Endoscopic closure of iatrogenic perforation

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A B S T R A C T

Iatrogenic perforation of the gastrointestinal (GI) tract is one of the serious complications in GI endoscopy. With the advancement in technique of GI endoscopy especially therapeutic endoscopy, the risk of perforation has increased. Prompt detection is the only way to avoid delay treatment and poor outcome. Recently, there are new instruments and techniques developed that can be reliably applied for an endoscopic closure without the need for surgery. Therefore, endoscopists should be familiar with these instruments as the result of successful endoscopic closure has lower rate of morbidity than surgery. In this review, the techniques of endoscopic closure are described according to the organs of perforation. In addition, the general knowledge and management of perforation in other aspects including tension pneumothorax, abdominal compartment syndrome, or infection induced by contamination of GI content are explained.

Keywords: Clip; Closure; Endoscopy; Iatrogenic; Perforation; Stent

Introduction

Gastrointestinal (GI) endoscopy provides both diagnosis and treatment of various GI disorders through the natural lumens. Many of therapeutic endoscopic procedures such as polypectomy, sphincterotomy, dilation, endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), peroral endoscopic myotomy, etc. require dissection or cutting the mucosal and submucosal layers of the GI tract, in a very rare occasion, an inadvertent full thickness injury so called “perforation” could develop. Traditionally, surgery is the only rescue treatment for this iatrogenic perforation. Recently, with the application of many endoscopic gadgets such as stent, band, endoclip, an endoscopic closure could be employed as the primary treatment for perforation and this in turn may result to the lower rate of morbidity than the previous surgical approach.

Incidence of Perforation

Iatrogenic esophageal perforation is a mishap associated with many diagnostic and therapeutic interventions of the esophagus, such as an insertion of duodenoscope/echoendoscope/transesophageal echocardiogram transducer/esophageal dilator and Sengstaken Blakemore tube misplacement. The incidences of perforation ranged from 0.09% to 4.1% depending on the types of procedure (Table 1). The reported overall immediate mortality rate of iatrogenic esophageal perforation was as high as 13.2%. Perforation in different esophageal locations had different rate of morality. For instance, cervical esophageal perforation had the lowest mortality rate at 0% to 5.9%, followed by 10.9% to 16.7% in thoracic esophageal perforation, whereas abdominal esophageal perforation had the highest mortality at 13.2% to 16.7%. The other factor that influenced the mortality rate was timing of detection, the mortality rate was reported to be at 3.0% to 7.4% when perforation diagnosed within 24 hours whereas the mortality rate would be as high as 20.3% to 36.4% when the diagnosis was made after 24 hours.

Gastric perforation is reportedly rare during esophagogastro-duodenoscopy with the incidence of 0.001%. The risk of perforation increased in therapeutic procedure of the stomach such as EMR (0%–5.3%) or ESD (0%–6.4%). ESD of the proximal part or the greater curvature of stomach portends a higher risk of perforation with the odds ratio (95% confidence interval) of 4.88 (2.21–10.75) and 7.0 (3.1–15.8), respectively. In certain pro-
cures, such as natural orifice transluminal endoscopic surgery and endoscopic full thickness resection (EFTR), the gastric wall is intentionally penetrated as a full thickness perforation, these procedures thereby need a complete closure.\textsuperscript{21,22}

