Perforated Duodenal ulcers – surgery or endoscopic stent treatment, a randomized multicentre study

Prof Per-Ola Park, Dr Maria Bergström, Dr Jorge Alberto Arroyo Vázquez
Boras, Sweden

Summary
Perforated duodenal ulcer is a life threatening complication of peptic ulcer disease. Despite the decline in ulcer disease during the last decades, ulcer perforations remain a serious condition with high morbidity and mortality. Many patients are old and co-morbid. The standard treatment is surgical closure using open or laparoscopic techniques. We started to treat some of the old and co-morbid patients, who had high operative risks, with covered duodenal stents together with percutaneous drain placement. The results are promising [1]. We now plan to start a randomised multicentre study comparing stent placement and surgical closure for perforated duodenal ulcers.

Background
Perforated duodenal ulcer is a life threatening complication of peptic ulcer disease. The incidence of uncomplicated peptic ulcer disease has decreased during the last decades but complications such as perforations still pose a serious threat. Both morbidity and mortality rates (10-40%) are still high [2,3]. In a recently published Norwegian epidemiological study the current incidence of perforated ulcers was 6.5/100 000 inhabitants/year and 1/3 of these were duodenal perforations. This study also shows that the population suffering from ulcer perforations are old and have a high degree of co-morbidity. The 30-day mortality rate was 16% for all ulcer perforations but as high as 23% for the duodenal localisation. The older patients had worse prognosis, mortality was 50 times higher for patients above 60 years [4].

The traditional treatment of a perforated duodenal ulcer is surgical closure, performed using open or laparoscopic surgical techniques. Results vary in the literature but high morbidity rates (up to 35%) due to surgical or medical complications are reported together with mortality rates of 5-16% [5,6]. The risks increase with age, co-morbidities and technically complicated surgical procedures [7]. Conservative treatment with antibiotics and nasogastric tube has been advocated and is still in use for old and co-morbid patients. However, this method has shown poor results with high mortality rates. In a Suisse retrospective study comprising 332 patients treated for perforated ulcer 12 were treated conservatively. Eight of them died (8/12) [8]. In a recent Egyptian study percutaneous drain placement through a mini-laparotomy was added to the conservative strategy. This technique seemed to slightly decrease the mortality rate (20%) [9].

Placement of covered stents has become the treatment of choice for oesophageal perforations, iatrogenic or spontaneous. The method has shown good results together with percutaneous pleural drainage [10,11]. The same principle is used to treat anastomotic leakages after gastric-bypass-surgery where covered stents together with abdominal drains are used to treat leakages in the gastroenteroanastomosis [12,13]. Also for these patients with good results. The main advantage of stent treatment is the avoidance of surgery, which in itself carries risks of further complications.
Inspired by these results we started to treat patients with perforated duodenal ulcers with placement of a covered duodenal stent (table 1) a couple of years ago. The first two patients had leakages after surgical closure, and the other 8 patients were primarily treated with a stent due to co-morbidities or high operative risks. 8/10 of these patients had an abdominal drain placed either at an initial laparoscopy or post stent placement using radiologic
techniques. The mortality in this series was 1/10. The first eight patients in our series constitute the case-series that we published in Endoscopy 2013 [1].

Early start of postoperative oral nutrition is advantageous for the all patients after major abdominal surgery as the gut flora is better preserved and the bacterial translocation from the gut is minimized [14]. Duodenal stent placement makes oral intake possible almost immediately after the placement. In our series the median time till oral intake was 3 days (0-7). The first 4 patients had nil per mouth for a few days after stents placement as we were more cautious, but the last 3 patients started oral intake immediately after the stent procedure [1].
Hypothesis

Based on the results from our series together with the reported good results from stent treatment of postoperative leakages and oesophageal perforations, we believe that stent treatment of perforated duodenal ulcers can be an option even in uncomplicated cases.

We expect stent treatment together with percutaneous drain placement to result in shorter operating times, a less pronounced surgical trauma, fewer complications and quicker recovery.

We also believe that old and co-morbid patients have the most to gain from this new method as they today have the poorest prognosis.

