ORIGINAL ARTICLE: Experimental Endoscopy

Endoluminal compression clip: full-thickness resection of the mesenteric bowel wall in a porcine model

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Background: Performing a full-thickness intestinal wall resection of a sessile polyp located on the mesenteric side with a compression clip may lead to compression of mesenteric vessels. The application of such a clip may therefore cause a compromised blood supply in the particular bowel segment, leading to perforation.

Objective: To evaluate the performance of a newly developed, nitinol compression clip, called the NiTi clamp, for full-thickness resection of the bowel wall, while the clip is deliberately deployed endoluminally on the mesenteric side.

Design: Prospective animal study. Multinational, multidisciplinary; gastroenterology and general surgery, research cooperation.

Setting: Animal research laboratory.

Intervention: Six pigs were operated upon and endoscopically evaluated and then killed after 3 weeks. Linear compression closure clips based on nitinol springs were used. Three longitudinal enterotomies were performed: in the cecum, spiral colon, and proximal rectum. Four clips were deployed in each animal.

Main Outcome Measurements: A total of 23 clips were deployed. The average expulsion day was 9 days.

Results: All but 3 clips were normally expelled. One pig developed bowel ischemia due to intussusception. In endoscopic procedures, no signs of significant segmental mucosal ischemia were found. The macroscopic appearance of the compression closure lines was thin and delicate, but epithelialization was significantly delayed at 5 sites.

Limitation: Differences between porcine and human colorectal anatomy.

Conclusion: Full-thickness clamping of the bowel with the NiTi clamp, including the local mesenteric vasculature, does not significantly impair local healing of the clamp site and gives hope to further development of novel full-thickness endoscopic resection technologies. (Gastrointest Endosc 2009;70:1146-57.)

DISCLOSURE: The following authors disclosed financial relationships relevant to this publication: D. Kopelman has a consulting/advisory and research support arrangement with Niti Surgical Solutions Ltd, Israel, InSightec Ltd, Israel, Serafix Ltd, Israel, and Lifebond Ltd, Israel. P. D. Siersema has a consulting/advisory/speaking arrangement with Janssen-Cilag BV, The Netherlands, and Niti Surgical Solutions Ltd, Israel, research support and travel grants from Janssen-Cilag BV and Astra Zeneca BV, The Netherlands, research support from Tramedico BV, The Netherlands and Life Support Technology, The Netherlands, and a travel grant from Alveolus Inc, NC, USA. Y. Nir is an employee of Niti Surgical Solutions. A. Szold has a consulting/advisory/speaking arrangement with Niti Surgical Solutions Ltd, Israel. A. Bapaye has a consulting/advisory/ speaking arrangement with Niti Surgical Solutions Ltd, Israel and Medigus Ltd., Israel. S. Lelcuk has a consulting/advisory/speaking arrangement with Niti Surgical Solutions Ltd, Israel. All other authors disclosed no financial relationships relevant to this publication.

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Large sessile polyps frequently contain villous components with appreciable premalignant potential and tend to recur locally if not completely excised. Clinical studies have shown that patients with colorectal adenomas have an increased risk of developing colorectal cancer and that resection of these adenomas substantially reduces the risk.^{1,2} Recent studies have stressed that finding and resecting advanced adenomatous polyps, thereby preventing cancer, is becoming the primary objective of screening programs.³

The endoscopist is unable to determine the orientation of polyps relative to the bowel mesenterium. Therefore, performing a full-thickness intestinal wall resection of a sessile polyp located on the mesenteric side with a compression clip may cause compression of mesenteric vessels and compromised blood supply in the particular bowel segment, leading to ischemia and eventually perforation. The purpose of this study was to evaluate the performance of a newly developed nitinol compression clip for full-thickness resection of the bowel wall, while the clip is deliberately deployed endoluminally on the mesenteric side of the colon.

