BACKGROUND & AIMS: Acute perforations of the gastrointestinal tract are rare, severe complications of endoscopy that usually require surgical repair. Endoscopic repair of perforations would reduce the need for surgeries; we evaluated the efficacy and safety of endoscopic closure of acute perforations of the gastrointestinal tract by using a new clip device.

METHODS: We conducted a prospective, international, multicenter study of 36 consecutive patients (15 male) with acute iatrogenic perforations (5 esophageal, 6 gastric, 12 duodenal, and 13 colonic perforation). Endoscopic repair was performed by using the Over-the-Scope-Clip according to a standardized operating procedure. Primary end point was successful closure, which was determined as endoscopic successful closure without leakage (detected by water-soluble contrast x-ray analysis), and absence of adverse events within 30 days after the procedure.

RESULTS: Immediate closure was endoscopically successful in 33 patients (92%). One patient developed an esophageal perforation while the cap was introduced, and in 2 patients the perforations did not close; these 3 patients were successfully treated with surgery. None of the patients had leakage of soluble contrast on the basis of contrast x-ray analysis, and absence of adverse events within 30 days after the procedure.

CONCLUSIONS: The Over-the-Scope-Clip is effective for endoluminal closure of acute iatrogenic perforations. It allows patients to avoid surgery, and 89% of patients had successful closures without adverse events.

Keywords: Clinical Trial; Humans; Endoscopy; Gastrointestinal; Wound Closure Techniques; Complications; Intestinal Perforation; Esophageal Perforation; Natural Orifice Endoscopic Surgery; Closure Technique; Surgical.
Recently a new device for endoscopic closure of perforations called the Over-the-Scope-Clip (OTSC) (Ovesco Endoscopy AG, Tübingen, Germany) has been tested in preclinical studies. This device is a bear trap–like, large clip with a wingspan of 12 mm that grasps much more tissue than the small endoscopic clips used previously. The clip is designed to create a full-thickness closure of perforations up to 3 cm in diameter. Ex vivo experiments showed that the acute strengths of closed gastric, duodenal, and colonic perforations by using the OTSC were comparable with surgical closure.18,21–24 Subsequent animal survival studies showed 100% success rates.25,26 Retrospective small clinical pilot studies confirmed these promising data.27,28 These outcomes led us to initiate a multicenter prospective human clinical trial with this device. The aim of the current study was to evaluate efficacy and safety of endoscopic closure of acute perforations of the gastrointestinal tract by using the OTSC.

Methods

Study Design
This is a prospective multicenter cohort study conducted at 11 tertiary care medical centers in Europe. The study was investigator-initiated and investigator-driven and performed in accordance with the principles of the Declaration of Helsinki. The medical ethics committees at each center approved the protocol. Data collection was done by local physicians, who completed online case record forms.

We recruited consecutive patients from April 2009 with documented acute esophageal, gastric, duodenal, or colonic perforations smaller than 3 cm. Perforation was defined as a complete disruption of the gastrointestinal wall, which was documented by an endoscopic view of extraintestinal structures and/or air leakage outside the gut wall shown on computed tomography scan. Perforations detected more than 24 hours after the endoscopic procedure, duodenal perforations after ampullectomy or sphincterotomy, tumor perforations, and patients younger than 18 years of age were excluded. All participating endoscopists were trained on an ex vivo animal model before participation in the study. Material support was supplied by Ovesco Endoscopy AG, Tübingen, Germany, without restrictions.

**Intervention**

After detection of the perforation, fluid and air were aspirated, and the endoscope was removed. All patients were given antibiotics according to local guidelines. After removal, a therapeutic endoscope fitted with a cap-mounted OTSC (Figure 1) was introduced by using carbon dioxide insufflation only. The clip is made of nitinol and can approximate perforation margins of large defects like a surgical clamp (Figure 2). Endoscopic perforation repair was performed according to a standardized operating procedure. The size of the perforation was endoscopically assessed with help of a grasping forceps. The edges of the perforation were approximated by using an endoscopic double-grasping forceps (“twin-grasper”) and by applying vacuum through the working channel of the endoscope. The twin-grasper forceps has 1 fixed middle branch and 2 independently movable lateral branches, which enable independent grasping of both perforation edges (Figure 3). The tissue was then pulled into the cap, and the clip was released by rotating the wheel attached to the shaft of the endoscope. After releasing the clip, the acute result of the closure was inspected endoscopically. An example of the closure procedure is shown in Supplementary Video 1. In case of inadequate closure, further treatment was at endoscopists’ preference and could exist of an additional OTSC, standard endoscopic clips, or referral for surgery.

