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Immediate technical and delayed clinical outcome of fistula closure using an over-the-scope clip device

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Abstract
Background and study aims An over-the-scope clip (OTSC) device was designed for closure of acute perforations, fistulas, leaks, and non-variceal gastrointestinal bleeding. Previous data show a high rate of early fistula closure using the OTSC; however, data on long-term fistula closure are scant. We report our experience using an OTSC for closure of chronic gastrointestinal fistulas.
Patients and methods Retrospective review of all patients, who underwent OTSC placement at Mayo Clinic Rochester and Virginia Mason Medical Center for closure of chronic fistulas from October 2011 to September 2012, was performed. Initial technical success was defined by lack of contrast extravasation immediately after OTSC placement. Delayed success was defined by resolution of the fistula without the need for additional therapies. Recurrent fistula was defined by the recurrence of symptoms and/or re-demonstration of fistula after initial success.
Results Forty-seven unique patients (24 men; mean age 57 ± 14 years) underwent 60 procedures using the OTSC for closure of gastrointestinal fistulas. Fistula locations were: small bowel ($n = 18$), stomach ($n = 16$), colo-rectum ($n = 10$), and esophagus ($n = 3$). Fistulas related to previous percutaneous endoscopic gastrostomy/jejunostomy ($n = 10$) or prior bariatric procedure ($n = 10$) were the most common etiologies. Initial technical success occurred in 42/47 (89 %) index cases; however, 19/41 (46 %) patients developed fistula recurrence at a median of 39 days (IQR 26–86 days). The retained OTSC was present adjacent to the fistula in 16/19 (84 %) at repeat intervention. Patients were followed for a median length of 178 days (IQR 63–326 days), and only 25/47 (53 %) patients demonstrated delayed clinical success using OTSC.
Conclusions Initial technical fistula closure can be achieved using OTSCs. Recurrent fistulas at the same location occur in approximately 50 % of cases despite frequent OTSC clip retention.

Keywords Over-the-scope clip · Gastrointestinal fistula · Fistula closure

Abbreviations

TTS	Through-the-scope
SEMS	Self-expandable metal stent
OTSC	Over-the-scope clip
IQR	Interquartile range
PEG	Percutaneous endoscopic gastrostomy
PEJ	Percutaneous endoscopic jejunostomy

A fistula is defined as an anomalous connection between epithelialized surfaces, one of which is a hollow organ [1]. Fistulas are generally classified as internal (internal origin and drainage) or external (internal origin/external drainage), and further subclassified by etiology and output

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volume [2]. Gastrointestinal fistulas can occur throughout the gastrointestinal tract and can occur after surgical intervention, secondary to inflammatory/infectious disorders and cancer, after radiation therapy or following removal of percutaneous tubes.

Endoscopists are increasingly called upon to attempt endoscopic closure, as endoscopy is less invasive compared to surgery. A variety of endoscopic therapies for fistula closure have been attempted, though without consistent success. Endoscopic closure techniques include endoscopic band ligation [3], placement of through-the-scope (TTS) clips [4], cardiac septal occluder devices [5], porcine small intestine submucosa [6], endoluminal self-expandable metal stents (SEMS) [7], endoscopic suturing [8], injection of glue [9, 10], and use of OTSC.

Historically, TTS clips have been the initial endoscopic therapy for closure of gastrointestinal perforations, leaks, and fistulas. TTS clips are useful for closure of small- to moderately sized endoscopic perforations, as apposition and healing of healthy tissue can be relatively easy to achieve; however, closure of post-surgical leaks and chronic fistulas are more challenging owing to fibrosis of the involved tissue, limited opening width, and inadequate closure force of available TTS clips [11]. An over-the-scope clip (OTSC) device was introduced for closure of acute perforations [12], fistulas/leaks [13], and treatment of non-variceal gastrointestinal bleeding [14]. The OTSC was designed to overcome the limitations of traditional TTS clips. Though radically different in design, the OTSC allows for increased tissue capture and improved closure force necessary for sustained defect closure. Chronic fistulas are more difficult to close and while immediate closure rates using OTSC are known, the delayed outcomes are not. We report our experience with the OTSC for closure of gastrointestinal fistulas.