MATERIALS AND METHODS

The compression clip

Compression closure clips based on nitinol springs connecting 2 linear rods were used (Niti surgical solutions, Nethania, Israel) (Fig. 1A). The clip creates a compression closure line, and, following a simultaneous necrosis and healing process, gradually detaches from the compression closure site over some days and is then expelled from the body.

All clips were marked with numbers (0-23). A specially designed clip applicator was used to apply the clip onto the bowel wall by using a transluminal approach via a longitudinal colotomy during laparotomy. The applier was made to part the 2 side rods of the clip (Fig. 1B). A tissue pusher was used to push the mesenteric side of the colon wall, including mesenteric vessels, from the serosal (external) side into the wide-opened endoluminal clip. The pusher was made of 2 parts: a curved flexible wire and a metal cylinder (Fig. 1C).

During the clip preparation process, a chart of the force characterization of each clip was generated. The recorded measurement was the force of the clip in a gap/opening of 2 mm when the clip was closed/released (Fig. 2).

Animal care and anesthesia

Six healthy female pigs, Sus scrofa domestica, 3.5 months old, weighing 44 to 50 kg were used. The study was approved by the local institutional review board for animal studies (#031107). A restricted, commercially available pig-mix (Nir Oz mixture institute, Nir Oz, Israel) was given to the pigs 48 hours prior to surgery and 72 hours thereafter. In the interval, solid food was replaced by a liquid diet and sweetened water. The large bowel of the animals was prepared by oral Soffodex solution (Dexxon Ltd, Or-Akiva, Hadera, Israel). Two hours prior to surgery, a cleansing enema was administered to the pigs. This operation being a clean-contaminated procedure necessitated the administration of a single dose of prophylactic antibiotics; therefore, cefazoline-sodium (Merck, Darmstadt, Germany) 30 mg/kg and vetrimoxine LA veterinary (Ceva Sante Animale S.A., Libourne, France) 15 mg/kg, was given intravenously. Premedication and induction of anesthesia were achieved by intramuscular injection of xylazine (Spectrum Chemicals and Laboratory Products, Gardena, Calif) 1.5 mg/kg and ketamine (Spectrum) 10 mg/kg, following 5 mg/pig diazepam (Hoffmann-La Roche Inc, Nutley, NJ) intravenously, orotracheal intubation, and isoflurane 5%

Capsule Summary

What is already known on this topic

• Full-thickness intestinal wall resection of a sessile polyp on the mesenteric side done with a compression clip may cause a compromised blood supply, leading to ischemia and perforation.

What this study adds to our knowledge

 In a prospective study in a porcine model, no signs of significant segmental mucosal ischemia were found after full-thickness clamping of the bowel with compression closure clips that were based on nitinol springs.

(Abbott Laboratories Ltd, Queenborough Kent, England). Anesthesia was maintained by isoflurane 2% to 3% and spontaneous breathing of oxygen 3.5 L/minute. The pigs were infused during the procedure with 10 mL/kg/hour of normal saline solution.

Surgery

The spiral colon from the cecum to the rectum was exposed through a midline laparotomy. The proximal rectum was released of its retroperitoneal attachments, so that it would remain freely mobile on the mesorectum. The mesenterium on both sides of the spiral colon at the planed segment of the enterotomy was carefully dissected in order to expose the site at which the mesenteric vessels penetrate the colon wall.

Three longitudinal enterotomies, 3 to 4 cm in length, were performed: one in the cecum, another in the spiral colon 30 cm distal to the cecum, and the third in the proximal rectum. Four clips were deployed in each animal. Two clips were deployed in the rectum via the same enterotomy: one distally, at the level of the promontorium, and a second at the proximal rectum. The clips in the rectum were 10 to 13 cm apart. The third clip was deployed in the spiral colon and the fourth in the cecum. The clips were opened by using the special applying forceps (Fig. 1B) and inserted into the lumen through the enterotomies. A segment of the bowel wall was pushed, by using the special pusher (Fig. 1C), from the serosal side into the wide-opened clip that was held against the bowel wall from the endoluminal side. The bowel wall segment that was forced into the clip included the mesenteric vessels penetrating the mesenteric aspect of the bowel wall. The clip was then released from the applier and allowed to close and compress the double layer of full-thickness bowel wall, with its mesenteric vessels and the 2 ends of the wire of the pusher in between (Fig. 3). Usually 4 to 5 visible end arteries were clamped. The wire of the pusher was pulled out, leaving the beanshaped metal part of the pusher caught in the compressed tissue. The 3 enterotomies in each animal were