A disadvantage with stent placement is that the patients need to return for gastroscopy with stent extraction after 2-3 weeks.

Aim

To compare stent placement and surgical treatment of a perforated duodenal ulcer in a prospective randomised multicenter study.

Table 1: Results from our series, the first 10 patients

<table>
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<tr>
<th>Patient</th>
<th>Age</th>
<th>Gender</th>
<th>Indication for stent treatment</th>
<th>Primary stenting</th>
<th>Abdominal drainage</th>
<th>Time from admission to stenting (days)</th>
<th>Stent removal after (days)</th>
<th>Hospital stay post stenting (days)</th>
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<tr>
<td>1</td>
<td>71 y Female</td>
<td>Postoperative leakage x 3</td>
<td>No, after surgery</td>
<td>At primary surgery</td>
<td>36</td>
<td>21</td>
<td>21</td>
<td></td>
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<tr>
<td>2</td>
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<td>Postoperative leakage x 1</td>
<td>No, after surgery</td>
<td>At primary surgery</td>
<td>10</td>
<td>56</td>
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<tr>
<td>3</td>
<td>87 y Female</td>
<td>Deteriorated condition, delayed diagnosis</td>
<td>Yes</td>
<td>No</td>
<td>7</td>
<td>1 (‡)</td>
<td></td>
<td></td>
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<tr>
<td>4</td>
<td>80 y Female</td>
<td>Technically difficult surgical closure</td>
<td>Yes</td>
<td>Yes, at laparoscopy</td>
<td>3</td>
<td>15</td>
<td>22</td>
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<td>5</td>
<td>87 y Female</td>
<td>Post ulcer stricture, perforation after dilatation</td>
<td>Yes</td>
<td>No</td>
<td>&lt;1</td>
<td>44</td>
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<td>6</td>
<td>62 y Male</td>
<td>Known dense abdominal adhesions, high technical operative risk</td>
<td>Yes</td>
<td>Yes, percutaneous</td>
<td>&lt;1</td>
<td>40</td>
<td>17</td>
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<tr>
<td>7</td>
<td>86 y Female</td>
<td>Refused surgery, leaking after 5 days of conservative treatment</td>
<td>Yes</td>
<td>Yes, percutaneous</td>
<td>7</td>
<td>14</td>
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<td>8</td>
<td>81 y Female</td>
<td>Severe comorbidities, High operative risk</td>
<td>Yes</td>
<td>Yes, percutaneous</td>
<td>3</td>
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<td>36</td>
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<td>9</td>
<td>77 Female</td>
<td>Difficult closure, frail patient</td>
<td>Yes</td>
<td>Yes, at laparoscopy</td>
<td>0</td>
<td>12</td>
<td>6</td>
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<tr>
<td>10</td>
<td>70 Male</td>
<td>Severe comorbidities, difficult closure, obese</td>
<td>Yes</td>
<td>Yes, at laparoscopy</td>
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<tr>
<td>Mean: 77 y</td>
<td>3 Female Male</td>
<td>Median:</td>
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</table>

Table 1: Results from our series, the first 10 patients
**Study design**
Prospective randomised multicenter study

**Method**

**Inclusion**

Patients presenting at the ER with symptoms and signs consistent with a G-I perforation together with findings of free air on a CT-scan, will be evaluated for inclusion. Randomisation will take place before confirmation of the diagnosis. (To give the endoscopist time to go to the hospital.)

Groups:
1. Stent placement
2. Surgical closure, open or laparoscopic technique

A diagnostic laparoscopy will be performed to establish the diagnosis. If a perforation is not evident a peroperative gastroscopy will be performed. If a perforated duodenal ulcer is not found the patient will be excluded from the study.

**Stent treatment:**

Laparoscopic lavage of the abdominal cavity will be performed as needed. A peroperative gastroscopy will be performed and a guide wire will be placed into the bowel distally to the duodenum. A covered duodenal stent will be introduced over the wire and placed with the oral end in the stomach and the covered part covering the perforation. The partially covered Hanaro duodenal stent from MI-tec Korea will be used.

