

Performance of the OTSC System in the endoscopic closure of iatrogenic gastrointestinal perforations: a systematic review

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Abstract

Background Reliable closure is a prerequisite for conventional and innovative endoscopic procedures, such as NOTES. The purpose of this study is the systematic evaluation of the procedural and clinical success rates in closure of iatrogenic gastrointestinal perforations and acute anastomotic leaks by means of the over-the-scope-clip system (OTSC®).

Design PubMed and other sources were searched systematically for clinical and preclinical research on the evaluation of the OTSC System for closure of gastrointestinal perforations and leaks. Appraisal of studies for inclusion and data extraction was performed independently by two reviewers using an a priori determined data extraction grid. Major endpoints to be extracted were data on procedural success (successful clip application) and clinical access (durable closure of defect without secondary adjunct therapy).

Results A total of 17 clinical research articles/abstracts and 22 preclinical research articles/abstracts were identified. The examined clinical studies comprised case series

and clinical single-arm studies. The reviewed studies revealed a consistently high mean rate of procedural success of 80–100 % and durable clinical success of 57–100 %. An identified major drawback preventing successful clip application was occurrence of fibrotic or inflamed lesion edges. Usage of the OTSC System was accompanied by neither major clip-related nor application-related complication. In experimental settings, closure of larger perforations and gastric access sites of NOTES or endoscopic full-thickness resection were achieved with high rates of success.

Conclusions Because randomized, clinical trials are not available in this field of indication, the evaluation is based on small case series. Nevertheless, by pooling all experience gained, we conclude that endoscopic closure of iatrogenic gastrointestinal perforations and acute anastomotic leaks by means of the OTSC System is a safe and effective method.

Keywords G-I < endoscopy · Gastrointestinal perforation closure · Over-the-scope-clip · Nitinol · Experimental trials

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One of the major challenges of current endoscopy and future development of endoscopic interventions is a reliable and safe method for closure of acute gastrointestinal perforations and leaks. Literature reported on perforation rates by accident of 0.06–0.12 % for colonoscopy [1–4]. Given the growing numbers of colonoscopies worldwide, the absolute numbers of complications reach a critical level of incidence. Also, endoscopic techniques in gastrointestinal oncology, such as endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), are associated with a nonnegligible rate of complications.

The reported perforation rates are 0.3–0.5 % in EMR and 4–10 % in ESD and hence are substantially higher than in conventional endoscopic procedures [5]. In addition, also increasingly complex surgical procedures within the gastrointestinal tract require minimally invasive solutions for closure of postoperative, acute anastomotic leaks. Depending on the type of the not yet universally defined colorectal anastomotic dehiscence, the reported prevalence of this type of complication is \sim 3–6 %, leading to enhanced morbidity and mortality [6]. For these indications and complications, an appropriate endoscopic closure procedure may circumvent stressful (re)surgery in affected patients. Furthermore, reliable closure by means of minimally invasive, endoscopic procedures is an indispensable prerequisite for the highly innovative, yet experimental, natural orifice transluminal endoscopic surgery (NOTES).

The concept of endoscopic closure of gastrointestinal perforations by endoclips dates back to 1997 and has since been applied successfully in many indications [7, 8]. However, the closure of larger perforations is hampered by the limited size of the jaws deliverable through the endoscope and their restricted closing force. The over-the-scope-clip[®] (OTSC) System (Ovesco Endoscopy AG, Tuebingen, Germany) introduced a new closure concept: the bear trap-like clip is stretched on an applicator cap on the tip of the endoscope, circumventing the constraints of the limited space within the endoscope's working channel (Fig. 1). The clip is made of nitinol, a biocompatible, MRI-safe material characterized by its superelastic shape-memory.

Mounted onto the endoscope's tip in its open, strained condition, the clip is released by a hand wheel on the operator's demand. Before clip release, the respective lesion is pulled to the cap opening by suction. Alternatively, the affected tissue may be approximated by the dedicated application aids, the anchor or the twin grasper, introduced through the working channel (Fig. 2). Complete and correct capture of the tissue is a critical point and prerequisite for optimal closure. After release by snapping

back into its neutral position, the clip maintains a permanent but dynamic full wall compression of 8–9 N onto the edges of the defect [9]. By striving toward its neutral state, the clip imposes its closing forces onto decongestant, healing tissue. Depending on the type of lesion and affected tissue, clips with different types of teeth are available: blunt teeth (a), spiked teeth (t), and longer, pointed teeth for gastric closure (gc). As a rule of thumb the sharp, spiked version (t) is suitable for any tissue, whereas the blunt version is rather recommended for fresh lesions with softer tissue, and the gc type is for the gastric application only.

The original field of indication of the OTSC System is the mechanical treatment of gastrointestinal hemorrhage. However, its performance in closure of gastrointestinal perforations and anastomotic leaks was reported by extensive animal experimentation as well as by clinical case series recently.

Hence, the purpose of this systematic literature research was to summarize comprehensively and to review the experience gained with the OTSC clipping in closure of acute gastrointestinal perforations and anastomotic leaks.

Materials and methods

Data sources/strategy of literature research

PubMed as well as the manufacturer's in-house database comprehensively registering relevant trials, publications, and conference abstracts on the OTSC System was searched systematically for articles and abstracts published until 25th July 2012. The search was conducted without language restriction. However, articles written in other languages than English, German, French, and Italian were assessed through their English abstracts only, if available. Literature search involved articles published in peer-reviewed journals, proceedings, and conference abstracts to display present research on this topic in its entirety.

Fig. 1 The bear-trap like shape of an OTSC clip (A). Position of the loaded clip onto the tip of an endoscope (B)