Figure 1. A, The closed clip; 2 metal bars held together by 2 nitinol springs. **B**, The clip applicator used in the open surgical procedures. Both arms of the applicator hold the clip in special notches on the medial aspect of the metal bars. **C**, A tissue pusher consists of a metal cylinder and a flexible wire. **D**, A schematic illustration of the metal cylinder pushing the bowel wall from the serosal side into the widely opened clip that is placed endoluminally. **E**, Dimensions of a fully opened clip.

closed by standard linear staplers. A total of 23 clips were deployed in all animals (Table 1). In 12 clips, the fullthickness bowel wall tissue with the mesenteric vessels that were clamped by the clip was resected via the enterotomy sites by using Metzenbaum scissors. The abdomen was closed with a continuous nylon loop for the linea alba, continuous 3-0 Vicryl for the subcutaneous fascia, and metal clips for the skin.

Follow-up

The pigs were allowed to recover and were followed daily by an experienced veterinarian. The clinical followup evaluation included general health status and weight gain. During the 72 hours after the procedure, the animals received drinking water and a liquid diet only. Regular nutrition dissolved in water was begun at the fourth postoperative day. The follow-up included behavioral evaluation, GI tract function, and blood samples for complete blood count on postoperative days 3 and 6. All of the clips were retrieved from the animal stools and evaluated.

Endoscopic evaluation

The tissue condition in close proximity to the clip deployment sites and of the entire segment of the colon



Figure 1 (continued)

that is supplied by the compressed blood vessels was evaluated by using endoscopy at predefined time intervals. For standardization purposes, a scoring system was generated. The mucosa was evaluated for the presence of edema, erythema, erosion, and bleeding. Each of these factors was evaluated according to the following scale:

- Edema: classified as (1) none-mild swelling of the mucosa not exceeding the level of the clip and less than 5 mm from either side of the clip, (2) moderate-swelling of the mucosa over the level of the clip and 5 to 10 mm from either side of the clip, (3) severe-swelling and pallor of the mucosa more than 10 mm from either side of the clip
- Erythema: classified as (1) none-mild to patchy light redness in close proximity to the clip up to 2 to 3 mm, (2) moderate-diffuse redness up to 10 mm from either side of the clip, or (3) severe-diffuse dark redness wider than 10 mm from either side of the clip
- Erosion: classified as no, erosion, ulcer, or perforation/ fistula
- Bleeding signs: classified as no, hematin-covered (oozing), visible vessel, or spurting.

The compression closure sites were monitored by using a colonoscopy system (Olympus CV-140). Colonoscopies were performed at time 0 approximately 1 hour post deployment, day 2, and day 5. Due to the anatomy of the pig's spiral colon, colonoscopies were limited to the 2 clips deployed in the rectum. The parameters for endoscopic follow-up were based on expected ischemic mucosal changes due to the clamping of mesenteric vessels and possible signs of mechanical trauma to the area immediately surrounding the clip. Various endoscopic indices are available for evaluating the endoscopic features of colonic inflammation, but those currently used in clinical trials are not uniform and vary considerably. The currently available qualitative indices (the Baron and the Matts and Blackstone scores) were introduced and validated decades ago.4,5 These indices assess 4 items: vascular



Figure 2. Force characterization of the compression clip. *F*2, Force (in Newtons [N]) that is applied by the clip during its closure at 2 mm opening between the clip bars.

pattern, friability, erosions, and ulcerations, but erythema, edema, granularity, and blood in the lumen are also signs of mucosal inflammation. However, it is not clear to what extent these different endoscopic features contribute to the overall assessment.⁶ These indices, although meant to evaluate mucosal changes in inflammatory bowel diseases, guided us in choosing edema, erythema, erosion, and bleeding as the visual mucosal parameters for the postoperative endoscopic surveillance.