**Surgical closure:**

Surgical closure can be performed using open or laparoscopic surgery, according to the surgeon’s preference. Lavage will be performed as above.

**Postoperative follow up:**

Intravenous PPI-treatment starts immediately postoperatively. Leakage test using methylene blue will be performed on the first postoperative day. If there is no leakage the patient can start oral intake of liquids at once and take oral medication the next day.

- Stented patients continue with liquid and soft food until stent-extraction.
- Operated patients start oral intake according to local guide-lines
- Ordinary mobilisation according to the patients’ capacity
- Body temperature twice daily during at least three days
- Blood samples for Hb, CRP and WBC levels during at least three days and more if needed
- All medication for pain relief, including regional anaesthesia will be recorded.
- Further radiologic examinations can be performed if clinically indicated
- Complications will be recorded and classified according to Clavien-Dindo
- Hospital stay will be recorded
- Endoscopic stent extraction will take place two weeks post stent placement
**Study design, flow chart:**

- Admitted with clinical supiscion of G-I perforation
- Free air on a CT-scan
- ASA score ≤ 4
- Autonomic patient
- No need for language translation

**Exclusion criteria**

- Age < 18 years
- ASA-score >4
- Non-autonomic patient
- Need language translation

**IRB**

We are currently working on the IRB application
Endpoints:

Primary endpoint:
- Complications according to Clavien-Dindo [15,16]

Secondary endpoints:
- Hospital stay
- Consumption of analgesics

Power calculation

The intention of the study is to show that stent treatment results in fewer complications than surgery. However, there are no previous results to base a power calculation on. The literature on perforated ulcer treatment is limited and mainly noncurrent.

We have performed a retrospective study at our own hospital including all patients treated for a perforated duodenal ulcer during 2009-2012. A total of 27 patients were identified, 19 were operated with surgical closure or resection and 8 received stent treatment (the last 8 in table1) [17]. 8/19 (42%) patients in the operated group and 2/8 (25%) in the stent group had complications showing a tendency towards fewer complications in the stent group but no statistically significant difference as the number of patients in this study was limited [17].

To show non-difference in outcome after stent treatment and surgery we assume that the new treatment (stent) results in 10% complications and that surgical closure results in 30%. Calculations give that 50 patients in each group will be needed to achieve 80% power with an $\alpha$-level of 5%. An intermediate analysis will be performed when 50% of the inclusions are completed for correction of these calculations.

Feasibility

This will be a regional study in the region of Västra Götaland with four cooperating hospitals. We have 1.7 million inhabitants. According to the recently published Norwegian study the incidens of perforated duodenal ulcers is calculated to 2/100 000 inhabitants / year. [4]. Leading to 30 cases/year in our region. To achieve more efficient inclusion, we plan to invite more surgical centres in other Swedish regions.

Statistics

All patient data will un-identified and handled group-wise. Group-wise comparisons will be performed using non-parametric statistic methods. Wilcoxon’s sign-rank test will be used for pair-wise comparisons and the Mann-Whitney-U test for non-pair-wise comparisons. The Chi-square test will be used for nominal comparisons. A p-value of $< 0.05$ will be considered statistically significant. All analyses will be performed using the SPSS software 20.

Available resources
We have the resources in the clinical setting in our hospital. Both for stenting and surgical procedures. We also have an organisation with study nurses and enthusiastic co-workers.

References

11. van Boeckel PG, Sijbring A, Vleggaar FP, Siersema PD. Systematic review: temporary stent placement for benign rupture or anastomotic leak of the oesophagus. Aliment Pharmacol Ther;33:1292-1301
**BIOGRAPHICAL SKETCH**

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2. Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

<table>
<thead>
<tr>
<th>NAME</th>
<th>POSITION TITLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per-Ola Park</td>
<td>Associate Professor of Surgery, Senior Consultant Surgeon</td>
</tr>
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</table>