Patients and methods

This is a two-center, retrospective review of all patients who underwent OTSC placement (OTSC system; Ovesco Endoscopy AG, Tubingen, Germany) for closure of a gastrointestinal fistula from October 2011 to April 2013. Patients who had OTSC placement for other indications (i.e., bleeding, acute perforation, leak, stent anchoring, etc.) were excluded from this analysis. The study was approved by the Institutional Review Boards at Mayo Clinic and at Virginia Mason Medical Center. Patient demographics, procedural information, and clinical details were abstracted from the electronic medical record and endoscopy database. Age was expressed as mean with standard deviation. Duration of patient follow-up was displayed as median with interquartile range (IQR).

Procedural technique

In each case, an initial endoscopy was performed to visually identify the fistulous tract. The endoscope was then removed and fitted with the OTSC system. The clip configuration (i.e., tooth-type, size, etc.) was chosen based on location and size of the lesion. The OTSC clips are available with three types of teeth with varying degrees of serration and length. These are described as A-type or atraumatic, T-type or traumatic, and GC-type or gastric closure. At our institutions, we generally use the GC (gastric closure) clips for gastric indications and T (traumatic) clips for all other indications. Further clip choice is based on the diameter of the endoscope being used and the goal volume of tissue being grasped. After clip attachment, the endoscope was re-introduced into the gastrointestinal lumen. The OTSC was deployed under direct vision after the fistula was centered in the middle of the cap housing the clip. In some cases, a guidewire was passed inside the fistula and grasped externally or vice versa and traction applied to center the fistula followed by suction and clip deployment. Tissue graspers and tract ablative therapies (i.e., argon plasma coagulation and cytology brush) were used at the endoscopist discretion. Most procedures were performed under fluoroscopic guidance, and contrast injection was performed before and after OTSC placement to facilitate and assess closure.

Definitions

Index procedure was defined as the initial endoscopic procedure in which an OTSC was used for fistula closure. Initial clinical success was defined by lack of contrast extravasation after initial OTSC placement. Delayed clinical success was defined by continued resolution of the fistula without the need for additional therapies after 8 weeks. A recurrent fistula was defined by the recurrence of symptoms and/or abnormal imaging secondary to a gastrointestinal fistula after initial clinical success was achieved during the index OTSC case. In the event of fistula recurrence, additional endoscopic evaluation and radiologic imaging were performed with special attention to clip retention.

Results

From October 2011 to April 2013, a combined total of 139 OTSC procedures were performed in 126 unique patients at Mayo Clinic Rochester and Virginia Mason Medical Center. Forty-seven unique patients (24 men; mean age 57 $\pm$ 14 years) underwent 60 procedures using the OTSC

for closure of gastrointestinal fistulas (representing 37 % of all OTSC indications during the study period). The remaining patients underwent OTSC placement for a variety of indications, including: bleeding/bleeding prevention ($n = 43$), acute gastrointestinal perforation ($n = 15$), post-surgical leak ($n = 12$), stomal narrowing after Roux-en-Y gastric bypass ($n = 12$), and SEMS anchoring ($n = 2$).

Fistulas were identified at various locations throughout the gastrointestinal tract, including: small bowel ($n = 18$), stomach ($n = 16$), colo-rectum ($n = 10$), and esophagus ($n = 3$). Fistulas related to previous bariatric procedures ($n = 12$) or percutaneous endoscopic gastrostomy/jejunostomy (PEG/PEJ) procedures ($n = 12$) were the most common etiologies. The remaining etiologies included: other post-surgical causes ($n = 10$), Crohn's disease ($n = 5$), acute necrotizing pancreatitis ($n = 3$), diverticulitis ($n = 3$), post-radiation ($n = 1$), and spontaneous esophageal perforation ($n = 1$). A variety of endoscopic tools were utilized to deliver the OTSC to the target fistula, including: standard gastroscope ($n = 24$), colonoscope/flexible sigmoidoscope ($n = 16$), and balloon enteroscope ($n = 7$). In cases where balloon enteroscopy was necessary for OTSC placement, the tripwire was lengthened by tying a silk suture to its proximal end to accommodate the added scope length.

Initial technical success was demonstrated in 41/47 (87 %) index cases. A total of 58 OTSCs were utilized during the 47 index procedures with the most common OTSC being the 12/6T ($n = 27$, 47 %). Other OTSC sizes utilized during the index procedure included: 12/6GC ($n = 19$), 11/6T ($n = 7$), and 14/6T ($n = 5$). In 34/47 (72 %) index procedures, only one OTSC was necessary to provide immediate fistula closure (initial technical success). In the remaining 13 procedures, 7 patients required multiple OTSCs to obtain fistula closure and 6 patients had failed closure.