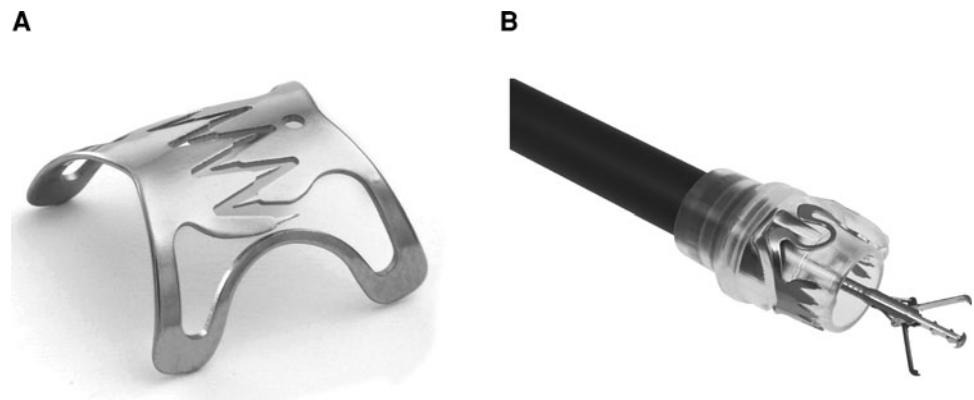
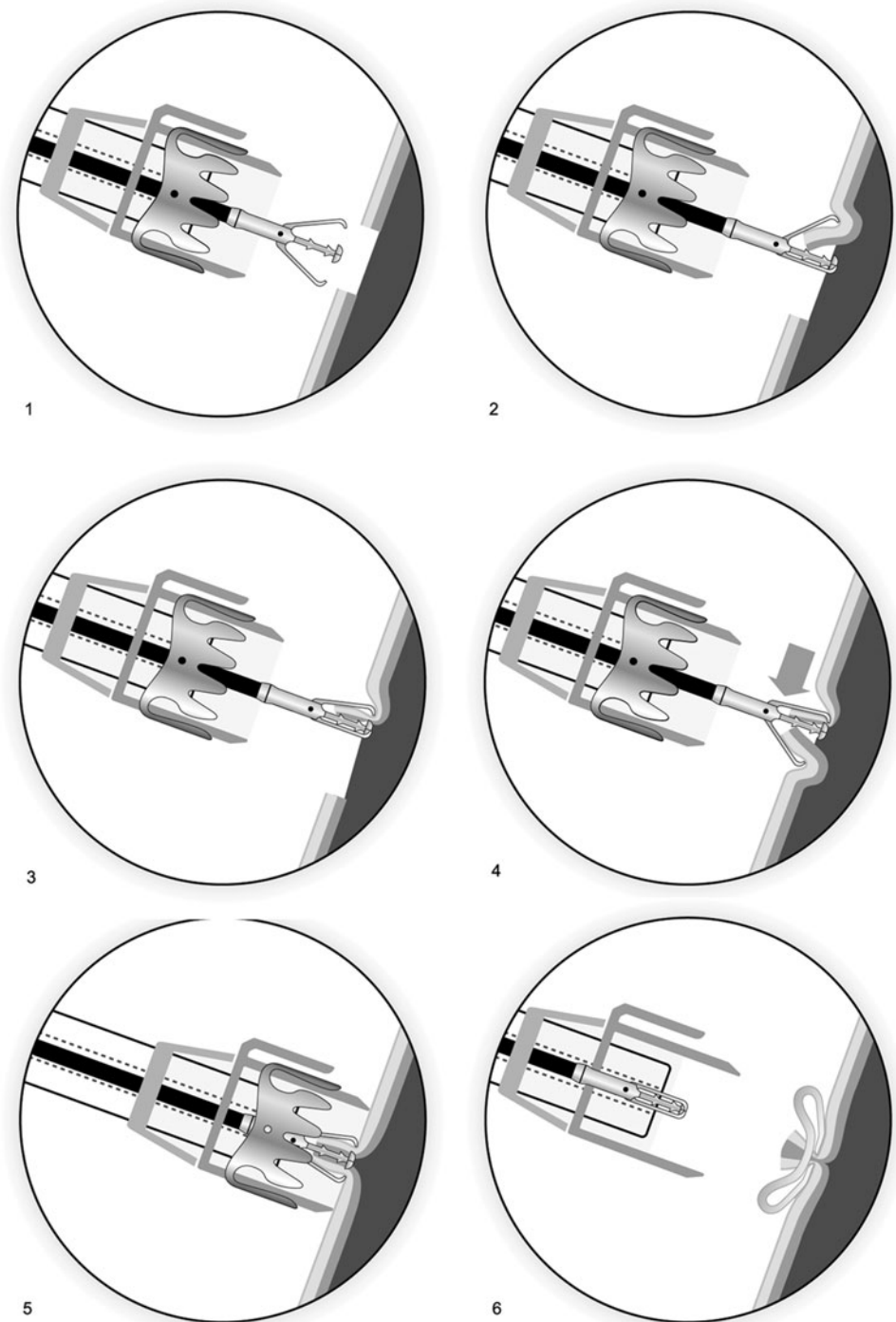


Fig. 2 A Process of clip application. The lesion margins were captured consecutively by the twin grasper (1–4) and approximated into the cap by retracting the twin grasper completely (5). Subsequently, the clips is released and the wound margins are pressed together firmly (6)



The search terms used are listed in Table 1. A number of citations were retrieved by more than one of the search terms. The identified articles were subsequently screened for duplicates and for relevance on the subject by their abstracts. In the second step, full-text versions of the remaining articles were screened according to the inclusion and exclusion criteria presented below. Literature search

and review of the identified articles for eligibility was done independently by two reviewers (TW, MF).

Inclusion criteria

Given the lack of randomized, controlled trials, all study types addressing the clinical use of the OTSC System for

Table 1 Keywords used in PubMed search

| Search terms |
|---|
| OTSC |
| OTSC AND anastomotic leakage* |
| OTSC AND (intestinal) perforation* |
| OTSC AND natural orifice endoscopic surgery* (NOTES) |
| OTSC AND eFTR |
| Over-the-scope-clip |
| Over-the-scope-clip AND anastomotic leakage* |
| Over-the-scope-clip AND (intestinal) perforation* |
| Over-the-scope-clip AND natural orifice endoscopic surgery* (NOTES) |
| Over-the-scope-clip AND eFTR |
| Ovesco |
| Ovesco AND anastomotic leakage* |
| Ovesco AND (intestinal) perforation* |
| Ovesco AND natural orifice endoscopic surgery* (NOTES) |
| Ovesco AND eFTR |

No methodological filters were applied. Terms in brackets were used synonymously. MeSH terms are labeled with an asterisk (*)

endoscopic closure either of accidentally induced, electively created, or postsurgically emerged acute gastrointestinal perforations, lesions, and anastomotic leaks were eligible for evaluation. Preclinical in vivo trials were included as endoscopic closure approaches are regarded as a crucial component of recently designed endoscopic procedures, such as NOTES or endoscopic full-thickness resection (eFTR), which are currently being investigated intensively. Only articles reporting on a study population of four or more participants were included. Otherwise, no limits were introduced with regard to a specific population under study. In cases in which studies involve multiple indications for clip application, closure of acute perforations and leaks were evaluated exclusively.

Exclusion criteria

Individual case reports and series with fewer than four participants on closure of acute perforations and leaks as well as pure review articles were omitted. Preclinical studies reporting on ex vivo animal experimentation were excluded. Studies, proceedings, and abstracts exclusively describing the hemostasis and the closure of chronic fistulae were excluded from evaluation.

Data extraction

Data of each study were extracted by two reviewers independently according to a predefined data extraction grid (TW, MF). Whenever conflicting evaluation emerged

between both reviewers, conflicting positions were discussed and resolved by objective reevaluation. Extracted primary endpoints were: (a) procedural success (defined as successful endoscopic deployment of the OTSC clip) and (b) clinical success (defined as complete, durable closure of the respective defect with clinical healing during follow-up). Extracted secondary data were: length of follow-up, continuance of the clip, duration of procedure, number of clips applied per lesion, diameter of defect, histological evaluation. Specific attention was paid to information on clip-related harms and complications as well as to information on reasons for failure of clip deployment or defect closure. An estimation of overall success rates of clinical trials was given by assessment of the pooled proportion $\pm 95\%$ confidence interval for successful clip deployment and durable closure of the lesions. Data were analyzed using the CMA software version 2.0 (Biostat Inc., Englewood, NJ). Because of variations in the design, setting, and patient populations of the selected studies, a random-effects model was used for pooling study results [10].