Duodenal perforation developed in 0.2\% to 1\% during endoscopic retrograde cholangiopancreatography (ERCP),\textsuperscript{23,24} 0.022\% during diagnostic endoscopic ultrasonography (EUS), and 0.09\% during EUS–fine needle aspiration.\textsuperscript{25} Stapfer et al\textsuperscript{26} proposed the classification of ERCP-related perforation as type 1: injury of lateral duodenal wall, type 2: injury at sphincter of Oddi, type 3: ductal injury, and type 4: retroperitoneal air alone. The proportion of ERCP-related perforation in each type were 34.5\% in type 1, 31.3\% in type 2, 23\% in type 3, and 0.8\% in type 4.\textsuperscript{23} Stapfer type 1 (caused by an endoscope) and some of Stapfer type 2 (caused by sphincterotomy) were recommended to be treated by immediate surgery while in types 3–4 or in selected type 2 patients can be treated by non-operative measure.\textsuperscript{26,27} The surgically altered anatomy, e.g., previous Billroth II anastomosis, may increase the risk for Stapfer type 1 perforation\textsuperscript{28} which is explained by alteration of gut direction, acute angulation of lumen, and adhesion from previous surgery. Risk factors for Stapfer type 2 or 3 perforations were sphincterotomy, sphincter of Oddi dysfunction, dilated common bile duct, and biliary stricture dilation.\textsuperscript{29} The overall mortality of ERCP-related perforation was reported at 8.0\% to 9.9\%.\textsuperscript{23,24}

Colonic perforation occurred about 0.01\% to 0.10\% during both diagnostic and therapeutic colonoscopies.\textsuperscript{30} Diagnostic colonoscopy had lower rate of perforation than colonoscopy with polypectomy (0.01\% vs 0.1\%)\textsuperscript{30,31} and sigmoid colon was reported as the most common location for perforation.\textsuperscript{31} Other factors that associated with perforation are polyp larger than 1 cm, numbers of polyp > 4, emergency colonoscopy, low volume colonoscopist,\textsuperscript{30} or polyp at the cecum.\textsuperscript{12} Colonic perforation during diagnostic colonoscopy is mostly caused by the scope and this injury seems to have a large colonic wall defect (mean size 19.3 mm). It cannot be treated conservatively.\textsuperscript{31,33} Contrastly therapeutic polypectomy induced perforation has a smaller defect (mean size 5.8 mm), and most patients can be treated conservatively.\textsuperscript{31,33} In addition, EMR related perforation can be immediately recognized if there is a “target sign” (Fig. 1) indicating muscularis propria injury in the resected specimen.\textsuperscript{34}

Management

General management

Early detection of perforation is crucial as the first step of

Table 1 Procedure and Incidence of Esophageal Perforation

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Incidence (%)</th>
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<tbody>
<tr>
<td>Pneumatic balloon dilation in achalasia cardia\textsuperscript{6}</td>
<td>2</td>
</tr>
<tr>
<td>Endoscopic mucosal resection for early cancer\textsuperscript{14}</td>
<td>1.6</td>
</tr>
<tr>
<td>Esophageal dilation in eosinophilic esophagitis\textsuperscript{7}</td>
<td>0.1–1</td>
</tr>
<tr>
<td>Esophageal dilation in post ESD stricture\textsuperscript{4}</td>
<td>0.37 (per procedure)</td>
</tr>
<tr>
<td>ESD for superficial esophageal carcinoma\textsuperscript{9}</td>
<td>1</td>
</tr>
<tr>
<td>Duodenoscope-induced\textsuperscript{10}</td>
<td>0.09</td>
</tr>
<tr>
<td>Echoendoscope (radial and linear)\textsuperscript{11}</td>
<td>0.009</td>
</tr>
<tr>
<td>Sengstaken-Blakemore tube misplacement\textsuperscript{14}</td>
<td></td>
</tr>
<tr>
<td>Sclerosing agent injection for esophageal varices\textsuperscript{48}</td>
<td></td>
</tr>
<tr>
<td>Traumatic insertion of mucosectomy cap\textsuperscript{36}</td>
<td>NA (case reports)</td>
</tr>
<tr>
<td>Removal of food bolus impaction\textsuperscript{17}</td>
<td></td>
</tr>
<tr>
<td>Transesophageal echocardiogram\textsuperscript{13}</td>
<td></td>
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ESD, endoscopic submucosal dissection; NA, not available.
management. Visualization of mediastinal organs (thoracic esophageal perforation), or intra-abdominal organs or omentum or retroperitoneum (abdominal esophageal, gastric, duodenal or colonic perforation) is evidenced for the diagnosis of perforation. While using a side-viewing duodenoscope, perforation may not be directly visualized by the scope. Therefore, endoscopists should be aware of other indirect signs such as patients’ discomfort, change in vital sings, cutaneous emphysema, and observation of pneumoperitoneum/pneumomediastinum under fluoroscopy (Fig. 2). When perforation is detected the endoscopists should not be panic. Instead he or she should promptly evaluate the perforation in term of size, shape, and location. Air insufflation should be switched to CO₂, if available. Intraluminal content should be cleaned out to prevent extra-luminal contamination, or patients’ position should be adjusted to shift the luminal fluid away from the perforation site. Patients’ vital signs should be closely monitored. If hemodynamic status of the patient is unstable, tension pneumothorax or abdominal compartment syndrome should be investigated and immediate air release should be instantaneously performed without delay. An intravenous broad spectrum antibiotic covering for enterobacteriaceae and anaerobic bacteria should be administered. After the procedure, patients should be kept fasting until mucosal healing is achieved. Nasogastric tube may be inserted for enteral nutrition in the case with esophageal perforation, or for GI luminal decompression in others. Before resuming an oral intake, water soluble contrast leakage test should be performed to confirm the complete closure of the defect.