Histological evaluation

The pigs were killed 3 to 4 weeks postoperatively. The previous laparotomy incision was opened, and the abdominal cavity was evaluated for signs of possible infection, leaks, or bowel obstruction. The segments with the linear compression closure sites were resected and histologically evaluated to detect ischemic damage and possible aberrations of the normal healing process. The compression closure lines were evaluated by using the following parameters:

- Thickness of the anastomotic line—at the level of the submucosa/tunica muscularis
- Degree of maturation of the fibrous tissue—indicates organization of the granulation tissue from no maturation with markedly reactive fibroblasts and a minimal amount of collagen to mature connective tissue with fewer fibroblasts and an abundance of collagen
- Foreign body reaction—either no reaction or a prominent reaction with the presence of microgranulomas, macrophages, and giant cells
- Inflammation—infiltration by either neutrophils, eosinophils, or lymphocytes in the area of the compression closure line
- Degree of epithelialization—attempts of mucosa adjacent to the compression closure line to cover the defect on the mucosal surface, either continuous epithelium and lamina propria or an ulcerated surface with no epithelialization.

Statistical analysis

It was calculated that a sample size of 23 clips achieved a minimum of 80% power at a 5% significance level by using



Figure 3. Applying the clip via the enterotomies. **A**, The applicator holds an open clip, and the bowel wall is being pushed between the clip's bars. **B**, The clip is then closed to compress the 2 layers of bowel wall. **C**, The clamped tissue is resected, exposing the metal cylinder of the pusher that was caught inside. **D**, An external view of the serosal aspect of a closed clip that clamps the mesenteric vessels of the cecum. The flexible metal wire of the pusher is still caught between the clip's bars and is about to be pulled out. **E**, A view of the mesenteric vessels clamped by the clip. **F**, A histopathological view of the resected bowel wall that was clamped, showing the mesenteric vessels. (*arrows*) and the mesenteric lymphatics (*arrowbeads*). *A*, Artery; *V*, vein; *m*, mucosa; *sm*, submucosa; *tm*, transverse sample muscularis.

Pig	Weight (kg)	Clip site	Clip no. r	Tissue esection	Day of clip expulsion
1	48	Distal rectum	1	Yes	6
		Proximal rectum	2	Yes	9
		Spiral colon	3	No	8
		Cecum	4	Yes	7
2	44	Distal rectum	5	Yes	9
		Proximal rectum	6	No	9
		Spiral colon		-	-
		Cecum	7	Yes	?
3	44	Distal rectum	8	Yes	9
		Proximal rectum	9	No	9
		Spiral colon	10	No	11
		Cecum	11	Yes	?
4	44	Distal rectum	12	Yes	5
		Proximal rectum	13	No	8
		Spiral colon	14	Yes	10
		Cecum	15	Yes	13
5	48	Distal rectum	16	Yes	13
		Proximal rectum	17	No	9
		Spiral colon	18	No	13
		Cecum	19	No	N/A*
6	50	Distal rectum	20	Yes	8
		Proximal rectum	21	No	9
		Spiral colon	22	No	11
		Cecum	23	No	11
A 4	verage: 6.3				Average: 8.94

No. of clips with resected tissue: 12 (52%).

*Clip was found free floating in the cecum, proximal to an

intussusception of the terminal ileum segment.

a 2-sided equivalence of proportions. Based on the assumption of normality for binomial distribution, the best estimation for 23 successive events out of a sample of 23 clips was calculated to be 96.0% (range 87.8%-100%). It should be noted that each clip is considered to be an independent

event regarding the primary success criteria of safety of deploying the clip on the mesenteric side. In addition, the secondary success criteria containing only the clips that were visually inspected produce a calculated best estimation of 52.2% (range 30.6%-73.2%). Criteria that were analyzed per animal regardless of the number of clips (eg, physical evaluation postprocedure) represent a calculated success rate of 83.3% (range 54.3%-100%). The calculated 95% confidence interval for the day of expulsion was 8.9 ± 1.89 days (range 8.0-9.9 days).