Results

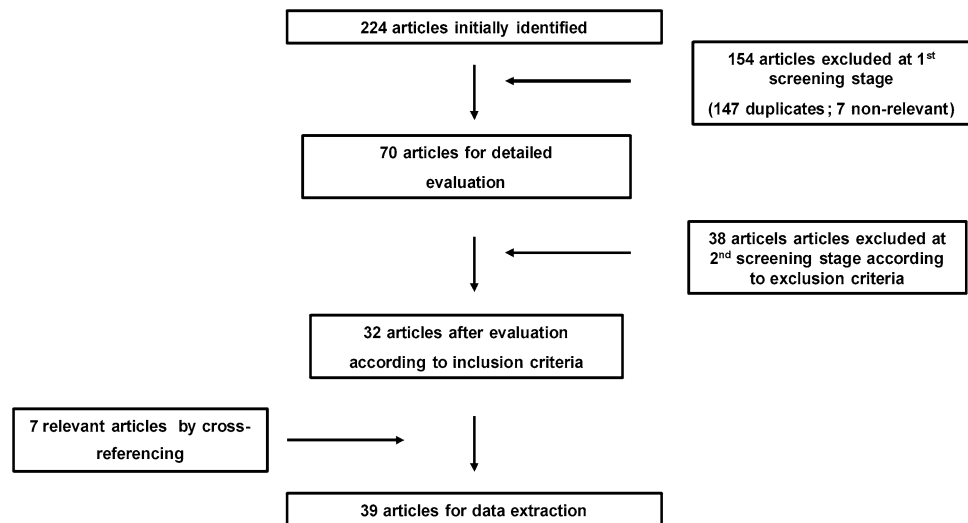
Literature research

A total of 224 hits were initially retrieved from searching the database. By subtracting all duplicates ($n = 147$) and nonrelevant articles ($n = 7$), 70 articles remained for evaluating in full text. In total, 38 articles had to be excluded according to the predefined criteria: 26 due to exclusion criteria, five review articles, and seven case reports/case series <4 participants. Thirty-nine citations were obtained for detailed evaluation inclusive seven relevant articles found by cross-referencing (Fig. 3).

Preclinical studies

The systematic literature research revealed in total 22 relevant articles reporting on 24 preclinical in vivo trials dealing with closure of iatrogenic gastrointestinal perforations ($n = 6$) and closure of lesions experimentally created by endoscopic full-thickness resection ($n = 4$). However, the majority of preclinical studies published recently addressed OTSC-mediated closure strategies of NOTES access sites ($n = 14$). Of a total of ten acute trials, six trials lacked a control group, whereas four trials involved a control group that compared the OTSC System with alternative closure techniques. Of them, two were designed as randomized, controlled study (Table 2). Of a total of 14 survival trials, 10 trials are lacked a control group, and four involved a control group comparing the OTSC System with

Fig. 3 Process of literature search and evaluation



alternative closure procedures. Two of them were designed as randomized, controlled study (Table 2).

Iatrogenic perforations

In 2008, Schurr and colleagues applied the OTSC System in an acute as well as survival porcine model of iatrogenic colonic perforations. Tight closure was demonstrated in resected colon segments. In case of survival studies, the postoperative course was followed for up to 12 weeks. Follow-up revealed an uneventful clinical course with absent signs of peritonitis, fever, elevated CRP levels, or blood counts [9, 11].

In 2009/2010, von Renteln et al. performed two randomized, controlled, acute porcine studies to compare either closure of large colonic perforations (18 mm) or closure of large duodenal perforations (~10 mm) by means of the OTSC System or by conventional open surgical suturing. Examination by necropsy and pressure leak test verified complete clip closure comparable to conventional suturing (OTSC mean burst pressure 62.8 ± 35.7 mmHg; surgical suture mean burst pressure 67.4 ± 19 mmHg; $p = 0.693$) [12, 13].

In 2012, Zhang et al. evaluated the successful usage of the OTSC System to close gastric fundus perforations in a canine model. In two of seven cases, Twin Grasper-assisted OTSC deployment failed due to the retroflexion maneuver of the endoscope necessary for the gastric fundus procedure. Hence, OTSC clips were forced into place by suction. Minor leakage was detected in one case [14].

According to the experimental data summarized from above-reviewed preclinical studies, the authors conclude that iatrogenic colonic and duodenal perforations can be closed with the OTSC System as reliably and safely as with

the “gold standard” of surgical suturing. None of the trials revealed clip-related complications.

Endoscopic full-thickness resection

In 2010, von Renteln and colleagues performed a two-armed porcine trial to evaluate the feasibility of a grasp-and-snare technique for endoscopic full-thickness resection (eFTR) combined with defect closure by OTSC clips. In group A, 20 eFTRs were performed in ten animals and OTSC closure was attempted after the resection. In group B, eight eFTRs were performed in four animals. In this case, an Endoloop was utilized to secure the resection base before eFTR was performed. In group A, adequate closure of eFTR resection sites ranging from 2.4 to 5.5 cm was achieved in 9 of 20 cases. Data stratification according to the lesion size revealed that the smaller the lesion, the higher the respective success rate. Five cases of larger lesions ranging from 3.4 to 5.5 cm were successfully closed by using two clips in three cases. However, under these circumstances, in two cases lumen obstruction was evident. In one case lumen obstruction occurred due to one clip; in two cases small bowel was incorporated by the clip. It is worthwhile to mention that the OTSC System used in this trial is designed for safe closure of lesions of up to 2 cm with one clip. Thus, these results are only of theoretical interest. In group B, all eFTRs with an Endoloop ligating the defect site were closed successfully [15].

In 2011, Schurr et al. [16] introduced a novel clip-and-cut device (full-thickness resection device FTRD[®]) based on the combination of the OTSC clip, an enlarged resection cap and an integrated snare. By utilizing the dedicated prototype device von Renteln et al. performed a porcine trial on an eFTR-procedure. A colonic target site was