**Endoscopic management**

**Esophageal perforation**

Through-the-scope (TTS) clip can be used for an immediate approximation of perforated mucosa and subsequently the healing of other layers occurs later. The available clips have an open-jaw width range from 9 to 16 mm, all have an outer sheath diameter of 7 Fr, and the sheath length range from 230 to 235 cm. Factors that should be considered before choosing TTS clip for closure are shape of the perforation, and compliance or viability of the perforation edge. In a prospective study of surviving porcine model on closure of esophageal perforation by TTS clip, endoscopic suture, and thoracoscopic repair, the mean length × width were 18 × 8, 15 × 6, and 18 × 7 mm, respectively. Only TTS clip group had no mortality, while the endoscopic suture and thoracoscopic closure groups had mortality at 17% in each group, however the difference did not reach statistical significance due to small sample size. In human, there has been no prospective controlled study, there were 8 reports include 17 cases that used TTS clip for iatrogenic esophageal perforation. The causes of perforation were; removal of food impaction, cap mucosectomy, dilatation of achalasia or esophageal anastomotic stricture, EMR, and ESD. The range of perforation length was 7 to 40 mm, the majority of location was distal esophagus (72%), and the healing time after clipping was 5%.

To enhance the visualization of defect while closing, a transparent cap may be used. In a larger defect, the combination of TTS clip and endoloop may be helpful. The technique includes multiple clippings the perforation edge and then tighten them with an endoloop to close the perforation. A double channels gastroscope is necessary in this technique. However the combination of endoloop and TTS clip in esophagus can be applied in a single channel gastroscope by inserting the endoloop directly into the patient’s mouth and apply the clip through the accessory channel.

Esophageal stent has been originally designed for the treatment of both benign and malignant strictures. The additional benefits of esophageal stent include closure of leakage, perforation, and fistula. The recommended esophageal stents for closure of perforation are fully-covered self-expanding metallic stent (FCSEMS), partially-covered self-expanding metallic stent (PCSEMS), and self-expanding plastic stent (SEPS). The FCSEMS have the diameter of 16 to 23 mm with the length of 60 to 150 mm. The delivery systems have diameter of 5.8 to 8 mm. The SEPS have the diameter of 16 to 21 mm with the length of 90 to 150 mm. The delivery systems have diameter of 12 to 14 mm, therefore theses stents cannot be inserted through the accessory channel of the scope and their uses have to be under non-TTS technique.