RESULTS

A total of 23 clips were deployed in 6 animals. All clips were successfully deployed on the mesenteric aspect of the large bowel, occluding mesenteric vessels in a 4-cm-long segment. The animal and clip data are summarized in Table 1. Five animals were killed according to the prede-fined protocol at 3 to 4 weeks postoperatively. In these 5 animals, the entire follow-up period was uneventful, and all the complete blood cell count results during the entire follow-up period were within normal limits.

One animal was killed after 2 weeks because of clinical deterioration. Emergency laparotomy revealed intussusception of the terminal ileum segment into the cecum with severe small-bowel ischemic changes. There was no spillage of bowel content into the peritoneal cavity. The clip placed in the cecum was detached and found caught between the intussuscepted small bowel and the cecum wall. This clip was excluded from the calculation of the average expulsion day. The other 3 clips of this animal were expelled from the bowel prior to the emergency laparotomy. The sites of the clip closure lines were unaffected by the ischemic changes, and the specimens were sent for histological evaluation.

By the time all pigs were killed, all but 3 clips had been normally expelled, identified, and collected by the animal laboratory staff. Two clips that were not detected in the pigs' stool were clip 7 (pig 2, cecum) and clip 11 (pig 3, cecum). Clip 19 (pig 5) was found in the cecum as described previously. The clip expulsion day ranged from day 5 to day 13, with an average of 8.94 days (n = 18, Table 1).

Endoscopic follow-up

Endoscopic follow-up was performed up to the proximal rectum. All endoscopies were uneventful, with no related morbidity. Findings are summarized in Table 2. No signs of significant segmental mucosal ischemia were found. The mucosal vascular pattern was normal with no cyanosis. The tissue caught between the 2 metal bars of the clip went through a necrotic process as expected. Mild to moderate localized mucosal redness and edema, only in close proximity to the clips, was found in 5 animals

TABLE 2. Colonoscopy findings

	Site	Clip no.	Day 0			Colonoscopy findings Day 2			Day 5					
Pig			Edema	Redness	Ulceration	Bleeding	Edema	Redness	Ulceration	Bleeding	Edema	Redness	Erosion	Bleeding
1	Distal rectum	1	None	None	No	No	N/A				No	Mild	Erosion	No
	Proximal rectum	2	None	None	No	No					No	Mild	Erosion	No
	Spiral colon	3	N/A				N/A				N/A			
	Cecum	4												
2	Distal rectum	5	None	None	No	No	None	None	No	No	None	Mild	Erosion	No
	Proximal rectum	6	None	None	No	No	Mild	Moderate	No	No	None	Mild	Erosion	No
	Spiral colon	N/A	N/A				N/A				N/A			
	Cecum	7												
3	Distal rectum	8	None	None	No	No	None	None	No	No	None	None	Erosion	No
	Proximal rectum	9	None	None	No	No	Moderate	Moderate	No	Oozing	None	Mild	Erosion	No
	Spiral colon	10	N/A				N/A				N/A			
	Cecum	11												
4	Distal rectum	12	None	None	No	Oozing	None	None	No	No	No Clip	o - Ulcer		
	Proximal rectum	13	None	None	No	No	Mild	Mild	Erosion	Oozing	Mild	Mild	Erosion	No
	Spiral colon	14	N/A				N/A				N/A			
	Cecum	15												
5	Distal rectum	16	None	None	No	No	None	None	No	No	None	None	No	No
	Proximal rectum	17	None	None	No	No	Mild	Mild	No	No	None	None	No	No
	Spiral colon	18	N/A				N/A				N/A			
	Cecum	19												
6	Distal rectum	20	None	None	No	No	Mild	Mild	Erosion	No	Mild	Mild	Erosion	No
	Proximal rectum	21	N/A				Mild	Mild	No	Oozing	None	None	No	No
	Spiral colon	22	N/A				N/A				N/A			
	Cecum	23												