Table 2 Result of data extraction from preclinical trials

| Author, year | Type of study | Indication | Procedural success rate (%) | Clinical success rate (%) | Follow-up (week) | Clip continuance | Duration of procedure (min) | Histological evaluation/ complications |
|-------------------------|---|---|--|---------------------------------|------------------|-------------------------|-----------------------------|--|
| Arezzo 2009 [24] | Survival study; 9 animals | Closure of transgastric defect after cholecystectomy (NOTES) | 100 | 100 (histopathology) | 4 | 7 in situ 2 lost | 6.8 ± 5 | Full thickness healing—1 × mild foreign body reaction |
| Azadani 2012 [32] | Acute 5-armed study, 6 animals/group | In vivo assessment of leak pressures after closure of gastrotomy (NOTES) utilizing various closing approaches | 50 (pressurized leak test) | n.s. | n.s. | n.s. | n.s. | n.s. |
| Armengol-Miro 2010 [31] | 2-armed survival study; 23 and 25 animals/group | Closure of gastric defect (NOTES) comparing the OTSC system with the Padlock G System | 100 | 100 | 2 | All in situ | 12.2 ± 2.9 | Uneventful, complete healing |
| Bernhardt 2012 [27] | Survival study; 5 animals | Closure of gastric defect (NOTES) in sigmoid resection | 100 ^a | 100 ^a | 5 | All in situ | | Complete healing; 1 × 5 mm lymph node close to access site |
| Donatsky 2012 [22] | Survival study; 10 animals | Closure of transgastric defect after pure NOTES | 100 (pressurized leak test) | 0 ^b (histopathology) | 2 | All in situ | Median 11 range 3–28 | Macroscopic closure; interrupted mucosal coverage with microscopic ulcerations, severe inflammation, and micro abscesses |
| Hucl 2010a [28] | Survival study; 10 animals | Closure of transgastric defect after cholecystectomy (NOTES) | 100 | 100 | 2 | n.s. | n.s. | Full-thickness healing |
| Hucl 2010b [29] | 2-armed survival study; 10 animals/group | Closure of transgastric defect after NOTES | 100 | 100 | 2 | n.s. | | Transmural healing 9 × purulent exsudate in mucosa |
| Kratt 2008 [19] | Acute study; 9 animals | Closure of transgastric defect after NOTES | 100 (macroscopic inspection) 89 (subtotal insufflation) 44 (max. insufflation) | n.s. | n.s. | n.s. | 12.3 ± 5.4 | Closed gastric incisions—1 × incomplete closure due to necrotic wound margins |
| Patrascu 2011 [26] | Survival study; 10 animals | Closure of transgastric defect after oophorectomy (NOTES) | 100 | 100 (pressurized leak test) | 2 | n.s. | n.s. | Complete healing—1 × gastric ulcer/perigastric lymph nodes abscesses |
| Rolanda 2009 [25] | 3-armed survival study; 5 animals/group | Closure of transgastric defect after bilateral testicular vessel ligation (NOTES) | 100 (pressurized leak test) | 87 | 2 | 10 clips in situ 5 lost | n.s. | i.g. Complete closure of defect |
| Schurr 2008a_I [11] | Acute study; 5 animals/10 perforations | Closure of iatrogenic colon perforations | 100 (pressurized leak test) | n.s. | n.s. | n.s. | n.s. | n.s. |
| Schurr 2008a_II [11] | Survival study; 3 animals/6 perforations | Closure of iatrogenic colon perforations | 100 (pressurized leak test) | 100 (pressurized leak test) | 2 | All in situ | n.s. | Healed perforation; slight chronic and moderate granulating inflammation |

Table 2 continued

| Author, year | Type of study | Indication | Procedural success rate (%) | Clinical success rate (%) | Follow-up (week) | Clip continuance | Duration of procedure (min) | Histological evaluation/ complications |
|---------------------------|---|--|-----------------------------|-----------------------------------|------------------|------------------------|-----------------------------|---|
| Schurr 2008b [9] | Survival study; 10 animals | Closure of iatrogenic colon perforations | 100 (pressurized leak test) | 100 ^a (histopathology) | 12 | 5 clips in situ 4 lost | n.s. | Uneventful, complete healing; 2 clips with slight overgrowth; discrete mucosal scar or low mucosal fold |
| Suhail 2012 [30] | Survival randomized, controlled study; 15 animals (8 OTSC; 7 T-bar) | Closure of transgastric defect after NOTES by T-bar sutures or OTSC System | 100 (methylene blue test) | 100 (histopathology) | 2 | n.s. | 27 (range 22–45) | Uneventful, complete healing |
| Voermans 2011 [23] | Survival study; 10 animals | Closure of transgastric defect after cholecystectomy (NOTES) | 94 (pressurized leak test) | 94 (macroscopic inspection) | 1.5 | 10 in situ 6 lost | 7 ± 3 | Full-thickness healing |
| Von Renteln 2009b [20] | Acute randomized, controlled study; 18 animals/group | Closure of transgastric defect after NOTES by surgical suture or OTSC | 100 (pressurized leak test) | n.s. | n.s. | n.s. | 9.8 ± 5.5 | n.s. |
| Von Renteln 2009c [21] | Survival randomized, controlled study; 10 animals/group | Closure of transgastric defect after NOTES by endoclip or OTSC | 100 (pressurized leak test) | 100 (macroscopic inspection) | 1.5–2 | n.s. | n.s. | Perigastric abscesses in both groups |
| Von Renteln 2009a [12] | Acute randomized, controlled study; 12 animals per group | Closure of large sigmoid perforations by surgical suture or OTSC | 100 (pressurized leak test) | n.s. | n.s. | n.s. | 6.8 ± 3 | n.s. |
| Von Renteln 2010a_I [15] | Acute study 10 animals/20 eFTRs | Closure of colonic eFTR sites | 45 (pressurized leak test) | n.s. | n.s. | n.s. | n.s. | n.s. |
| Von Renteln 2010a_II [15] | Acute study 4 animals/8 eFTRs | Closure of colonic eFTR sites | 100 (pressurized leak test) | n.s. | n.s. | n.s. | n.s. | n.s. |
| Von Renteln 2010c [13] | Acute randomized, controlled study; 12 animals per group | Closure of large duodenal perforations by surgical suture or OTSC | 100 (pressurized leak test) | n.s. | n.s. | n.s. | 5 ± 2 | n.s. |
| Von Renteln 2011 [17] | Survival study; 8 animals | Closure of colonic eFTR sites | 88 (visual inspection) | 88 (microscopic inspection) | 1–4 | 5 clips in situ 2 lost | n.s. | Complete healing |
| Von Renteln 2012 [18] | Acute study; 6 eFTR in 3 animals | Closure of gastric eFTR sites | 100 (pressurized leak test) | n.s. | n.s. | n.s. | n.s. | n.s. |

Table 2 continued

| Author, year | Type of study | Indication | Procedural success rate (%) | Clinical success rate (%) | Follow-up (week) | Clip continuance | Duration of procedure (min) | Histological evaluation/ complications |
|-----------------|------------------------|--|-----------------------------|---------------------------|------------------|------------------|-----------------------------|--|
| Zhang 2012 [14] | Acute study; 7 animals | Closure of gastric fundus perforations | 86 (pressurized leak test) | n.s. | n.s. | | 18.5 ± 6.4 | n.s. |

^a Strict definition of a full-thickness healing evaluated by histologic examination; 90 % success rate by macroscopic inspection

^b One animal died due to unrelated reason and was excluded

ns not specified

grasped and pulled into the applicator cap. Subsequently, a modified 14-mm OTSC, designed for eFTR, was released, creating a double-layer, full-thickness pseudopolyp, which was resected by a snare. In one case, the clip deployment failed. In a second case, two additional clips were utilized for complete closure of the lesion. In seven animals, the follow-up evaluation after 1 or 4 weeks, respectively, revealed most of the clips still in situ. A subsequent necropsy and histopathologic examination revealed completely healed resection sites without signs of ischemia, necrosis, or incompletely closed defects [17]. In 2012, von Renteln and colleagues evaluated the above described FTRD[®] prototype device on six artificially created submucosal tumors in a porcine model. In all cases, the eFTR site was closed completely by the OTSC System [18].

In summary, above-mentioned, full-thickness colonic resection techniques in combination with the OTSC System result in adequate closure of eFTR defects of approximately 30 mm in diameter in an experimental context. However, for closure of larger defects, application of multiple clips is recommended by the authors.

Notes: Kratt et al. closed transgastric access sites successfully in eight pigs. Only nonphysiological maximum insufflation revealed four cases of slight air leakage. Post-mortem examination revealed gastric incisions tightly closed by an OTSC clip except in one case of an incision characterized by electrocautery-related necrotic wound edges [19].