The optimal size of the stent depends on the location, length of the perforation, and the associated stricture. Stenting across the upper esophageal sphincter can cause patients’ discomfort and that of across the lower esophageal sphincter can cause reflux symptoms. The reports of esophageal stent in term of technical and clinical success in treatment of iatrogenic perforation were 91% to 100% and 81% to 86% respectively. When esophageal mucosa is friable, e.g., post-sclerosing agent injection, or fragile, e.g., eosinophilic esophagitis, stent placement has been reported to be more effective than endoscopic clipping. When compared with esophagectomy, esophageal stenting caused lower mortality (13.8% vs 7.3%). The average time of stent removal ranged from 15 to 56 days. Tissue hyperplasia developed 0.4%, 50.5%, and 0% in FCSEMS, PCSEMS, and SEPS, respectively. Unfortunately tissue hyperplasia in the uncovered area of the stent causing significant stenosis occurred exclusively in PCSEMS with the rate of 50%. The successful rates of stent removal were 98.4% and 100% in FCSEMS and SEPS, respectively. The PCSEMS had the lowest of successful removal rate (29.5%) due to tissue ingrowth at the bare area of the stent; however, the success rate increased to 96.6% after stent-in-stent technique to ablate the ingrowth tissue. The migration rate were different among stent types, 22% for FCSEMS, 11% for PCSEMS, and 27% for SEPS. As the majority of those esophageal perforation had no stricture to maintain the contour of stent then stent migration could develop. To prevent distal migration, clipping reduced migration rate from 34% to 13% and over-the-scope clip (OTSC) anchoring FCSEMS reduced the migration rate to 16.4%. and more importantly both adjunctive treatments did not preclude the FCSEMS removal.

OTSC is another useful device for esophageal perforation closure. It is made of nitinol, stretched on an applicator cap, and has a wing span of 11 to 14 mm. Perforation closure is done by suctioning the edge of defect, with or without using endoscopic twin-grasping forceps, into the cap and then the OTSC is deployed. Full thickness approximation can be achieved by this technique and it can close up to 30 mm perforation. In a prospective multicenter study included 5 iatrogenic esophageal perforations, OTSC provided 100% success rate of closure. Although it is a very rare event, additional esophageal perforation caused by the OTSC cap itself has been reported with the incidence of 0.03%.

Endoscopic band ligation (EBL) is usually used for esophageal variceal ligation. There was a study using EBL for a closure of perforation in porcine model. The appropriate size of esophageal perforation that EBL could be successfully performed had to be equal or smaller than 10 mm whereas EBL failed to close the perforation size that larger than 15 mm.

**Gastric perforation**

TTS clip is commonly used for closure of gastric perfora-
tion. Most data were reported from EMR or ESD series and TTS clip showed technical and clinical success rate of 96.1% to 100% without reported mortality. The perforation size developed from this procedure is usually small. In one report, the mean size of perforation caused by ESD was 2.5 mm with the maximum size of 5 mm. When the perforation size is more than 10 mm, the omental-patch technique performed by closing the defect after suction the omental fat into the perforation hole, has been reported to be useful. TTS clip alone is used to close gastric perforation from EFTR with 100% success rate for the mean lesion size at 2.8 cm (range, 1.2–4.5 cm). TTS clip was used in conjunction with the endoloop in “purse-string” fashion (the TTS clip was applied to capture both the perforation edge and endoloop) with the reported 100% success rate for closure the defects after EFTR. The reported mean tumor size was 1.9 cm (range, 0.3–4.2 cm). However, this technique requires double-channel therapeutic gastroscopy for the simultaneous insertion of both endoloop and TTS clips. Another technique that used TTS clip and endoloop for closure after EFTR by applying the TTS clip first followed by placing endoloop over the TTS clips for trapping and then tightening all TTS clips together. The reported mean lesion size was 2.4 cm (range, 1.3–3.5 cm) and the success rate was 100%. This technique does not require the double-channel scope.