on the second postoperative day. Mild oozing from the margins of resected clamped tissue was noted in 4 clip sites out of 12 rectal clips (33%). This mild oozing was detected only on postoperative days 0 and 2 and was self-limited, with no hemodynamic effect and no drop in the concentration of blood hemoglobin. Peri-clip mucosal erosions of up to 1 to 2 mm on each side of the clip were detected in 5 out of 6 animals and in 8 out of 12 rectal clips on the fifth postoperative day. An ulcer was found in the site of 1 clip that was detached from the rectal wall

(Fig. 4). In pig 5, some contralateral mucosa was caught into the clip in the distal rectum (Fig. 5). At day 0 colonoscopies, minor mucosal injuries were demonstrated in 3 of 12 rectal clips (25%). All of these injuries were hardly detected on the second postoperative day and no longer detected on postoperative day 5. Two deviations from the protocol included were the result of technical difficulties. In animal 1, we performed colonoscopy on day 0 and day 5 only. In animal 2 we deployed only 3 clips because of a technical error.



Figure 4. Endoscopic views of the clips in the distal and proximal rectum. **A**, Ischemic full-thickness proximal rectum wall clamped by the clip, 5 days postoperatively, without tissue resection. The metal part of the pusher is caught inside. **B**, Ischemic full-thickness proximal rectum wall clamped by the clip, 2 days postoperatively, without tissue resection. **C**, **D**, A clip in the distal rectum 5 days postoperatively and resection of the clamped tissue. **E**, A clip in the distal rectum 2 days postoperatively and resection of the clamped tissue. **A** deep ulcer in the rectal mucusa is seen 2 cm proximal to the clip. **F**, A clip in the proximal rectum 5 days postoperatively and resection of the clamped tissue.

Histological evaluation

Macroscopic view. The macroscopic view of the compression closure lines revealed longitudinal healing scars. Some of them were very delicate and almost invisible, whereas others were more prominent with remnants of the necrotic tissue adjacent to the site of the detached clip (Fig. 6).

Microscopic evaluation. Low-power views of transverse section samples through the resected tissue of 12 clips verified the presence of mesothelial vessels in the specimen (Fig. 3F). The diameter of the veins was about 450 μ m, and the diameter of the arteries was about 320 μ m. Additional multiple blood vessels including small-caliber veins, arteries, and lymphatic veins were present in the mesenteric fat. All closure lines were sent for histo-

logical evaluation. The average closure line thickness was 4.19 mm, range 0.4 to 15.0 mm.

Epithelialization appeared to be significantly delayed at 5 sites (22%) (Fig. 7). We had the chance to compare compression clip sites to stapled colotomies. Most compression closure lines had several common characteristics: organization of fibrous tissue and formation of granulation tissue at the compression closure line with different degrees of sero-cellular crust on the epithelial surface. The foreign body reaction was significantly more prominent in the stapled colotomies than in the compression clip sites. A common phenomenon in the stapled colotomies was invagination of mucosa deep into the healing scar (Fig. 8).

Focal inflammation, which was most likely due to mucosal invagination into the closure line (the scar area),



Figure 5. Endoscopic view of a clip in the proximal rectum. **A**, At time 0, immediately after clip deployment. **B**, Five days later the pinched mucosa is detached from the clip. A superficial ulcer is noted.

was present in a sample from clip 13, forming a small organized abscess. In a sample from the closure line of clip 15, the abscess was slightly larger and was apparently not associated with the closure line but probably was related to the surgical procedure. Focal mechanical damage to the mucosa with some fecal material into the submucosa probably incited the inflammatory reaction and subsequent surrounding fibrosis.

