Doctoral (Ph.D.) thesis

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1. Introduction

After endoscopic examination of the gastrointestinal tract and the possibility of histological sampling became routine, the possibility of therapeutic, minimally invasive interventions were developed within a short time. Restoring the integrity of the alimentary canal, which can be performed reliably with the flexible endoscope, has become an essential requirement for endoluminal resections performed with oncological and benign indications. In addition to primary endoscopic interventions, these devices can in some cases be excellent for the treatment of postoperative complications of gastroenterological operations (anastomosis insufficiency, bleeding, etc.). The possibility of endoscopic suturing has already opened the way to manage GERD and even bariatric procedures. In the modern endoscopic therapeutic field, endoscopic clips, suturing devices, negative pressure therapy and certain glues have become available.

2. Aims

Our aim was to evaluate the usefulness of the Overstitch™ (Apollo Medical, Austin, TX, USA) endoscopic suturing device in the area of the upper and lower gastrointestinal tract, to perform full thickness flexible endoscopic endoluminal closure. We pursued to find the most safe and effective closure technique by suturing. All the acquired data were examined based on objective markers.

We used ex vivo and in vivo animal models also to perform the endoscopic suturing. We hope that our findings will promote and further develop the field of interventional flexible endoscopic procedures.

3. Material and methods

To perform all the interventions, we used the Overstitch™ device. The study was divided into four parts.

Throughout the first phase, intact, untouched stomachs were harvested from euthanised swine (sus scrulfa domesticus -large white) within the research institute. On these stomachs a full thickness incision was performed and the most optimal suturing method was determined. For this phase, twenty explanted swine stomachs were used to close a 3 cm transmural incision. Three suturing techniques were evaluated: single stitching, figure of eight and running suturing. The time of the procedure, the demand of the suturing material and the maximal burst pressure in mmHg were recorded.

In the second phase, in proper operative setting after the required preoperative preparations, a 3 cm full thickness incision was performed on surviving swine models. The closing technique was chosen considering the results of the ex vivo data. On the tenth postoperative day a control endoscopy and mercy killing was performed. After the euthanasia a

laparotomy was performed and the intraabdominal adhesions were ranked on a scale from zero to four.

For the third phase two animals were operated on at the level of the rectosigmoid junction, 12 and 20 centimeters away from the anal verge. A 3 cm transverse full thickness incision was performed. This incision was made using a needle knife with monopolar energy, then the hole was sutured. Following the closure, after satisfactory endoscopic review, with the help of the laparoscope a bubble test was performed. By positive air leak additional sutures were placed. After the procedure a laparotomy was performed, the sutured segments were resected, and the positive results of the full thickness sutures were confirmed. The time of the operation along with the used material and burst pressure in mm Hg were recorded.

In the fourth phase five live swine were used as models. 20 cm from the anal verge, after marking the spot, a 3 cm long transverse full thickness incision was performed with use of monopolar energy. The duration of the procedure was calculated between the beginning of the suturing, until the negative air leak test. After a 10 days survival period, a control endoscopy was performed. Following the termination, a laparotomy was also performed. The abdominal adhesions

were ranked as previously mentioned, on a scale from zero to four.

Before the above experiments, the instrument was introduced and the application of the device was demonstrated by an experienced surgeon trained by Apollo Medical. Subsequently so called dry cycles and tests were used to acquire the mandatory skills. Before the procedures, the whole operating team had access to practice in ex vivo swine tissues, so the learning curve did not influence the study.

4. Result

4.1 Evaluation of the optimal suture pattern for endoscopic suturing on swine stomachs

In total 20 explanted pig stomachs were assigned and used for the suturing patterns. No statistically significant differences were identified in suturing time. Suturing time was slightly shorter with the figure of 8 technique at 41.14±4.6 minutes, versus interrupted 45.75±1.1 minutes, versus continuous 51.44±10 minutes. No significant difference was found in burst

pressure: figure of 8 45.85±26.2 mmHg versus interrupted 30.5±22.89 mmHg versus running suture 32±26.5 mmHg. After data analysis and consideration of technical feasibility we concluded that the figure of 8 suture is the most secure and easy to perform pattern. For subsequent experiments we were striving to use this suturing method.

