An over-the-scope clip (OTSC) system for closure of iatrogenic colon perforations: results of an experimental survival study in pigs

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Background and study aim: Perforation of the colon is a relatively rare complication of flexible endoscopy of the lower gastrointestinal tract. It has a reported incidence from between 0.2% in diagnostic procedures to 0.5%–3% in therapeutic procedures. Given the growing number of colonoscopies, the absolute number of iatrogenic perforations is not unimportant. The treatment of choice is most often surgical repair, since reliable and simple endoscopic techniques for perforation closure are currently unavailable. We aimed to evaluate our novel over-the-scope clip (OTSC) system for closure of iatrogenic perforations.

Material and methods: We have developed a nitinol clip that will capture perforations of 10–15 mm, compressing the lesions until healing. The OTSC was studied in a prospective experimental trial in pigs (50–60 kg, n = 10) for the closure of an iatrogenic perforation of approximately 5–10 mm on the serosal side, that was created by repeated endoscopic biopsy. The follow-up period was 12 weeks. Follow-up colonoscopy was performed at 4 and 12 weeks. Successful, tight closure of the lesion with absence of peritonitis in the postoperative course was the primary endpoint of the study.

Results: Nine animals had an uneventful clinical course. At termination of the study, macroscopic and microscopic examination of the clipping sites in the bowel wall showed normal tissue healing. One animal died 1 day postoperatively for reasons unrelated to the procedure.

Conclusions: In this experimental study the OTSC clip system was found to be a simple and secure closure method for iatrogenic colon perforations, and thus might be an alternative to surgical repair.

Introduction

Iatrogenic perforation of the colon during flexible endoscopic procedures is a serious complication [1–4]. The literature records perforation rates varying from 0.2% in diagnostic procedures to 0.5%–3% in therapeutic procedures [2–4]. In spite of this low relative risk, the absolute number of iatrogenic colonic perforations is not unimportant, given the high and still growing case numbers for polyp removal and the increasing invasiveness of tissue acquisition with flexible endoscopy. At present, in many cases iatrogenic perforation of the bowel wall entails abdominal surgery for the patient in order to close or remove the defect. However, there is currently no generally accepted consensus on the adequate treatment of colonic perforations. Some authors consider conservative therapy sufficient in smaller lesions [1,3]; however the risk of peritonitis is increased, and therefore open or laparoscopic surgical repair of the perforation is a preferred option in many cases [4,5]. Flexible endoscopy techniques for the treatment of bowel wall lesions are presently limited. Small perforations or bleeding can be treated with commercially available endoscopic clips deployed via the working channel [6]. Partial success in closing larger perforations has also been reported in experimental studies; this however seems to depend on the direction of the perforation [7]. Larger full-thickness wall defects or heavier bleeding from deep wall lesions are difficult to treat colonoscopically with currently available techniques. The over-the-scope clip (OTSC) system has been developed as an alternative device for closing defects from within the lumen without surgical repair. After initial experimental pilot studies [8], the OTSC system was assessed in an animal experimental trial in domestic pigs (n = 10).
Material and methods

The OTSC system

The OTSC system has been developed in collaboration with Ovesco Endoscopy, Tuebingen, Germany. In this study prototypes of the OTSC system were used. The OTSC system consists of the clip itself and a clip-release mechanism that is attached to the tip of the flexible endoscope.

The OTSC clip is made of nitinol, a superelastic shape-memory alloy, which is biocompatible as a long-term implant and is widely used in medical devices, for example, in endoscopic stents [9–11]. The clip studied in this trial has a diameter of 11 mm. The branches are equipped with teeth that have additional spikes (Fig. 1), that anchor the clip at the target site while approximating and compressing the wound margins. The neutral position of the OTSC is the closed position, and the clip is mounted on its release mechanism by opening the branches to about 90°, thus storing energy in the clip branches. Once released around the tissue, the clip returns to its neutral, closed shape, delivering a compression force of approximately 8–9 N to the target tissue.

The application cap (Fig. 2) has an outer diameter of 15 mm and covers the clip during its introduction. The clip is released from the cap by means of a thread attached to the tip of the cap. The thread runs through the working channel of the endoscope and is tightened by means of a wheel fixed to the handle of the endoscope. The application system does not restrict the flexibility of the endoscope. The inner part of the application cap protrudes from the endoscope for 3 mm, creating a space into which tissue can be pulled.

The OTSC is designed for use in gastrointestinal endoscopy, of both the upper and lower gastrointestinal tract. The system can be used for different purposes, including hemostatic compression, for example in peptic ulcers or the compression of gastrointestinal tract wall perforations, as investigated in this study.