DISCUSSION

Choosing the proper animal model involved the following considerations: The anatomy of the porcine

colon differs from human anatomy; nevertheless, rat and porcine models are the most commonly used animal models with regard to colonic ischemia, colorectal injuries, colorectal wall histology, and colorectal vascular anatomy. Physiologically, the pig has been determined to be analogous to the human in terms of digestive function and splanchnic blood-flow characteristics.⁷ In this study it was imperative to use a large animal model to enable application of the full-size clip and endoscopic follow-up. The blood supply pattern of the porcine cecum, descending colon, and proximal rectum is similar to that of the human colon. The blood vessels penetrate the colonic wall from 1 direction of a narrow mesenterium. The porcine spiral colon is supplied in a different manner by blood vessels that enter the colonic wall, from 2 opposite directions on both sides of the bowel.

This study showed that occluding several mesenteric vessels in close proximity to the bowel wall with the nitinol clip in a porcine model was safe. The endoluminal deployment of the clip on the mesenteric side of the colon created a solid and comprehensive compression closure. In spite of these vessels being end arteries, there were no signs of segmental ischemia in the relevant colon and rectum segments. There was no severe impairment to the compression closure healing process. The major concerns of segmental ischemia and/or inadequate healing that could lead to local ischemia and dehiscence of the closure line proved not to be a clinical problem.

Although no clinically significant signs of perforation or hemorrhage were detected, some effect was noted that particularly involved the healing process of the mucosa at the site of the detached clip. A delay in bridging the gap across the closure line was evident, but there was no effect on the outer layers of the bowel, and the line of the compression closure was sealed properly. This delay in epithelialization that was evident in 22% of the clips may be the result of relative hypoperfusion or limitations of our model. This phenomenon requires further research.

The clips were disconnected from the bowel wall and naturally expelled from the body around the ninth postoperative day (range 5-13 days), as could be expected based on previous human and animal studies of compression devices in the small bowel, colon, and rectum.⁸⁻¹² Two clips were not recovered, whereas 1 was "caught" by the intussuscepted ileum. The clips that were not identified in the stool did, however, detach from the tissue, as could be determined at the time of scarification. It seems likely that the animal-laboratory staff may have missed these clips or that the pig swallowed the expelled clip.

The most significant characteristics of nitinol that make it suitable for the creation of compression closure of defects in the bowel wall are the super



Figure 6. Macroscopic endoluminal views of scars after clip detachment, taken immediately after killing, 3 to 4 weeks postoperatively. **A** and **B**, Both scars demonstrate almost invisible compression closure lines. **C**, A more prominent scar, 55 mm long and 3 mm wide, at its widest segment. **D**, The scar that demonstrated the worst healing process, with a large ulcer $(30 \times 10 \text{ mm})$ partly covered by a fibrin layer, with cyanotic appearance of the mucosa immediately surrounding the ulcer.

elasticity and the temperature-dependent shape memory of the alloy. These characteristics enable continuous controlled compression with a constant force that does not diminish nor rise as the gap between the 2 compressing elements is gradually closed. The compression closure line is being created between 2 metal bars compressed toward each other by the nickel-titanium springs. The process of pressure necrosis and healing detaches the clip into the lumen after a few days.¹³

The compression clips demonstrated good hemostatic capability. There were 3 occurrences of immediate minor oozing of blood after the resection of the tissue that was clamped by the clip, which did not necessitate intervention. In 1 pig, some contralateral mucosa was caught in the clip (Fig. 6). Unlike that in regular colonoscopy, the lumen could not be kept inflated because of the open surgical approach via an enterotomy. These short-term results do not give information about late complications such as ischemic stricture of the bowel in the clamped segment, and further studies are needed. This type of nitinol-based compression closure device is another addition to the published armamentarium of devices for full-thickness bowel wall resection and/or closure.^{14,15}

We conclude that full-thickness clamping of the bowel with the NiTi clamp, including the local mesenteric vasculature, did not significantly impair local healing of the clamp site or result in perforation 2 to 3 weeks after application. It resulted in no bowel perforations and no severe ischemic lesions. On the other hand, the procedure caused a delay of the healing process of the mucosal layer in 22% of events, creating a longitudinal mucosal ulcer up to a few millimeters in width. We believe that these results give hope to the further development of novel technologies for full-thickness endoscopic resection as well as for endoscopic closure of colotomies related to natural orifice surgery, endoscopic mucosal resection, and endoscopic submucosal dissection.