Following the index procedure, 19/41 (46 %) patients who demonstrated initial technical success developed fistula recurrence at a median of 39 days (IQR 26–86 days). In 6/19 (32 %) patients, repeat intervention was performed within 30 days of the index procedure. A retained OTSC was observed in 16/19 (84 %) repeat intervention cases and was seen adjacent to an obvious fistulous tract. A repeat endoscopic procedure with additional OTSC placement was performed in 9/19 (47 %) patients who had evidence of recurrent fistula, all of which demonstrated technically successful fistula closure after repeat OTSC deployment. In the remaining ten patients, a variety of interventions (either alone or in combination) were performed, including: surgery ($n = 7$), TTS clips ($n = 3$), endoscopic suturing ($n = 3$), and SEMS ($n = 1$). Following the second intervention, 3/9 (33 %) patients treated with the OTSC went on to require a 3rd closure procedure. One patient underwent five attempts using a variety of closure devices, including three OTSCs, but maintained a persistent colovesical fistula. Additional outcomes data are outlined in Table 1.

Patients were followed for a median length of 178 days (IQR 63–326 days). During the study period, only 25/47 (53 %) patients demonstrated sustained fistula closure (delayed clinical success) secondary to OTSC placement. The median length of follow-up for patients with delayed clinical success was 84 days (IQR 35–225 days). The remaining 22 patients required alternative therapeutic measures for fistula closure or never achieved fistula closure.

Discussion

Current literature supports the use of OTSC for hemostasis or closure of perforations within the gastrointestinal tract [14–16]; however, the data on closure of fistulas are less robust. Our data suggest that a high rate of initial technical success can be achieved when OTSCs are placed for closure of all types of gastrointestinal fistulas; however, delayed closure remains a challenge. We found that nearly 50 % of patients with endoscopic and radiologic evidence of fistula closure at completion of the index procedure went on to require additional interventions in the subsequent days to months due to fistula recurrence.

A systematic meta-analysis by Weiland et al. [12] evaluated multiple small case series and case reports (67 total cases) using the OTSC system for endoscopic closure of gastrointestinal fistulas from publications spanning from January 2007 through January 2012. Results were similar to our study with respect to initial procedural success (88 vs 89 %), but quite discrepant when comparing "long-term" success (73 vs 53 %). In several studies, similarly poor rates of durable fistula closure were seen, as three studies yielded clinical success rates of 38, 50, and 67 %, respectively [17–19]. The definition of "long-term" is unclear in the study by Weiland et al. [12], as the follow-up interval was $\leq$4 weeks or not specified in 45/67 (67 %) patients included in the meta-analysis. A recent study by Mercky et al. [20] had only 53 % success of fistula closure following the primary intervention. In our study, nearly 2/3 of patients with fistula recurrence manifested >4 weeks after demonstrating initial technical success, suggesting that longer term follow-up is necessary to determine delayed outcome in these patients.

Despite the advent of the OTSC system, closure of gastrointestinal fistulas using endoscopic methods remains a challenging endeavor. As previously mentioned, multiple closure techniques have been utilized, yet no single technique has demonstrated reliability for definitive closure of

Table 1 Outcomes following fistula closure using OTSC

Type of fistula	Etiology	Initial OTSC type attempted	Immediate clinical success	Need for repeat intervention	Delayed clinical success from OTSC
Enterocutaneous ($n = 18$)	Post PEJ ($n = 6$)	12/6T ($n = 13$)	89 % ($n = 16$)	39 % ($n = 7$)	61 % ($n = 10$)
	Post-surgical ($n = 6$)	11/6T ($n = 4$)			
	Other ($n = 3$)	12/6GC ($n = 2$)			
	Acute pancreatitis ($n = 2$)	14/6T ($n = 2$)			
	Crohn's disease ($n = 1$)				
Gastrogastric ($n = 8$)	Post-surgical (RYGB) ($n = 8$)	12/6GC ($n = 6$)	75 % ($n = 6$)	63 % ($n = 5$)	50 % ($n = 4$)
		12/6T ($n = 4$)			
		11/6T ($n = 1$)			
Gastrocutaneous ($n = 8$)	Post-PEG ($n = 6$)	12/6GC ($n = 11$)	88 % ($n = 7$)	50 % ($n = 4$)	63 % ($n = 5$)
	Post-surgical ($n = 2$)	12/6T ($n = 1$)			
Colocutaneous ($n = 5$)	Post-surgical ($n = 3$)	14/6T ($n = 3$)	100 %	100 %	40 % ($n = 2$)
	Diverticulitis ($n = 1$)	12/6T ($n = 2$)			
	Crohn's disease ($n = 1$)				
Colovesical ($n = 3$)	Diverticulitis ($n = 2$)	12/6T ($n = 2$)	67 % ($n = 2$)	67 % ($n = 2$)	33 % ($n = 1$)
	Post-surgical ($n = 1$)	11/6T ($n = 1$)			
Entero/colovaginal ($n = 2$)	Crohn's disease	12/6T ($n = 2$)	100 %	100 %	0 %
	Post-surgical				
Pancreatocolic ($n = 1$)	Acute pancreatitis	12/6T ($n = 2$)	100 %	No	100 %
Tracheoesophageal ($n = 1$)	Radiation	12/6T	100 %	No	100 %
Esophagocutaneous (n = 1)	Boerhaave's syndrome	11/6T	100 %	No	100 %

