randomly assigned to groups (1:1) that underwent hemostasis with either OTSC or standard therapy. Standard therapy was defined as hemostasis with through-the-scope clips (TTSC, n = 31) or thermal therapy plus injection with diluted adrenaline (n = 2). The primary endpoint was further bleeding (a composite endpoint of a persistent bleeding despite endoscopic therapy according to the protocol or recurrent bleeding within 7 days after successful hemostasis). Patients with further bleeding were allowed to cross over to OTSC therapy. Main secondary endpoints were mortality, necessity of surgical or angiographic salvage therapy, duration of stay in the hospital or intensive care, number of blood units transfused, and complications associated with endoscopic therapy. **RESULTS:** Persistent bleeding after per-protocol hemostasis was observed in 14 patients (42.4%) in the standard therapy group and 2 patients (6.0%) in the OTSC group ($P = .001$). Recurrent bleeding within 7 days occurred in 5 patients (16.1%) in the standard therapy group vs 3 patients (9.1%) in the OTSC group ($P = .468$). Further bleeding occurred in 19 patients (57.6%) in the standard therapy group and in 5 patients (15.2%) in the OTSC group (absolute difference 42.4%; 95% confidence interval 21.6–63.2; $P = .001$) Within 30 days of follow-up, 1 patient in the standard therapy group (3.0%) and 1 patient in the OTSC group (3.0%) required surgical therapy ($P = .999$). Within 30 days of the procedure, 2 patients died in

the standard therapy group (6.3%) and 4 patients died in the OTSC group (12.1%) ($P = .672$). There were no significant differences in the other secondary endpoints. **CONCLUSIONS:** In prospective randomized trial, we found endoscopic treatment with OTSCs to be superior to standard therapy with TTSCs for patients with recurrent peptic ulcer bleeding. Clinicaltrials.gov no: NCT1836900.

Q3 *Keywords:* STING Study; Stomach; Clinical Trial; Comparison.

CLINICAL AT

Despite a decline of uncomplicated peptic ulcer disease over the past years, peptic ulcer bleeding remains a common clinical challenge with substantial economic impact. The annual incidence worldwide ranges from 19.4 to 57.0 cases per 100,000.[1] Reported mortality rates differ substantially between studies and are approximately 3% to 10%.[1–3] Endoscopic hemostasis is initially successful in approximately 90% of patients, but recurrence of hemorrhage occurs in approximately 10%.[1,4] Rebleeding is a predictor of increased mortality and success of endoscopic retreatment drops to approximately 75%.[4,5] In case of insufficient endoscopic control of bleeding, patients are generally referred to angiographic or surgical salvage therapy. The latter is associated with a mortality of between 14% and 29% and high complication rates.[2,5,6] Very likely, improvement of endoscopic hemostasis for recurrent bleeding directly impacts clinical outcome. Although injection of diluted adrenaline only is not adequate for hemostasis, combination with through-the-scope clips (TTSCs) or thermal methods is considered to be the standard endoscopic therapy.[7] Over-the-scope clips (OTSCs) were initially developed for closure of gastrointestinal perforations or leaks,[8] but are increasingly used for hemostasis. Various case series and retrospective studies have shown high efficacy even in "high-risk" ulcers, but to date there are no prospective comparative data.[9–13] The aim of the present study was to compare OTSCs with standard endoscopic care in patients with recurrent peptic ulcer bleeding.

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

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LIMITATIONS

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Methods

Trial Design

We conducted a prospective, randomized, controlled multicenter study. The study protocol was approved by the institutional review board at each center and the study was conducted in accordance with the declaration of Helsinki. Written and informed consent was obtained from all patients before enrollment. The study was registered at clinicaltrials.gov (NCT1836900). The full trial protocol can be obtained from the corresponding author.

Participating Centers

The study was conducted at 9 international academic referral centers in Germany, Switzerland, and Hong Kong. There was an investigator meeting at initiation of the study with thorough instruction and training of participants on the protocol; there was a second meeting after 1 year. Three centers were excluded from participation within the first year after initiation of the study because of lack of recruitment. Instead, 4 additional centers were included (University of Ulm, University of Munich, University of Hong Kong, University of Bern). Those centers also received instruction on the protocol.

Participants

Eligibility criteria were endoscopically confirmed rebleeding from peptic ulcer within 7 days after initial successful endoscopic hemostasis and patient age ≥18 years.

Exclusion criteria were variceal bleeding, tumor bleeding, pregnancy or breast feeding, perforated ulcer with requirement of surgical therapy, lack of written and informed consent, or American Society of Anesthesiologists classification of V. Intubated patients were included only when informed consent could be obtained from close family members.

Criteria for endoscopy before study inclusion and for repeat endoscopy after successful hemostasis within the study were as follows: hematemesis >6 hours after endoscopy, melena or hematochezia after normalization of stool color, development of tachycardia (≥110/min) or hypotension (systolic blood pressure ≤90 mm Hg), tachycardia or hypotension not resolving within 8 hours after endoscopy despite appropriate volume resuscitation (in the absence of alternative explanation) associated with persistent melena or hematochezia, and drop in hemoglobin ≥2 g/dL or increase <1 g/dL per transfused blood unit within 24 hours.[14]

Abbreviations used in this paper: **CI, confidence interval; ICU, intensive care unit; IV, intravenous; OTSC, over-the-scope clip; PPI, proton pump inhibitor; RCT, randomized controlled trial; TAE, transarterial embolization; TTSC, through-the-scope clip.**

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