Figure 7. Low-magnification photograph (\times 4) from 3 different rectal compression clip anastomotic lines. **A**, There is organization of fibrous tissue and formation of granulation tissue at the line of anastomosis. Note the serocellular crust on the surface. **B**, There is organization of fibrous tissue and formation of granulation tissue. There is good vascularization, marked congestion, and apparent thickening of arterial walls. **C**, There is organization of fibrous tissue and formation of granulation tissue at the line of anastomosis. Note the serocellular crust on the surface. The *arrow* indicates a small granuloma.



Figure 8. A comparison of a stapled colotomy to compression clip closure line. **A**, A stapled colotomy in the cecum (H&E, orig. mag. \times 2). Note the invagination of the mucosa within the muscularis. The *arrows* indicate the staple spaces. **B**, The compression clip site in the rectum (H&E, orig. mag. \times 2). Note the large separation of the 2 ends of the muscularis.

REFERENCES

- Levin B, Lieberman DA, McFarland B, et al. American Cancer Society Colorectal Cancer Advisory Group; US Multi-Society Task Force; American College of Radiology Colon Cancer Committee. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. Gastroenterology 2008;134:1570-95.
- Kahi CJ, Rex DK, Imperiale TF. Screening, surveillance, and primary prevention for colorectal cancer: a review of the recent literature. Gastroenterology 2008;135:380-99.
- 3. Bond JH. Colon polyps and cancer. Endoscopy 2003;35:27-35.
- Baron JH, Connell AM, Lennard-Jones JE. Variation between observers in describing mucosal appearances in proctocolitis. Br Med J 1964;1: 89-92.
- 5. Matts SG. The value of rectal biopsy in the diagnosis of ulcerative colitis. Q J Med 1961;30:393-407.
- Fumihito H, Toshiyuki M. A critical review of endoscopic indices in ulcerative colitis: inter-observer variation of the endoscopic index. Clin J Gastroenterol 2008;1:40-5.
- 7. Swindle MM, Smith AC, Hepburn BJ. Swine as models in experimental surgery. J Invest Surg 1988;1:65-79.
- Nudelman IL, Fuko VV, Morgenstern S, et al. Gastrointestinal anastomosis with the nickel-titanium double ring. World J Surg 2000;24: 874-7.
- Nudelman IL, Fuko V, Greif F, et al. Colonic anastomosis with the nickel-titanium temperature-dependent memory shape device. Am J Surg 2002;183:697-701.
- Nudelman I, Fuko V, Rubin M, et al. A nickel-titanium memory-shape device for colonic anastomosis in laparoscopic surgery. Surg Endosc 2004;18:1085-9.
- 11. Kopelman D, Lelcuk S, Sayfan J, et al. End-to-end compression anastomosis of the rectum: a pig model. World J Surg 2007;31:532-7.

- 12. Aggrawal R, Darzi A. Compression anastomoses revisited. J Am Coll Surg 2005;201:965-71.
- 13. Kopelman D, Hatoum AO, Kimmel B, et al. Compression gastrointestinal anastomosis: a review. Expert Rev Med Devices 2007;4:821-8.
- Raju GS, Ahmed I, Shibukawa G, et al. Endoluminal clip closure of a circular full-thickness colon resection in a porcine model (with videos). Gastrointest Endosc 2007;65:503-9.
- Sporn E, Bachman SL, Miedema BW, et al. Endoscopic colotomy closure for natural orifice transluminal endoscopic surgery using a T-fastener prototype in comparison to conventional laparoscopic suture closure. Gastrointest Endosc 2008;68:724-30.

Received December 18, 2008. Accepted May 1, 2009.

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