**Follow-up**

After successful endoscopic closure, a real-time fluoroscopy of the perforation site was performed within 6 hours. In case of leakage or clinical deterioration, surgical or radiologic intervention was performed. Follow-up was continued during hospital stay. Long-term follow-up imaging (endoscopy or radiology) was scheduled 6 months after closure to verify presence or migration of the clip(s).

**Evaluation of End Points**

Primary end point was successful closure by using the OTSC and, if needed, additional endoclips. Successful closure was defined as endoscopic adequate closure combined with

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Figure 1.
A 12-mm transparent cap with the OTSC mounted on the tip of endoscope, and the wheel is attached to shaft of endoscope.

Figure 2.
An OTSC.
absence of leakage on water-soluble contrast x-ray plus absence of adverse events within 30 days after endoscopic closure. Adverse events were defined as death, life-threatening situations, persistent leakage, and bleeding within 30 days after the procedure. Persistent leakage was defined as need for additional endoscopic or surgical intervention for perforation closure or percutaneous or surgical drainage of abscesses.

The individual components of the primary end point were analyzed as secondary end points as well. Secondary end points also included closure time (starting from introduction of the endoscope with the OTSC system until adequate closure), perforation-associated infection leading to prolonged hospital stay (treated conservatively), day of successful resumed oral intake, length of hospital stay, and presence of the OTSC at 6-month follow-up imaging.

Sample Size and Statistical Analysis

The goal was to evaluate closure efficacy of iatrogenic perforation by using the OTSC. On the basis of the results of animal studies with the OTSC, the failure rate was expected to be low. Assuming a successful closure rate of 95%, 36 patients were needed to achieve a lower end of the 95% confidence interval (CI) of at least 80%. A threshold of the 95% CI of 80% was considered adequate for translation into further human clinical studies. End point analysis consisted of an intention-to-treat analysis (except closure time). Data are presented as mean plus standard deviation and in case of skewed distributions as median plus interquartile range (IQR). All statistical analyses were done with SPSS (version 16.0.2; SPSS Inc, Chicago, IL).

Results

Baseline Characteristics

Between April 2009 and August 2010 thirty-nine consecutive patients with gastrointestinal perforations were enrolled. Thirty-six patients met inclusion criteria; 2 patients were excluded because the perforations existed over 24 hours at inclusion, and 1 perforation was excluded because it was larger than 3 cm in diameter. Baseline characteristics are summarized in Table 1. Five perforations were located in the esophagus (14%), 6 in the stomach (17%), 12 in the duodenum (33%), and 13 in the colon (36%). Eighteen patients (50%) experienced a perforation during a therapeutic endoscopy procedure (6 in endoscopic submucosal dissection, 8 in endoscopic mucosal resection, 4 in colonic polypectomy). In 13 cases (36%) a perforation occurred during a diagnostic endoscopy (8 in colonoscopy, 5 in duodenal endosonography). The remaining 5 perforations were not endoscopy-related. One gastric perforation occurred postoperatively after sleeve gastrectomy and another because of a dislocated percutaneous endoscopic gastrostomy. An esophageal perforation was caused by a dislocated tracheostomy tube after lung transplantation, and a duodenal perforation was caused by a migrated pancreatic duct stent. Finally, an acute colonic perforation occurred during percutaneous drainage of a paracolic fluid collection.

Outcome

Primary outcome is summarized in Table 2. Immediate endoscopic closure was macroscopically successful in 33 of 36 patients (92%). Failures included 1 patient with an endoscopic

Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n = 36)</th>
</tr>
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<tbody>
<tr>
<td>Age, y (SD)</td>
<td>67 (11)</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>15 (42)</td>
</tr>
<tr>
<td>Perforation location (%)</td>
<td></td>
</tr>
<tr>
<td>Esophagus</td>
<td>5 (14)</td>
</tr>
<tr>
<td>Stomach</td>
<td>6 (17)</td>
</tr>
<tr>
<td>Duodenum</td>
<td>12 (33)</td>
</tr>
<tr>
<td>Colon</td>
<td>13 (36)</td>
</tr>
<tr>
<td>Etiology of perforation</td>
<td></td>
</tr>
<tr>
<td>Therapeutic (%)</td>
<td>18 (50)</td>
</tr>
<tr>
<td>ESD</td>
<td>6 (17)</td>
</tr>
<tr>
<td>EMR</td>
<td>8 (22)</td>
</tr>
<tr>
<td>Polypectomy</td>
<td>4 (11)</td>
</tr>
<tr>
<td>Diagnostic (%)</td>
<td>13 (36)</td>
</tr>
<tr>
<td>EUS</td>
<td>5 (14)</td>
</tr>
<tr>
<td>Colonoscopy</td>
<td>8 (22)</td>
</tr>
<tr>
<td>Other (%)</td>
<td>5 (14)</td>
</tr>
</tbody>
</table>

EMR, endoscopic mucosal resection; ESD, endoscopic mucosal dissection; EUS, endoscopic ultrasonography; SD, standard deviation.
duodenal perforation in whom an esophageal perforation was caused on introduction of the endoscope with the OTSC cap mounted on its tip. The patient was referred for immediate thoracoscopic closure of the esophageal perforation as well as management of the duodenal perforation. In 2 other duodenal perforations it proved impossible to maneuver the endoscope in a proper position to place the OTSC. In both cases no clip was released, and patients were referred for surgical closure.