4.2 Endoscopic suturing of full thickness incisions on porcine stomachs in a survival study

In all four cases the operations were performed successfully, anesthesiologic complications did not occur. Median suturing time was 57.4 minutes (39-70 minutes). In three cases four, in one case three threads were used to close the incision, amounting to a total of fifteen threads and cinch devices. However, due to misuse and accidental suture tearing five additional threads and cinches had to be used. As a result of this in some cases instead of figure of 8 sutures, simple stitches were placed. In most of the cases, as expected from the preliminary data, the closure was feasible using the figure of 8 pattern. The postoperative period was uneventful. During the control endoscopy the suture lines were found to be intact,

ulcers, intramural abscesses were not identified. After euthanasia the suture lines and the intraabdominal adhesions were assessed, the median adhesion score was 2.76±0.95. Major complication was not found, but certain cases showed strong adhesions, occurring on the serosal side of the suture line. This was probably caused by contamination from the stomach content.

4.3 Endoscopic closure of a colonic transmural incision on porcine models

In both cases the sutures were placed successfully endoscopically. In both operations two threads were used with an operation time of 34 and 25 minutes. The bubble test did not indicate any leakage. Out of the four figure of 8 stitches three were full thickness, in one case only the mucosa was adapted. At the burst pressure test in one model the dyed liquid was discovered in the submucosal layer at 64 mm Hg, however in the other case the resistance of the suture line was at a relatively high 240 mm Hg.

4.4 Endoscopic suturing of colonic full thickness incisions in survival porcine models

In one model, the size of the incision was over four cm. Additionally, probably due to the movement of the endoscope, the size of the transmural defect got enlarged to 5 cm. After many attempts, we had to apprehend that an endoscopic closure was not achievable. The pig was later excluded from the study, due to this oversized defect. In another model, after the placement of two figure of 8 stitches, the air test gave a positive result, so a third suture was placed. The procedure time was 58 minutes. Later in this animal, because of abdominal discomfort and fever, an early euthanasia had to be done. At the following exploration a purulent peritonitis was found, without suture insufficiency, collateral injury was not identified. The case of the peritonitis was suspected to be an intraoperative contamination.

As for the remaining three cases, the procedure times were the following: 55, 39 and 48 minutes. In two cases the suturing was performed with two threads and in one case three threads were used. The air leak tests were negative. The postinterventional period was uneventful, the animals gained

weight, enteral feeding and bowel movements were sufficient. On the tenth day at the laparotomy we awarded two points twice and in one case, three points according to the adhesions.

5. Discussion

Therapeutic, flexible endoscopic procedures and devices are continuously evolving and can reduce the invasiveness of modern procedures. With newly developed instruments, mortality can be reduced and the quality of life of the patients can be increased. The current state of advanced flexible endoscopy proves that these new, advanced instruments open the way to more complex procedures. The purpose of our study was to find an universal, in the upper and lower gastrointestinal tract useful mucosal and/or full thickness closing device. Due to the surgical practice, our attention moved to suturing modalities. The presented Overstitch^{TM} device holds an enormous potential to perform current and future flexible endoscopic complex interventions. The current, third generation of the device, which is compatible with most of the currently used therapeutic endoscopes is utilized in many

advanced endoscopic units. According to currently available data, in selected cases, effective closure and good tissue regeneration were observed both in the upper and in the lower gastrointestinal tract. In the ex vivo phase of our experiment, the figure of 8 pattern was chosen objectively, although significant difference was not observed between this and other suturing techniques. At the survival phases of the experiment safe and secure adaptations and good tissue regeneration were observed. The inflammation and adhesions at the suture line could be attributed to limitations of the porcine model. In the lower gastrointestinal tract, a lack of preoperative bowel preparation and the lack of compliance is a major disadvantage. Moreover, the anatomy of the young porcine models differs from human structures. The adaptation of the tissue and the intraluminal manipulation is more difficult in these models compared to the human patients. Despite of this, the tissue adaptation was successful. In conclusion, we can summarize that with the use of the Overstich^{TM} device endoscopic suturing can be a reliable alternative to major surgical operations. Our results and the literature prove the fact that with the help of this device, full thickness endoscopic suturing is feasible. Obviously, when selecting a case, the appropriate equipment

park, the expertise of the examining surgeon, appropriate preparations and the size of the defect together determine the feasibility of the intervention.