Animal trial

The study was a prospective, single-arm experimental survival trial in domestic pigs (n = 10, both sexes, 50–60 kg). The primary endpoint was the successful endoluminal clip closure of an iatrogenic colon perforation, with absence of peritonitis over the course of follow-up (12 weeks).

The animal experiments were conducted in compliance with the Declaration of Helsinki and the German animal protection law and were approved by the appropriate government authority. All the OTSC bowel repair procedures were done with the animals under general anesthesia and in the supine position. The colon was prepared before the procedure with water enemas until it was visually clean.

In one animal, bowel cleaning was not satisfactory. This animal was excluded from the study and directly replaced by another animal. The excluded animal was not counted as a study animal. Perforations were brought about at different levels of the intra-abdominal part of the colon, usually between 20 and 40 cm from the anus. To produce the perforations biopsies were repeatedly taken from the same location. The perforations thus created had a diameter of approximately 5–10 mm on the serosal side and were larger on the mucosal side, as a result of the repeated biopsies (Fig. 3). The size of the defect was estimated by comparison with the tip of an endoscopic instrument. The full-thickness nature of the perforation was verified by advancing the biopsy forceps into the free abdominal cavity. All animals had
single-shot intravenous antibiotic treatment with 500 mg of metronidazole and 2 g of cefotaxim at the time of perforation. Prior to closure of the perforation we waited for 5 minutes, though the device had been pre-installed, in order to reflect the time that would be needed in practice to withdraw the endoscope, mount the OTSC system, and reintroduce the device. The wound margins were then grasped and approximated with a standard endoscopic grasper with pointed teeth and an opening of approximately 15 mm (Olympus Europa, Hamburg, Germany), deployed through the working channel, which was effective in grasping both sides of the lesion. The OTSC application cap was advanced under gentle pullback of the grasper. Additional suction was applied through the endoscope to further optimize the wall contact of the device. The OTSC was then released by rotating the hand wheel. The clip application site (Fig. 4) was visually inspected for signs of leakage, and also under insufflation to check that it was airtight. The laboratory animal was then sent to the animal care ward for further follow-up. Follow-up consisted of an intensified phase and a regular phase. The animal was seen daily in the intensified phase and weekly in the regular phase, for clinical examination and measurement of body temperature. In addition C-reactive protein (CRP) levels and blood count were taken intraoperatively and at days 3 and 5 postoperatively. On the 28th postoperative day follow-up colonoscopy and abdominal fluoroscopy were performed. On the 90th postoperative day the animals had a second follow-up colonoscopy. After colonoscopy the animals were sacrificed and autopsy was conducted. The resected bowel segment was longitudinally opened, assessed macroscopically and then sent for histological examination.

Results

In all animals endoluminal closure of the perforation using the OTSC clip was completed successfully. No bowel injuries caused by introduction of the device were seen. The tightness of the closure of the lesion was verified by colonscopic air inflation. One animal died on the first postoperative day due to ileus and mesenteric infarction after colonic torsion. This is a known problem in stock farming of pigs that receive no solid food for a couple of days. Therefore the death was classified as unrelated to the procedure by the study veterinarian.

The nine animals that completed the follow-up had an uneventful clinical course. There were no signs of peritonitis and no fever or pathologically elevated CRP level or blood count. At the follow-up colonoscopy on the 28th postoperative day, the clip was seen to be still in place in five animals; a mucosal fold was found between the branches of the clip (Fig. 5a). In four animals the clip could no longer be seen, by colonoscopy and fluoroscopy, and a low mucosal fold marked the site where the clip had been attached (Fig. 5b). There were no ulcerations at the clip implantation sites. Minimal epithelial overgrowth was seen in some cases in the contact area of the clip brackets and the tissue. Another endoscopy and re-operation at 3 months revealed no intracolic or intra-abdominal disease. In two out of the five animals where the clip was present after 4 weeks, it was also found after 3 months. In three animals who had lost the clip a low mucosal fold was seen at the former clipping site; in the other animals a discrete mucosal scar was found. The two clips still seen at 3 months had little sign of epithelial overgrowth at the lateral brackets in direct contact with the colonic wall. No macroscopic disease was seen at the repeat endoscopy or abdominal autopsy, apart from a small scar on the serosal bowel surface. There were no signs of resolved peritonitis, and no adhesions between the clipping site and other tissues or anywhere else in the abdominal cavity. Histological examination of the clipping site demonstrated older scar tissue in all bowel wall layers. There was no foreign body granuloma, and a discrete inflammatory foreign body reaction in only one case. There was no ulceration or signs of ischemia, including in the animals where the clip was still present after 4 or 12 weeks. In summary histological examination showed that following colonic perforation closure with the OTSC clip, only circumscribed inflammatory or scar formation processes were present with no perifocal or peripheral reactions of the bowel wall.