In 2009, von Renteln et al. performed two randomized, controlled animal trials to compare OTSC closure to open surgical repair or endoclip closure. In the nonsurvival setting, clip application was successful in 17 of 18 cases. Postprocedure laparotomies revealed no injuries related to OTSC closure. The pressure leak test revealed an OTSC closure mean burst pressure of 83 ± 27 mmHg and surgical suture mean burst pressure of 67 ± 27.7 mmHg ($p = 0.063$) [20]. In the survival trial, a laparoscopic leak test revealed no leaks in case of OTSC closure, whereas three minor leaks and one major leak were detected in case of endoclip closure. Necropsy conducted 10–14 days after intervention demonstrated complete sealing of gastrotomy sites in case of OTSC closure. In both groups small,

localized perigastric abscesses were found in several cases. Three endoclip-treated animals developed peritonitis [21]. The authors rated the OTSC closure of NOTES gastric access sites as safe and efficient, whereas closure with endoclips is associated with an increased risk of leakage and intra-abdominal infection.

Donatsky et al. performed a pure, transgastric NOTES procedure by endoscopic sonography guiding in ten pigs. Immediate closure was achieved in all cases by using the OTSC system. A 2-week follow-up revealed an uneventful postoperative course. By macroscopic inspection and leakage testing, the gastrotomy sites appeared to be closed successfully in nine pigs. However, in the author's strict terms of histologically assessed full-thickness healing, a successful closure was achieved in none of the cases. The authors rated their histopathologic results as critical in terms of potential risks of spontaneous, postoperative perforation [22].

Animal survival studies on endoscopic closure after transgastric cholecystectomy were conducted by Voermans as well as Arezzo and colleagues. Voermans et al. documented successful OTSC closure of all transgastric access sites except in one incompletely closed defect, which was resolved by an endoclip. A necropsy performed 10 days later revealed a histologically confirmed full-thickness healing without signs of complications [23]. The trial by Arezzo et al. revealed successful closure in all cases. Necropsy conducted 4 weeks postintervention revealed full-thickness closure of the wound with seven clips still in situ. In one case, histopathologic inspection revealed a mild foreign body reaction without further signs of ischemic necrosis, local infection, or inflammation at the gastric defect [24].

An elaborate trial by Rolanda et al. evaluated the reliability of the OTSC System in closing gastric access sites of varying dimensions (13–18 mm) with varying numbers of clips (1 or 2 per lesion, respectively) after transgastric testicular vessel ligation. In two animals, necropsy revealed signs of incomplete closure. In both cases, an 18-mm access site was closed by just one clip. The remaining animals developed no evidence of infections with complete closure of the defects [25].

A trial by Patrascu et al. reported on histopathologic evaluation of postoperative complications of a NOTES approach in ten pigs that underwent transgastric endoscopic oophorectomy and tubectomy. A leak test revealed efficient OTSC closure of the gastric access sites. Evaluated access sites exhibited excellent healing [26].

In 2012, Bernhardt and colleagues developed a NOTES procedure for sigmoid resection combining transgastric and transvaginal access. Gastric access was closed by using the OTSC System in all cases. One pig died due to reasons unrelated to OTSC closure. Remaining animals gained weight until day 35 postoperation. Subsequent necropsy revealed sealed gastric access sites [27].

In two abstracts presented at the 19th United European Gastroenterology Week (UEWG) 2011 in Stockholm, Sweden, Hucl and colleagues reported on the usage of the OTSC System for closure of NOTES access sites. One trial evaluated feasibility and safety of laparoscopic cholecystectomy assisted by transgastric NOTES specimen removal followed by successful OTSC closure in a porcine survival model involving ten animals [28]. The second trial reported on successful OTSC closing of either gastric or colonic NOTES access in all cases. 2 weeks after intervention, no signs of infection were visible on macroscopic level. Histological examination revealed transmural healing in all cases. However, in the gastric group five animals and in the colonic group four animals developed gram-positive purulent exudate in the mucosa [29].

Suhail et al. performed a trial comparing the OTSC System with T-bar sutures in a porcine survival model. In both groups consisting of 15 pigs a standardized transgastric approach to the peritoneal cavity and a peritoneoscopy was performed. During a 2-week follow-up, neither perioperative complications nor leakages were detected. No differences between the efficacy and safety of the OTSC System and those of T-bar sutures used in closing gastric incisions in NOTES were revealed [30].

In 2010, Armengol-Miro and colleagues presented a trial at the EURO-NOTES conference in Rome, Italy, comparing the OTSC System with the Padlock-G clip (Aponos Medical, Kingston, NH, USA). Closure of a transgastric access was performed with the OTSC System in 25 animals and with the Padlock-G system in 23 animals. Application of the Padlock-G was accomplished significantly faster than the OTSC System (8.0 ± 2.3 min vs. 12.2 ± 2.9 min; $p < 0.0001$). Uneventful gastric closure and complete healing was achieved in all animals without signs of bleeding and infection. In case of the OTSC System, all clips were still found in situ, whereas 22 of 23 Padlock-G clips were detached [31].

In 2012, Azadani et al. introduced a nonsurvival porcine in vivo model for testing different approaches to NOTES closure. For this, a tube for air inflation and a tube for manometry were inserted gas tight into the stomach via the pylorus. Subsequently, gastric access was created and

closed randomly by surgical suturing, T-tags, Padlock-G clips, traditional clips, or by the OTSC System. Leak pressure of each approach was tested. The tests revealed that OTSC System clips (3/6) and traditional clips (5/6) leaked at significantly lower pressures than the other devices and approaches ($p = 0.007$), whereas T-tags (1/6) and surgical sutures (0/6) leaked significantly less than the other groups ($p = 0.01$). Padlock-G clips leaked in two of six cases [32].

In summary, treatment of NOTES access sites by means of the OTSC System results in reliable and easy-to-apply closure in the majority of papers. The examined studies involving a control treatment revealed that the safety and performance of OTSC System is comparable if not superior to conventional endoclips and surgical suturing with regard to evaluated parameters. However, few studies described divergent data with regard to full-thickness wound healing and mucosal inflammation on a histological level. Generally, the OTSC System is regarded as an appropriate closure strategy in yet experimental NOTES procedures and suitable to be applied in the human context.

To sum up evidence provided from preclinical research, 24 studies provided data on procedural success rates ranging from 44 to 100 % success in clip deployment. Fourteen studies provided data on clinical success rates ranging from 0 to 100 % success in healing of the respective lesion. However, these data were collected and evaluated on highly diverse criteria for success as applied by the respective study authors, which may explain the obvious wide range of data obtained for procedural and clinical success. Hence, summarizing data into a pooled estimation of overall success rates is prevented by the inhomogeneous, highly biased nature of the studies. Length of follow-up as one important criterion for evaluation of success rates ranged from 1 to 12 weeks in maximum. However, most survival studies were limited to 2 weeks. The majority of applied clips were recovered in situ after follow-up examination.

Clinical studies

The systematic literature research revealed in total 17 clinical studies involving closure of acute gastrointestinal perforations and leaks by OTSC clip application. All evaluated studies were prospective ($n = 6$) or retrospective ($n = 9$) small, noncontrolled, case series with maximal 50 participants of a variety of indications. Two case series provided no definitive statement whether they were designed as retrospective or prospective study (Table 3).