In none of the 33 x-rays of endoscopically successfully closed perforations could leakage of contrast be demonstrated. However, 1 patient in whom a colonic perforation after polypectomy was shown to be adequately closed at postprocedural contrast study suddenly deteriorated 5 hours later. The patient underwent an immediate laparotomy that showed a detached clip and persistent perforation. Despite successful resection of the perforation site and construction of a colostomy, the patient died within 36 hours after inclusion. Autopsy did not show signs of an abdominal catastrophe. Follow-up of the remaining 32 patients was uneventful, leading to an overall successful closure rate of 89% (95% CI, 75%-96%). Successful closure rate per anatomic location is summarized in Table 3.

The mean time for endoscopic closure time was 5 minutes 44 seconds (standard deviation, 4 minutes 15 seconds). In 28 patients a single OTSC was used, in 3 patients 1 OTSC was combined with additional endoclips, and 2 OTSCs were necessary in 2 patients. Besides the esophageal perforation, no other adverse events occurred. Additional interventions were performed in the 4 cases described above and concerned surgery in 19 (79%), the OTSC was still in situ at 6-month follow-up imaging, 12 (92) patients was available for 6-month follow-up imaging. Two patients died of unrelated causes during the 30 days after surgery without a clear cause. Although autopsy did not show a persistent perforation, this case underlines the need for thorough inspection after endoscopic closure to make sure the perforation is adequately closed. However, as proven in this case, endoscopic appearance is not always predictive of long-term success; therefore, intensive clinical observation for 24 hours and immediate surgical intervention in case of clinical deterioration are of utmost importance.

Although after immediate endoscopic closure of a perforation a patient might not even notice that a perforation occurred, iatrogenic perforations of the gastrointestinal tract still represent a severe complication. When looking at the surgical literature, the largest series of surgical management of perforations (>30 perforations included) show a mortality rate >7%. The mortality rate of 3% in our series therefore seems to be within an acceptable range.

In one patient an esophageal perforation occurred while introducing the endoscope with the OTSC. Perforations are known, yet rare, complications during introduction of endoscopic devices mounted on the tip of the endoscope. The OTSC cap has blunt edges and is comparable in diameter, but it has a 2-mm protruding plastic rim that might make it slightly more traumatic than standard plastic caps widely used for rubber band ligation. This could be of major concern because a 3% perforation rate is unacceptable for any endoscopic device. However, with standard precautions such as only introducing the cap under vision and stopping if any resistance is felt, we expect this complication to remain an extremely rare event.

Therefore, the current gold standard for gastrointestinal perforations, could be avoided in 89% of cases. Consequently, general anesthesia, abdominal incisions, temporary ostomies, and their associated morbidity were avoided in these patients. The procedure took a limited amount of extra endoscopy time and proved to be rather uncomplicated after training.

Discussion

This multicenter prospective human trial that was investigating a new endoscopic closure device (OTSC) resulted in a sustained successful endoscopic closure in 89% (32/36) of acute iatrogenic perforations of the gastrointestinal tract. The mortality rate of 3% in our series therefore seems to be within an acceptable range. In one of our patients, initially successful endoscopic closure of a colonic perforation turned out to be inadequate a few hours later because the clip apparently had slipped off. In this case surgery was delayed by the endoscopic procedure. Although the patient was successfully operated on within 12 hours after onset of the perforation, he died within 24 hours after surgery without a clear cause. Although autopsy did not show a persistent perforation, this case underlines the need for thorough inspection after endoscopic closure to make sure the perforation is adequately closed. However, as proven in this case, endoscopic appearance is not always predictive of long-term success; therefore, intensive clinical observation for 24 hours and immediate surgical intervention in case of clinical deterioration are of utmost importance.