OTSC over-the-scope clip, *PEJ* percutaneous endoscopic jejunostomy, *RYGB* Roux-en-Y gastric bypass, *PEG* percutaneous endoscopy gastrostomy

gastrointestinal fistulas. Due to these difficulties, some have advocated the use of adjunctive measures, in addition to OTSC placement, to promote fistula closure. Attempts to denude or disrupt the epithelialized tract by mechanical (e.g., standard cytology brush) or thermal (e.g., argon plasma coagulation) processes have been previously described [15]. Additional adjunctive therapies, such as injection of fibrin glue or cyanoacrylate and placement of a small intestinal submucosal plug into the fistula tract, have also been attempted by the authors with disappointing results.

The natural history of fistula formation remains poorly understood. It is generally accepted that over time the fistulous tract epithelializes, or matures, with gradual progression from inflammation to fibrosis. The degree of fibrosis in and around the fistulous tract is a decidedly important factor in whether or not a closure will be successful as time to intervention may be inversely

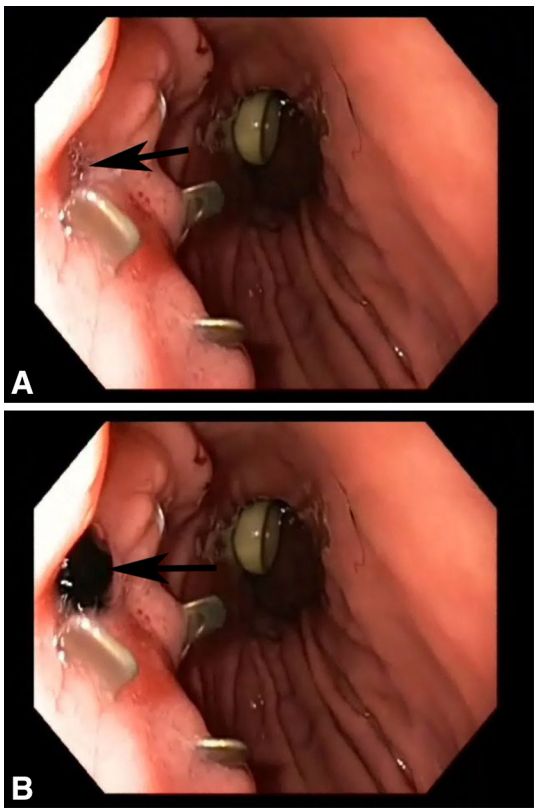

Fig. 1 **A** Displacement of the OTSC after closure of a PEG fistula, **B** confirmation of persistent PEG fistula with methylene blue despite previous OTSC closure

proportional to closure success [17]. Even less is known about how fistulas behave after treatment is undertaken. In several cases, we observed an obvious fistulous tract adjacent to a still-attached OTSC on repeat endoscopy (Fig. 1) after initial technical success was achieved on the index procedure. This scenario could represent clip migration due to peristaltic mechanisms, but could also represent fistula recurrence. Given this scenario, it seems plausible that reliable definite closure of gastrointestinal fistula can only occur if the entire fistulous tract is treated, including both the origin and insertion site.

In conclusion, we believe that the OTSC provides an additional therapeutic option for the treatment of gastrointestinal fistulas, but certainly does not represent a panacea for durable, long-term closure. Much like previously utilized modalities, the OTSC may or may not be successful in certain clinical scenarios. Future studies are needed to determine which types of patients are most likely to respond and which adjuvant therapies are needed to facilitate closure.

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