In 2011/2012, four prospective case series were issued on OTSC closure of acute iatrogenic perforations or post-surgical leaks of the gastrointestinal tract. Within the multicenter CLIPPER study, the clip could be deployed

Table 3 Results of data extraction from clinical studies

| Author, year | Type of study | No. of defects | Type of defect | Etiology | Procedural success rate (%) | Clinical success rate (%) | Follow-up (week) | Clip continuance | Clips per lesion | Dimension of lesion (mm) | OTSC-related complications and limitations |
|----------------------|---------------------------------------|----------------|-----------------------------|--|-----------------------------|---------------------------|-------------------|-------------------|---------------------|--------------------------|---|
| Albert 2011 [38] | Retrospective consecutive case series | 5 | GI leaks | Gastric wall necrosis; resection of epiphrenic reticulum; leakage at gastroesophageal anastomosis; perforation after ESM; dehiscence (9 mm) | 80 | 80 | 3–68 ^a | 4 in situ | i.g. 1 ^b | n.s. | Fibrotic changes on older lesions decrease success rates |
| Arezzo 2012 [6] | Prospective case series | 8 | Colorectal leaks | Acute colorectal postsurgical leaks, mainly after anterior rectal resection | n.s. | 87 | ≥4 | n.s. | 1 | 8–12 | No clip-related complications observed |
| Baron 2012 [37] | Retrospective case series | 8 | Iatrogenic perforation | Iatrogenic perforation of the esophagus ($n = 1$), the stomach ($n = 2$), the jejunum ($n = 1$) and the colon ($n = 1$), anastomotic leaks ($n = 3$) | n.s. | 62 | n.s. | n.s. | n.s. | n.s. | Jejunal lumen obstruction due to clip placement |
| Disibeyaz 2012 [41] | Case series | 6 | | Anastomotic leaks and perforations | n.s. | 66 | n.s. | n.s. | 1 | 5–20 | Fibrotic changes on older lesions decrease success rates |
| Gubler 2012 [34] | Prospective consecutive case series | 14 | GI perforations | Iatrogenic perforation of the colon ($n = 9$), the stomach ($n = 3$) and the duodenum ($n = 2$) | 93 | 78 ^c | 4–92 | 12 in situ 1 lost | 1 | 6–30 | No clip-related complications observed |
| Hagel 2012 [40] | Retrospective consecutive case series | 17 | GI perforations | Iatrogenic perforation due to diagnostic and therapeutic endoscopic intervention | n.s. | 65 ^d | n.s. | n.s. | 1/2 ^d | Given in main text | Necrotic and inflamed wound margins decreased success rates |
| Kirschniak 2007 [42] | Retrospective case series | 4 | Gastric and colonic lesions | Iatrogenic colon perforation; deep colon wall lesion; deep lesion after mucosal resection | 100 | 100 | Up to 4 | 2 in situ 2 lost | 1 | n.s. | No clip-related complications observed |
| Kirschniak 2011 [43] | Retrospective case series | 11 | GI perforations | Perforations of the upper and lower GI tract of varying causes | 100 | 100 | Up to 3 | 5 in situ 3 lost | n.s. | n.s. | No clip-related complications observed |
| Manta 2011 [39] | Retrospective consecutive case series | 5 | GI leaks | Post-surgical dehiscence; decubitus by surgical drainage on jejunal wall | 100 | 80 ^e | 4 to 6 | 3 in situ 2 lost | 1/2 ^f | n.s. | Fibrotic leak edges decrease success rates. |
| Parodi 2011 [36] | Prospective single arm pilot study | 6 | GI leaks | Iatrogenic perforations; peptic perforation; peptic ulcer | 83 | 83 | Up to 12 | n.s. | 1 | 5–20 | No clip-related complications observed |

Table 3 continued

| Author, year | Type of study | No. of defects | Type of defect | Etiology | Procedural success rate (%) | Clinical success rate (%) | Follow-up (week) | Clip continuance | Clips per lesion | Dimension of lesion (mm) | OTSC-related complications and limitations |
|---------------------|---|----------------|---|---|-----------------------------|---------------------------|------------------|------------------|------------------|--------------------------|---|
| Sandmann 2011 [45] | Retrospective case series | 7 | Penetrating defects within the GI tract | Postsurgical suture insufficiencies; suture dehiscence; perforations of the gastric fundus; the retroperitoneum and the colonic wall; endoscopic R1 resection of an adenocarcinoma of the sigma | 100 | 86 | 4–32 | n.s. | 1/2 ^f | Up to 20 | n.s. |
| Sandmann 2012 [46] | Retrospective case series | 15 | GI leaks | Perforations, anastomotic dehiscence, endoscopic tumor resection | n.s. | 93 | n.s. | n.s. | n.s. | n.s. | n.s. |
| Schlag 2011 [35] | Prospective study | 4 | Gastric perforation | Perforation following endoscopic resection of gastric subepithelial masses | 100 | 100 | n.s. | n.s. | n.s. | n.s. | Early and late onset side effects were not observed |
| Seebach 2010 [44] | Case series | 7 | GI leaks | Anastomotic leakages; sigmoid perforations; stomach perforation; perforation of descending colon | 85 | 57 | 10–38 | 3 in situ 3 n.s. | 1/2 ^f | n.s. | n.s. |
| Vijverman 2011 [48] | Retrospective case series | 8 | Perforations | Iatrogenic esophageal and duodenal perforations due to EUS; ERCP; EMR; ESD | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. |
| Voermans 2012 [33] | Prospective consecutive multicenter trial | 36 | Acute perforations | Esophageal, gastric, duodenal and colonic iatrogenic perforations due to therapeutic and diagnostic interventions | 92 | 89 | 4 | n.s. | n.s. | n.s. | Esophageal perforation due to cap introduction |
| Wedi 2012 [47] | Prospective case series | 15 | GI perforations | Iatrogenic GI perforations; EMR; ESD | n.s. | n.s. | n.s. | n.s. | i.g. 1 | n.s. | Grasper was kept within the clip in EMR |

^a One patient deceased after 3 weeks due to unrelated reasons

^b Two clips in case of gastric wall necrosis

^c Two colonic lesion sites were treated with three overstitches in addition to successful clip application, depending on lesion dimension

^e One clip had to be repositioned due to detachment

^f Singular case

n/s not specified, ig in general

successfully in 33 of 36 patients. The authors rated the endoluminal closure with the OTSC System in large iatrogenic perforations as relatively easy and fast. On an intent-to-treat basis, adequate closure was achieved in 89 % of cases within a median of 5.44 ± 4.15 min. Three patients never received a clip, only 1 of 36 patients needed a surgical intervention with the defect being an indication for operation in the pre-OTSC era [33]. Gubler et al. examined procedural success of OTSC system-mediated closure after an observation period of 24 h in 13 of 14 patients. Lesion size ranged from 6 to 30 mm. The follow-up after discharge ranged between 1 and 23 months, and no adverse events were noted [34]. Arezzo and colleagues reported on a prospective series of eight patients suffering of acute, postsurgical leaks after anterior rectal resection. The leaks, ranging from 8 to 12 mm in diameter, were closed successfully by utilizing the traumatic version of the OTSC System. A single clip was deployed in each case. The follow-up assessment of at least 4 months revealed an overall clinical success in seven of eight patients. In one patient, a redo surgery was required [6]. Schlag et al. presented results of a study on the endoscopic resection of subepithelial gastric masses at the UEWG 2011 in Stockholm. Four patients experienced gastric perforations. However, all perforations could be durably closed by utilizing the OTSC System as assessed in a follow-up examination 3 months postintervention [35].