**EDUCATION/TRAINING** *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

<table>
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<th>INSTITUTION AND LOCATION</th>
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<td></td>
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<tr>
<td>University of Uppsala, Thesis</td>
<td>PhD</td>
<td>11/1991</td>
<td>Surgery</td>
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<tr>
<td></td>
<td>Associate Professor</td>
<td>12/2009</td>
<td>Surgery</td>
</tr>
<tr>
<td>Sahlgrenska University of Gothenburg</td>
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</table>
A. Personal Statement

The goal of the proposed research is to investigate if endoscopic stent treatment is as safe and efficient as surgical closure of a perforated duodenal ulcer. It is planned as a multi-center study. I have the expertise, leadership and motivation necessary to successfully carry out and lead the proposed study. I have been both participating in as well as organizing multicenter studies. I also have a well organized working staff an co-workers to carry out the study. I and my co-workers are experienced surgeons and interventional endoscopists. I have a long experience in advanced endoscopic treatments both experimentally and clinically. My research field is “mini-invasive surgery and NOTES” and I was together with my co-worker first to publish NOTES transgastric cholecystectomy. We are well experienced in stent treatment of the esophagus, bile ducts and colon. We have published articles on experimental and clinical endoscopic stent treatments including a case series of stent treatment of perforated duodenal ulcers. The current application builds logically on my prior work, and I have chosen co-investigators (Drs. Maria Bergström and Jorge Alberto Arroyo Vázquez) who provide additional expertise. The project is also planned to be a part of Dr Jorge Alberto Arroyo Vázquez’s thesis. In order to speed up the inclusions we have invited all the hospitals in the region to participate in the study. They have accepted the invitation.

In summary, I have a demonstrated record of successful and productive research projects in the field of therapeutic endoscopy as well as surgery and my expertise and experience have prepared me to lead the proposed project.

B. Positions and Honors

Positions and Employment

Appointments after Specialist in General Surgery:

  Malmö Allmänna Sjukhus 1983-1987: Junior Staff Surgeon
  Värnamo Sjukhus 1987-1996: Senior Consultant
  6 months appointment at Dep of Surgery, Uppsala Akademiska sjukhus 1989
  3 months appointment at Dep of Surgery, Lindkőping University Sjukhus 1993
  7 months appointment at Dep of Surgery, Ryhov Sjukhus, Jönköping 1995
  Centrallasarettet, Växjö 1996-2002: Senior Consultant
  Sahlgrenska University Hospital/Östra 2002-2009: Consultant at Dep of Surgery
  Member of Upper Gastrointestinal team
  Head of Endoscopic Unit/Östra 2002-2008

Present appointment:

  South Älvsborgs Hospital, Borås 2009--: Consultant at Dep of Surgery
  Member of Upper Gastrointestinal team
  Head of Upper Gastrointestinal team 2012 –

Other Experience and Professional Memberships

Member of Editorial Board, Endoscopy 2006-2008, and Gastrointestinal Endoscopy
Member of the Swedish Medical Society 1978—
Member of The Swedish Surgical Society 1983—
Member of the Executive Board of the Swedish Laparoscopic Society 1992-1994
Member of the Swedish Gastroenterology Society 2007—
Member of the Executive Board of the Swedish Gastroenterology Society 2007-2009
Honors

Mentor of the Year at Växjö Central Hospital 2002

C. Selected Peer-reviewed Publications

Most relevant to the current application


Additional recent publications of importance to the field (in chronological order)


D. Research Support

**Ongoing Research Support**

Borås Forsknings- och utvecklingsfond mot cancer

*Swedbank Sjuhärads stiftelse för forskning vid Södra Älvsborgs Sjukhus*

**Completed Research Support**

Familjen Erling-Perssons Stiftelse

Greta Andersons fond för vetenskaplig forskning

Walter Andersons fond för vetenskaplig forskning

Euro-NOTES

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**BIOGRAPHICAL SKETCH**

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2. Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

<table>
<thead>
<tr>
<th>NAME</th>
<th>POSITION TITLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maria Bergstrom</td>
<td>Senior Consultant Surgeon</td>
</tr>
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<table>
<thead>
<tr>
<th>eRA COMMONS USER NAME (credential, e.g., agency login)</th>
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**EDUCATION/TRAINING** *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