Discussion

Iatrogenic colon defects have been classified by Wullstein et al. into three types [12]: type 1 are perforations up to 10 mm in diameter; type 2 covers lesions with thermal damage to the margin with diameters of more than 10 mm; and type 3 includes perforations longer than 25 mm, and those with necrotic areas or thermal tissue damage of unclear extent (Table 1).
In most cases bowel perforations are detected directly during the procedure. If a bowel perforation remains undetected, symptoms usually start 6 to 24 hours after the procedure. To avoid peritonitis, an endoscopic clipping technique for secure closure of iatrogenic perforations represents an attractive treatment option. Conventional working channel-based clips are used in current clinical practice, and this has yielded positive results.

For the treatment of type 1 perforations (Table 1) Wullstein et al. recommended surgical oversewing; for type 2, the resection of necrotic areas with subsequent oversewing of the wound margins; and for type 3, segmental bowel resection with end-to-end anastomosis. In this framework, the OTSC system might be applicable as an alternative to surgical oversewing in perforations of types 1 and 2 according to Wullstein’s classification, although type 2 perforations have not been investigated in this trial. Our series of experiments has shown that endoscopic treatment of iatrogenic colon perforations is feasible with the OTSC; the bowel lesion was successfully closed in all animals included in the study.

During the clinical follow-up over 12 weeks, no problems were seen in the nine animals in which the study was completed. Autopsy at the end of the survival period revealed normal healing conditions on the inner and outer surface of the bowel and in the abdominal cavity. Histological investigation also confirmed adequate wound healing and absence of significant foreign body reactions.

From the technical point of view, the handling of the OTSC system prototype was found to be simple and reliable. The maneuverability of the endoscope and the endoscopic field of view were slightly reduced, as commonly happens when devices are mounted on the tip of the scope, but not to an important extent. After perforation of the organ wall, air inflation and distension of the lumen are usually impaired. Consequently in our study too, several attempts at correct endoscopic targeting of the lesion were needed before an optimal capture of the wound margins was achieved and the clip was released.

Our study has some limitations. One is that the study was designed as a single-arm trial of device effectiveness, and not as a comparison with conventional clipping techniques. Therefore no conclusions about the comparative performance of the OTSC and other clips can be drawn at this point. Another limitation is the porcine animal model per se, which does not allow adequate simulation of all sectors of the human colon. Applications in the cecal area that were technically more demanding could not be investigated in the porcine model. The potential advantages of the OTSC system lie in its simple and effective application, and in its particular geometric shape which supports the closure of perforations.

The OTSC system has therefore been found, in experimental use, to be an alternative to laparoscopic surgery for the treatment of colon perforation [13,14]. Other groups have also recently shown the feasibility of secure perforation closure with clips in an experimental model [15].

Folding clips have also proved to be of value for the closure of hollow organs in other fields. Mentges et al. have reported an experimental technique of clip closure of the gallbladder after laparoscopic cholecystectomy [16]. The OTSC clip has now been applied clinically as a CE-marked medical device, with positive first experiences in the treatment of perforations [17].

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Competing interests: Marc O. Schurr and Andreas Kirschniak are among the founders of Ovesco Endoscopy and hold shares in the company. Study devices were supplied for free and third-party costs of animal experiments were covered by Ovesco Endoscopy.

References

8 Schurr MO, Hartmann C, Kirschniak A et al. Experimental study on a new method for colonoscopic closure of large bowel perforations with the OTSC clip. Biomed Tech 2008 [In press]

Table 1 Classification and recommended treatment of iatrogenic colonic perforations, according to Wullstein et al. [12]

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<thead>
<tr>
<th>Perforation type</th>
<th>Recommended treatment</th>
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<tr>
<td>Type 1</td>
<td>Very small with no macroscopic signs of thermal damage or necrosis (&lt; 10 mm). Oversewing of the perforation.</td>
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<tr>
<td>Type 2</td>
<td>Small lesion with thermal damage of wound edges, or necrosis (&gt; 10 mm). Small tangential resection of the necrotic tissue or areas of thermal damage, suture of the wound edges.</td>
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<tr>
<td>Type 3</td>
<td>Large perforations (&gt; 25 mm), and perforations with a large amount of necrosis or with unclear extent of thermal damage due to coagulation. Large perforations should be treated with a segmental resection of the injured colon segment.</td>
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