In 2011, Parodi and colleagues reported on closure approaches of GI perforations of up to 20 mm conducted in a prospective, single-arm pilot study. In total, six iatrogenic perforations, peptic perforations, and peptic ulcers were closed each with one OTSC clip. After 12 weeks, complete sealing of the leaks could be confirmed in five cases. In one case of an anastomotic leak, clip deployment failed due to lumen deformation, hence a stent was placed [36].

A set of four identified retrospective consecutive case series involving up to 50 patients analyzed the benefit of the OTSC System for closure of GI leaks and perforations of varying etiology among other indications [37–40]. The revealed procedural and clinical success rates ranged from 65 to 100 % depending on the respective study and examined indication. In neither of these studies a clip-related complication became evident except in the study of Baron et al. In four of five patients with iatrogenic perforations in whom a clip placement was attempted, the defect was closed successfully without further intervention. However, the closure attempt of a large jejunal perforation occurred after double-balloon, enteroscopy-assisted endoscopic retrograde cholangiopancreatography for treatment of a pancreatic duct leak failed. After clip deployment, the opposite jejunal walls were fixed together. Therefore, surgery was necessary to recover the jejunum [37]. In case of the other trials, clip application failed in some cases as fibrotic lesion edges complicated tight

approximation to the tissue [38, 39]. In case of the study performed by Hagel et al., OTSC application sealed the perforation completely in 11 of 17 patients. The closed perforations were characterized by small dimensions (length 5.5 ± 1.9 mm, width 3.7 ± 0.9 mm, 21.1 ± 9.1 mm²) and vital wound margins in contrast to the nonresolved perforations. These were characterized by larger dimensions (length 13.4 ± 8.8 mm, width 5 ± 4.5 mm, 97.6 ± 149 mm²) as well as necrotic and inflamed wound margin [40].

A set of six retrospective case series, published between 2007 and 2012, involving between 4 and 15 cases of GI lesion, perforations as well as anastomotic leaks obtained comparable high procedural success rates ranging from 83 to 100 % and clinical success rates ranging from 57 to 100 %. No study reported on clip-related complications [41–46].

In 2012, Wedi et al. presented a mixed case series of 40 patients treated with the OTSC System due to a variety of indications, among them three perforations. The overall success rate for all indications was 85 %. All three perforations could be closed successfully. The success rates of the other indications in the scope of evaluation were not specified in detail [47]. At the UEWG 2011, Vijverman and colleagues reported on positive experiences of treating GI leaks and perforations with the OTSC System characterized by high rates of successful and durable closure [48].

Definitions of success were comparable between the evaluated clinical studies. In summary, ten studies provided data on procedural success rates ranging from 80 to 100 % success in clip deployment. Fifteen studies provided data on clinical success rates ranging from 57 to 100 % success in healing of the respective lesion. The overall, pooled estimate of procedural success was 89 % (95 % confidence interval 81–94) and the overall, pooled estimate of clinical success was 80 % (95 % confidence interval 72–86). In general, one clip per lesion was applied by default in the majority of cases. In cases of larger anastomotic leaks, two clips were applied occasionally. Most studies provide no specifications whether the clip was found in situ at reexamination. In cases where the authors provide these data, between 50 and 92 % of the deployed clips were still in situ after follow-up. The point in time of follow-up examination was highly diverse between the studies ranging from several days to 92 weeks postintervention.

In summary, the evaluated clinical studies acknowledge the capacity of the OTSC System to close defects in the whole range of the gastrointestinal system. All studies consistently revealed a high rate of procedural and clinical success. No study observed a clip-related problem. Most causes of clip failure were ascribed to fibrotic changes or necrotic, inflamed tissue surrounding the respective lesions. Hence, the existence of non-vital wound edges may complicate successful closure.

Discussion

Traditionally, gastric perforations have been managed by open or laparoscopic surgical intervention. However, recent studies indicated that endoscopic management of gastrointestinal perforations and leaks by endoclips is feasible [49, 50]. This study reviewed the preclinical and clinical experience gained by OTSC-mediated closure of acute gastrointestinal perforations and leaks. The evaluation is based on the available preclinical and clinical literature published in medical journals as well as in conference proceedings. This approach is both weakness and strength of this systematic review at the same time. It gives a comprehensive picture of this definitive field. However, evaluated data were partly derived from abstracts providing only limited information. The second major limitation is the lack of high-quality studies in terms of evidence-based medicine. Most data were derived from small retrospective or prospective case series. Overall, the evaluated studies are inhomogeneous with regard to application sites, indication for OTSC usage, study design and outcome definition bearing the potential for various biases. Hence, interpreting the results of the preclinical and the clinical data, it is important to be aware of these constraints.

The performance of the OTSC System in porcine *in vivo* models meets or exceeds that of conventional techniques of closing iatrogenic GI leaks [12, 13, 20, 21]. Furthermore, the capacity of the OTSC System to also close larger defects in the whole range of the gastrointestinal system qualifies it as an ideal candidate for the urgent problem of suitable closure in NOTES. Currently used closing techniques, such as utilization of endoclips, still yielded unacceptably high rates of leakage of 20 % as found in animal studies [51]. The 2005 ASGE/SAGES White paper on NOTES states that “if NOTES is to reach human trials, a 100 % reliable means of gastric closure must be developed” [52]. The report of the official EURO-NOTES working groups presented at the 4th EURO-NOTES meeting in Rome, 2010 states that several studies mentioned safe access and closure of transmural access lesions with new devices, such as anchor systems or the OTSC large scale clip [53]. A high rate of successful OTSC clip deployment and closure of transgastric access sites was achieved in the majority of evaluated experimental studies. However, reports of individual failure in experimental procedures, such as NOTES and eFTR, warrant a closer reflection. The study by Rolanda et al. yielded by necropsy two cases of incomplete clip closure despite an initially successful application. Affected pigs died or had to be sacrificed prematurely due to peritonitis, respectively. Both cases were deployed into the same experimental group of an 18-mm incision closed by a single 12-mm OTSC clip.

The common ground shared by both failures stressed the need to find the perfect match of clip and gastrotomy size for a durable and complete closure. As attempt at a solution, the authors recommend to choose a clip that is larger than the endoscope used for transgastric surgery. Furthermore, the study revealed the possibility to apply two clips partly overlapping in case of large gastrotomies [25]. In our experience, however, the size of the OTSC used is merely defined by the size of the endoscope and not the size of the lesion. Regarding the stomach, it is recommended to use Butylscopolaminbrimid for better handling of the tissue. The study by Kratt et al. noticed process-related formation of a local mucosal hematoma by needle-knife incision in two cases as well as incisions characterized by electrocautery-related necrotic wound edges inflicted unintentionally. Air insufflation for checking tightness of clip closure revealed that these incisions were not sealed completely. Hence, in case of oversized lesions with necrotic wound edges as well as gastric tissue swelling due to access procedure may limit OTSC's capacity to seal the access site completely. Thus, for clinical application, any endoscopist must carefully examine the conditions and dimensions of the wound margins to ensure tight closure and/or take special care in choosing a suitable access strategy [19]. A second important topic besides the condition of the wound edges in OTSC closure is avoidance of lumen obstruction. The necessity of closing wide gaping defects in eFTR by deploying two clips was not uncommon in experimental studies bearing the chance of bowel obstruction. Von Renteln and colleagues described a case where application of two clips in eFRT led to a lumen obstruction preventing the passage of the endoscope beyond the clipping site [15, 17]. Therefore, the endoscopist should always try to close large perforations transversally like in a stricturoplasty. Also, by closure of colonic perforations, cases of incorporated adjacent small intestine or peritoneum were noticed [12]. The authors recommend strongly the usage of the twin grasper rather than suction to approximate the edges of the defect. By applying suction, special vigilance must be exercised to avoid faulty incorporation of adjacent tissue [12, 15].