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Table 2. Primary Outcome

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Total (n = 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Successful endoscopic closure (%)</td>
<td>33 (92)</td>
</tr>
<tr>
<td>Esophageal perforation during introduction</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Failed adequate placement of OTSC</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Leakage of soluble contrast (%)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Persistent perforation</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Other adverse events</td>
<td>0</td>
</tr>
<tr>
<td>Successful closure (%)</td>
<td>32 (89)</td>
</tr>
</tbody>
</table>

Table 3. Outcome per Location

<table>
<thead>
<tr>
<th>Location</th>
<th>Total (n = 36)</th>
<th>Successful endoscopic closure (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esophagus</td>
<td>5 (14)</td>
<td>5 (100)</td>
</tr>
<tr>
<td>Stomach</td>
<td>6 (17)</td>
<td>6 (100)</td>
</tr>
<tr>
<td>Duodenum</td>
<td>12 (33)</td>
<td>9 (75)</td>
</tr>
<tr>
<td>Colon</td>
<td>13 (36)</td>
<td>12 (92)</td>
</tr>
</tbody>
</table>
hypothesis was very recently confirmed by a study concerning the use of the OTSC to narrow the pouch outlet in patients who underwent gastric bypass surgery. An esophageal perforation or laceration occurred in none of the 94 patients.30

In 2 cases immediate adequate endoscopic closure could not be achieved. Both cases concerned duodenal perforations. In the relatively confined space of the duodenum in combination with air leakage through the perforation, it can be challenging to properly grasp both perforation edges to secure closure. In the remaining 9 duodenal cases, surgery was successfully avoided, leading to a success rate for duodenum perforations of 75%.

Some perforations might have been successfully closed by using standard endoclips alone. However, all currently published series regarding endoclip closure are retrospective in nature, with the obvious drawback of a potential selection bias.3,6,7,31 Therefore, the mortality and morbidity rates of endoclip closure are unknown. The only way to answer such a question is to perform a prospective study in a consecutive series of perforations. In our opinion, such a trial is and will not be performed because endoclip closure is probably only appropriate in a highly selected group of patients, results in approximation of the mucosal layers instead of full-thickness serosa-serosa apposition, and might result in an unacceptably high leak rate.15–18 We therefore choose to evaluate a device that could be used for any perforation <3 cm.

Pilot studies with OTSC closure of gastrointestinal perforations have been described earlier but were all retrospective in nature and included only limited patient numbers (<5 perforations).27,28

Because of the low incidence of iatrogenic perforations we decided to include all perforations of the gastrointestinal tract irrespective of their location. We therefore accepted potential drawbacks of a relative heterogeneous population for this human prospective cohort of endoscopic closure of acute perforations. A randomized controlled trial in a more homogenous population could now become appropriate after this trial has confirmed the promising results of small retrospective case series. A randomized study comparing endoscopic vs surgical management of acute perforations will however require many more patients and will be very difficult to perform in view of the rarity of these complications. On the other hand, an initial endoscopic attempt takes 5–10 minutes and does not seem to hinder subsequent surgery. A controlled trial would not be required to demonstrate that endoscopic closure is less invasive than surgery, especially if a (temporary) colostomy is needed to manage the perforation.

A final caveat concerns the fact that participating study sites were all tertiary referral centers. Consequently, success rates in this series might not be applicable to arbitrary centers.

Several factors must be considered when determining appropriate treatment of an acute gastrointestinal perforation. We focused on acute, uncomplicated perforations <3 cm without contamination. Late (>24 hours) recognition of a perforation with or without signs of peritonitis is regarded a contraindication for endoscopic treatment. Perforations >3 cm were excluded in this study and should be referred for surgery until evidence of successful endoscopic closure becomes available.

At 6-month follow-up, the majority of OTSCs were still present at the perforation site. At endoscopic inspection of these patients, the groove behind the clip appeared to increase slowly, indicating that the OTSC might fall off later. However, this is speculative, and longer follow-up is needed. None of the patients had complications or complaints from the continued presence of the OTSC, and there seems to be no indication that the clip will migrate through the gut wall. The OTSC is magnetic resonance imaging safe; therefore, there does not seem to be an acute reason to mandate spontaneous or medical removal.

Endoluminal closure with the OTSC of acute iatrogenic perforations of the gastrointestinal tract was shown to be relatively quick and easy and resulted in adequate closure and avoidance of surgery in 89% of patients in this multicenter prospective human trial. Although caution is warranted until further evidence is available, these results indicate that the preferred treatment strategy for patients with acute perforations could consist of a step-up approach consisting of endoscopic OTSC closure that is followed, if not completely successful, by surgical treatment.

Appendix: Investigators of the CLIPPER Study Group

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Supplementary Material

Note: To access the supplementary materials accompanying this article, visit the online version of Clinical Gastroenterology and Hepatology at www.cghjournal.org, and at doi:10.1016/j.cgh.2012.02.005.

References


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Acknowledgments
Investigators of the CLIPPER Study Group are listed in the Appendix. Over-the-Scope-Clips and twin graspers were supplied by Ovesco Endoscopy AG, Tübingen, Germany without restrictions.

Conflicts of interest
The authors disclose no conflicts.