6. Novel findings

- The endoscopic suturing device is capable of performing various suturing patterns. No statistically significant difference was found among these. The author suggests that the most efficient and secure suturing method is the figure of 8 pattern.
- Our experiments proved in ex vivo and in survival settings also, that the Overstitch^{TM} endoscopic suturing device is capable of closing planned full thickness incisions of the stomach wall up to 3 cm in length. In the survival study proper healing was observed.
- With the use of the suturing device, up to 3 cm full thickness, suturing is possible, which is exceeding the limitation of other currently available endoscopic clips. However, in the lower gastrointestinal tract, defects over the half of the circumference cannot be managed endoluminally according to our observations.

- The device can also be used properly in the lower gastrointestinal tract. In order to evaluate longer-term data, it is advisable to develop a better colorectal model.

7. List of publications

7.1 Publications related to the theses

Halvax P, Diana M, Lègner A, Lindner V, Liu YY, Nagao Y, Cho S, Marescaux J, Swanström LL. Endoluminal full-thickness suture repair of gastrotomy: a survival study. Surg Endosc. 2015 Nov;29(11):3404-8. **IF: 3,149**

Halvax P, Diana M, Nagao Y, Marescaux J, Swanström L. Experimental Evaluation of the Optimal Suture Pattern With a Flexible Endoscopic Suturing System. Surg Innov. 2017 Jun;24(3):201-204. **IF: 1,785**

Halvax P, Nemeth B, Kiss I, Papp A, Vereczkei A. Endoluminal Suture-technique for the Stomach Closure of an Experimental Model. Anticancer Res. 2023 Jan;43(1):59-61. **IF: 2,48**

Cumulative impact factor of publications related to the Theses: 7,414 (2022)

7.2 Abstracts and oral presentations related to the theses

Flexible endoscopic suturing of full-thicknes colonic incisions in a survival model **P. Halvax**, M. Diana, A. Legner, Y.Y. Liu, H.J. Lee, L. Swanström, J. Marescaux, 23rd International Congress of the E.A.E.S, Bucharest, Romania 3 - 6 June 2015

Endoscopic full thickness suturing with an endoscopic suturing device on porcine sigmoid colon **P. Halvax**, L. Swanström, M. Diana, S. Perretta, A. Legner, Y.Y. Liu, S. Cho, A. Alzaga, J. Marescaux 22rd International Congress of the E.A.E.S, Paris, France 26 - 28 June 2014

Tervezett gyomorincízió flexibilis endoszkóppal történő zárása túlélő állatmodellen **Halvax Péter**, Vereczkei András MST Kísérletes Sebészeti Szekció XXV. Kongresszusa, Pécs 2015.04.14-16

Flexibilis endoszkóppal végzett teljes falvastagságú varrattechnika vizsgálata **Halvax Péter**, Vereczkei András MST Kísérletes Sebészeti Szekció XXV. Kongresszusa, Pécs 2015.04.14-16

Flexibilis endoszkópos varrattechnikák aktuális lehetőségei **Dr. Halvax Péter** MST Sebészeti Endoszkópos és Coloproctológiai Szekció Közös Kongresszusa, Tapolca 2022.05.26-28.

7.3 Other abstracts and oral presentations not related to the theses

Légner A, Tsuboi K, Stadlhuber R, Yano F, **Halvax P,** Hunt B, Penka W, Filipi CJ. Mucosal excision and suturing for obesity and GERD. Surg Innov. 2013 Dec;20(6):586-93. **IF: 1,785**

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Diana M, **Halvax P**, Dallemagne B, Nagao Y, Diemunsch P, Charles AL, Agnus V, Soler L, Demartines N, Lindner V, Geny B, Marescaux J. Real-time navigation by fluorescence-based enhanced reality for precise estimation of

future anastomotic site in digestive surgery. Surg Endosc. 2014 Nov;28(11):3108-18. **IF:3,149**

Diana M, Dallemagne B, Chung H, Nagao Y**, Halvax P**, Agnus V, Soler L, Lindner V, Demartines N, Diemunsch P, Geny B, Swanström L, Marescaux J. Probe-based confocal laser endomicroscopy and fluorescence-based enhanced reality for real-time assessment of intestinal microcirculation in a porcine model of sigmoid ischemia. Surg Endosc. 2014 Nov;28(11):3224-33.. **IF:3,149**

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Diana M, Agnus V, **Halvax P**, Liu YY, Dallemagne B, Schlagowski AI, Geny B, Diemunsch P, Lindner V, Marescaux J. Intraoperative fluorescence-based enhanced reality laparoscopic real-time imaging to assess bowel perfusion at the anastomotic site in an experimental model. Br J Surg. 2015 Jan;102(2):e169-76 **IF: 5,572**

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