A major limitation affecting the evaluation of preclinical studies was the inconsistent design and the varying endpoint criteria. Furthermore, the animal studies were designed as either acute or survival trials relying on a highly heterogeneous set of criteria of success ranging from pure visual inspection to deep histopathological evaluation of full-thickness wound healing. This fact explains the broad range in clinical success rates. However, most preclinical studies indicate that OTSC-mediated closure is highly suitable for closure of examined defects and conditions.

By design and conceptually comparable, the Padlock-Clip achieved high rates of success of 90–100 % in closing

gastric NOTES access sites in acute and survival experimental settings performed on pigs [31, 32, 54–56]. The evaluated *in vivo* studies rated the Padlock-G clip procedure for closure of NOTES access sites as feasible, effective, and easy to perform. Results obtained by the Padlock-G system corroborate the principal concept of delivering clips on the tip of the endoscope. However, to date only five preclinical studies *in vivo* are available on PubMed. Whether the Padlock-G system may reach OTSC's versatility and success rates also in a clinical setting remains speculative.

All identified clinical studies are characterized by high individual procedural and clinical success rates. In contrast to preclinical trials, procedural and clinical success rates of clinical studies were rated by more homogeneous criteria, such as macroscopic endoscopic reexamination, application of suitable imaging techniques, and clinical progress. However, as limitation, intratrial indications for clip application were heterogeneous due to the varying etiology of gastrointestinal perforations. Until now, no randomized, controlled, clinical study was performed to compare the OTSC System with other experimental or conventional approaches, because such studies are not feasible in this field of indication. Procedural and clinical success rates of the OTSC System range from 80 to 100 % and from 60 to 100 %, respectively. Hence, the examined clinical studies provide a consistent picture compared with conventional endoclips, although literature data on the treatment of GI perforations by conventional endoclips are scant. A recent study by Cho et al. on closure of iatrogenic colon perforation by endoclips revealed an initial procedural success rate of 92 %. However, after endoscopic clip closure, 22 patients (76 %) required medical treatment for colon perforation, and 7 patients (24 %) had surgical treatment. Of the 22 patients, only 59 % of patients (17/22) exhibited a favorable clinical course [57]. A retrospective study by Jovanovic examined the attempt of immediate endoclip closure of an iatrogenic perforation. In 8,601 colonoscopies, 12 patients experienced a perforation (1.4 %) of which 5 were closed successfully by means of an endoclip (42 %). The remaining seven patients were treated surgically due to large defects, stool contamination, and unsuitable localization [58]. Also, Trecca and colleagues reported on successful endoscopic closure of colonic perforation of up to 30 mm by multiple endoclips in single cases [49]. However, the management of colonic perforation by endoscopy remains controversial. Conventionally, perforations larger than 10 mm are generally treated surgically to maximize patients' benefit [59]. Preclinical and clinical studies with the OTSC System stratifying for the lesion sizes revealed a correlation with success rates. As expected, the studies yielding rather success rates below average were challenged by large lesion dimensions [15, 36, 40]. However, multiple studies report on lesions larger than 10 mm, which were closed successfully by OTSC

application [34, 36, 41, 44]. Gubler et al. [34] recommend to treat perforations of up to 30 mm diameter by the OTSC System whenever the application is technically applicable.

Despite most evaluated preclinical study reporting on complete, uneventful wound healing, some authors are concerned about ulceration of the mucosa and microscopic signs of inflammation with neutrophil granulocytes and focal microabscesses in relation to the OTSC clip 2 weeks post-intervention [21, 22, 29]. However, moderate inflammation is a necessary component of wound healing followed by proliferation and tissue remodeling. Studies by Schurr et al. and Arezzo et al. extended the follow-up period to up to 12 weeks indicating that 2 weeks may just be too short to judge a full-thickness healing also on histological level [9, 24]. Often, in preclinical and in clinical studies, the clips were found *in situ* at follow-up examination or, if detached, only small scars were visible at the former application site. For example, Gubler et al. [34] found 86 % of applied clips *in situ* months after application, which is rated as accomplished transmural closing. Also, other clinical studies found the majority of applied clips still *in situ* after follow-up. Failure of clip deployment is mainly attributed to unsuitable tissue conditions. Vital tissue around wound margins is regarded as essential to obtain tight closure as the clip will not grip into necrotic, chronically inflamed tissue sufficiently [37–41, 44]. Another cause of failure was identified in aligning the endoscope tip with the lesion. Sucking or grasping of hardened, fibrotic tissue may be difficult to achieve [6, 39]. In few cases, two clips were applied to close larger anastomotic leaks; however, this depends on the anatomical location of this defect [36, 39]. Also, colonic lumen obstruction may occur, especially in cases where two clips were applied for closure of larger lesions as described in an animal study [12]. By deploying the OTSC System into angulations of the small intestine, an accidental inclusion of opposing walls may occur, causing complete intestinal obstruction [37]. In case of misplacement, procedures are described in literature to remove the clip by means of a ND:YAG laser or by argon plasma coagulation [37, 60]. In general, in case of inadequate closure of a lesion alternative, available therapies, such as surgical intervention or stenting are available and have been successfully applied [36–60]. Two cases of complications during the passage of the loaded endoscope to the site of application were reported. In one case a patient developed an esophageal perforation due to cap introduction, and in a second case the patient's tongue was pierced due to releasing the OTSC clip accidentally. By applying standard precautions, such as introducing the cap under vision and stopping in case of resistance, both events are expected to remain exceptional cases [33, 61]. Furthermore, the design of the OTSC usually enables the closure of even larger lesions with only one single clip. Hence, the

necessity of endoscope retraction for reloading and further passage is prevented in the majority of cases.

Conclusions

The increasing case numbers of performed endoscopic procedures lead to higher incidence of iatrogenic perforations. Furthermore, the fast development of new endoscopic techniques, such as eFTR and NOTES, requires reliable endoscopic closure approaches of larger defects, applicable in the whole gastrointestinal system. Conventional through-the-scope endoclips meet their limits for these indications. The advantage of the OTSC System is its simple and effective application as well as its versatility. Its particular, geometric shape supports effective and safe closure of GI perforations of varying etiology. Until now, the clinical evidence was limited to retrospective and prospective case series with a minor pool of participants. However, available data yield promising procedural and clinical success rates without major clip-related complications. Hence, application of the OTSC System may expand therapeutic options and reduce the frequency of surgical interventions without exclusion of surgery or other alternatives in case of clip failure.

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