OTSC has been used for closure of perforation, leakage, or fistula. Most of publications reported OTSC performance in the mixture of these indications. However, the success rates were different among these indications. By pooled analyses the success rate for closure of fistula, post-operative leak, and acute perforation induced by duodenoscope, echoendoscope, EUS-guided fine needle aspiration, stent migration, EMR, or ESD, was 59%, 68%, and 90%, respectively. Failure of closure was affected by size and area of defect, and vitality of perforation edge. When focusing on the closure of iatrogenic gastric perforation, the overall success rate was 93%. EBL has been reported as an effective closure for gastric perforation with the size of 10, 15, and 20 mm in porcine model. Numbers of band used for closure were 2, 3, and 6 bands depending on the size of defect. In the porcine models, all 3 pigs survived until 14 days before sacrificed, and histology confirmed the complete closure of all perforations. In clinical study, EBL has been used as rescue tool after failure of clipping for gastric perforation. All 5 patients (100%) with gastric perforation were successfully closed by rescue EBL, average duration of fasting was 4 days (range, 2–7 days), and all patients were discharged after average of 7.4 days (range, 2–14 days). However, EBL itself has been reported to be the cause of gastric perforation after the attempted ligation for small stromal tumor in 3 patients with the onset of perforation at 24, 35, and 41 hours after procedure. This may be explained by premature tissue necrosis in the banded area prior to a complete formation of adhesion onto the adjacent structures.

The endoscopic suturing devices, e.g., OverStitch, Eagle Claw, or successive suturing devices, have been recently developed. These instruments provided effective closure of gastric perforation ex vivo, and in vivo of animal models. The success rate of closure ranged from 87.5% to 100%. In human, OverStitch has been reported in a retrospective study of 15 patients with iatrogenic perforation. The locations located in esophagus in 13 patients, duodenum in 1 patient, and colon in 1 patient. The mean defect sizes were 30 mm (range, 25–50 mm). The success rate of OverStitch for closure of perforation was 93.3%.

Duodenal perforation

Iatrogenic Stapfer type 1 duodenal perforation results to a large defect causing systemic toxicity, traditionally all patients with this type of injury require surgical management. Once perforation is detected, surgical consultation should be carried out immediately. However, in surgically unfit patients, endoscopic closure has been reported to be successful. For those Stapfer types 2 and 3 the non-surgical approach is well accepted as majority of the patients improve after this conservative treatment and surgery is only reserved as the rescue. The non-surgical approach for Stapfer types 2 and 3 has been described elsewhere.

In the lateral duodenal wall perforation, TTS clips use was reported in 2 case-series of 8 patients that successfully closed. The scopes used for closure were cap-assisted gastroscope (Fig. 3) in 4 patients, gastroscope only in 2 patients, and side-viewing duodenoscope in 2 patients. After procedure, patients resumed an oral diet in 3 to 10 days, and stayed in the hospital for 7 to 30 days. Four patients underwent additional percutaneous biliary drainage, but did not receive nasogastric or nasoduodenal tube decompression. In contrast, nasogastric or nasoduodenal tube decompressions were inserted in the other four patients without biliary drainage. There was no mortality or intra-abdominal infection during the short-term follow up. TTS clip was reported to be successful for a closure of duodenal perforation after EMR, EUS, biliary stenting, or full thickness duodenal perforation. Endoloop and EBL have been used to recue after closure failure by TTS clip in some reports.

OTSC has been reported to be useful for a closure of duodenal perforation induced by duodenoscope, echoendoscope, EUS-guided fine needle aspiration, stent migration, EMR, or ESD. In prospective study with mixed causes of duodenal perforation, OTSC provided 75% success rate for closure. The reasons for failure were esophageal perforation induced by OTSC cap and the inability to maneuver of the scope in a proper position for another OTSC deployment to close the duodenal defect. When using OTSC with double-grasping forceps, before deployment of the OTSC endoscopists should make sure that the forceps is fully pulled inside the scope to prevent the forceps trapping inside OTSC in such case an emergency surgery to remove the system is required.

Although most of sphincterotomy-related perforation can be treated conservatively, a closure should be carried out when large

Fig. 3. Cap-assisted through-the-scope (TTS) clips for closure of lateral wall duodenal perforation. Note TTS clips were deployed earlier but failed to close the rent.
perforation is detected to prevent major spillage of GI content. TTS clip has been reported to achieve successful closure in this type of perforation. According to the location that is difficult to approach by the forward-viewing scope, the side-viewing scope could be used for a closure. The drawback of using the side-viewing scope is that the endoclipping device can become kinking and malfunctioning because of the tension made by the elevator of the side-viewing scope. FCSEMS has been reported for the treatment of Stapfer type 2 perforations in 6 patients, the duration of stent placement was 10 to 30 day, with 100% success rate. Spontaneous stent migration occurred in one after the complete closure of perforation.