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<td>Med. school</td>
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<td>Värnamo Hospital, Sweden</td>
<td>Authorization</td>
<td>12/90</td>
<td>Internship</td>
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<tr>
<td>Gothenburg University</td>
<td>Ph.D.</td>
<td>12/07</td>
<td>Laparoscopic surgery</td>
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**PHS 398/2590 (Rev. 06/09)** Page

**Biographical Sketch Format Page**
A. Personal Statement

The goal of the proposed research is to investigate if endoscopic stent treatment is as safe and efficient as surgical closure of a perforated duodenal ulcer. It will be a multi-center study. I will be participating faculty and co-PI. I have a broad experience from research in experimental cell-lines, animal studies and human clinical studies. I also have good organizing capacity and writing skills. My thesis work was carried out on laparoscopic surgery and peritoneal physiology including both experimental and human studies. I am both a senior surgeon and interventional endoscopist. I have together with our research team taken part in the early development and research on NOTES, publishing the first NOTES transgastric cholecystectomy and early survival studies with NOTES gastroenteroanastomoses.

Our current research projects focus on mini-invasive surgery. We are all experienced in GI stent placement and carry out these procedures in our daily practice. As surgeons in an emergency hospital we also treat perforated ulcers on a regular basis. As we already see and treat these patients, inclusion for the study will be fairly easy. In summary I believe I have the experience, enthusiasm and capacity to launch this study and also to complete it together with my co-workers.

B. Positions and Honors

1989-1990 Internship, Värnamo, Sweden
1991-1993 Residency, Skene, Sweden
1993-1996 Residency, Östra hospital, Gothenburg, Sweden
1996-2006 Staff surgeon, Östra hospital, Gothenburg, Sweden
2006-2009 Consultant surgeon, Sahlgrenska University Hospital /Östra, Gothenburg, Sweden
2009- Senior Consultant surgeon, South Älvsborg Hospital, Boras, Sweden

C. Selected Peer-reviewed Publications

Most relevant to the current application

Additional recent publications of importance to the field (in chronological order)


D. Research Support

List both selected ongoing and completed research projects for the past three years (Federal or non-Federally-supported). *Begin with the projects that are most relevant to the research proposed in the application.* Briefly indicate the overall goals of the projects and responsibilities of the key person identified on the Biographical Sketch. Do not include number of person months or direct costs.
BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2. Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

<table>
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<th>POSITION TITLE</th>
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<tbody>
<tr>
<td>Jorge Alberto Arroyo Vázquez</td>
<td>Resident surgeon</td>
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**EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)**

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**A. Personal Statement**

I will participate as junior researcher. I will work hard on this project that will be a part of my thesis. I am a minimal invasive fellow.

**B. Positions and Honors**

- 2001-2002 Internship, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain
- 2002-2003 General practitioner, Secretaria de Salud Jalisco, Mexico
- 2005-2007 Assistant doctor, Sahlgrenska University Hospital, Gothenburg, Sweden
- 2008-2009 Internship, South Älvsborg Hospital, Borås, Sweden
- 2009- Residency, South Älvsborg Hospital, Borås, Sweden

**C. Selected Peer-reviewed Publications**

Program Director/Principal Investigator (Last, First, Middle): Prof Per-Ola Park

SAGES RESEARCH GRANT APPLICATION
BUDGET SHEET

Detailed budget for 12 month period from _______ through _______.

Dollar amount requested (Omit cents) 30000

Total for the grant request may not exceed $30,000.

* Salary funds should be used for staff required to execute the study, but should not be used for salary support investigator. If salary support exceeds 50% of the project budget, then specific justification is required.

**Funds requests for travel for the presentation of a SAGES funded study should be limited to $1,000.

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<tr>
<td>1. Dr Per-Ola Park</td>
<td>Principal Investigator*</td>
<td></td>
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<tr>
<td>2. Dr Maria Bergstrom</td>
<td>Co-investigator</td>
<td>10</td>
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<td>3. Dr Jorge Arroyo Vázquez</td>
<td>Co-investigator</td>
<td>20</td>
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<td>4. Sari Karhu, nurse</td>
<td>Study nurse</td>
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