Colonic perforation

TTS clip has been proven to provide a comparable leak-pressure control to the hand-sewn closure ex vivo porcine models. In human, TTS clip (Fig. 4) provided successful closure rate at 75.86% to 95.65% in retrospective series. Predictors for the need of surgery within 24 hours after clipping are perforation size 10 mm or more, leukocytosis, fever, severe abdominal pain, and large amount of peritoneal free air indicated by a distance between right diaphragm and upper border of liver of 3 cm or more. TTS clip provided comparable fasting time (4.2 days) and hospital stay (9 days) to surgery (5.1 and 14.5 days, respectively). In cases of failed TTS clipping from awkward angle and/or large size of perforation, a rescue EBL (Fig. 5) has been successfully used for endoscopic closure as case reports.

OTSC also has compression force comparable to hand suture in ex vivo porcine model. In a prospective study included 12 colon perforations, OTSC showed technical success rate of 100%, and clinical success rate of 92%. One patient developed OTSC detachment at 5 hours after the procedure which caused persistent perforation.

Conclusion

The incidence of iatrogenic GI perforation has increased especially in the era of advanced therapeutic procedures. Surgery is still the standard treatment for perforation. However, endoscopic closure can be attempted in certain situations. Each location and size needs different therapeutic techniques (Table 2). TTS clip can be used to close the perforation in esophagus, stomach, duodenum, and colon. The main limitation of application of TTS clip is the width of the defect should be less than the span of the clip. EBL or endoloop can be used in conjunction with TTS clip in a larger perforation. OTSC can be applied at all anatomical location similar to TTS clip except Stapfer type 2 duodenal perforation near the ampulla, and the size of perforation that can be closed by OTSC is up to 30 mm. FCSEMS can be used in esophagus or Stapfer type 2 duodenal perforation because of straight tubular

![Fig. 4. Through-the-scope clips for closure of colon perforation.](image1)

![Fig. 5. Rescue banding after failure of through-the-scope clip closure in colonic perforation. Asterisks represent part of omentum and arrow is the band.](image2)

<table>
<thead>
<tr>
<th>Location</th>
<th>Size of perforation (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 10</td>
</tr>
<tr>
<td>Esophagus*</td>
<td>TTS clip</td>
</tr>
<tr>
<td>Stomach</td>
<td>TTS clip</td>
</tr>
<tr>
<td>Duodenal wall</td>
<td>TTS clip</td>
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<tr>
<td>Sphincterotomy-related</td>
<td>Biliary FCSEMS or TTS clip</td>
</tr>
<tr>
<td>Colon</td>
<td>TTS clip</td>
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</tbody>
</table>

TTS, through-the-scope; OTSC, over-the-scope clip; FCSEMS, fully-covered self-expanding metallic stent.

*Determine by width of perforation.
structure of esophagus and bile duct. In esophageal perforation FCSEMS can cover the larger area of perforation. However, FCSEMS migration could develop in non-stricture related perforation, thereby anchoring technique is helpful. After closure patients should be closely monitored, when clinical deterioration detected, surgery will be the definite treatment. Nevertheless, endoscopic suture device is still in its developmental phase and the technique has to be refined for more reliable use.

Conflicts of Interest
No potential conflict of interest relevant to this article was reported.

Acknowledgments
Authors would like to thank Assoc. Prof. Rajvinder Singh, MBBS, MRCP, MPhil, FRACP, AM FRCP, Director, Consultant Gastroenterologist, Clinical Associate Professor, The Lyell McEwin Hospital & University of Adelaide, Endoscopy Unit, Haydon Road, Elizabeth Vale 5112 SA, Australia for providing Fig. 1 and 4.

References


