Surgery for inflammatory bowel disease, crossing borders
Gardenbroek, T.J.

Citation for published version (APA):

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Early reconstruction of the leaking ileal pouch-anal anastomosis: a novel solution to an old problem.

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Submitted
ABSTRACT

Background
In this study we determined the effectiveness and direct medical costs of early surgical closure of the anastomotic defect after short course of Endo-sponge® therapy of the presacral cavity, compared to conventional treatment in patients with anastomotic leakage after ileal pouch-anal anastomosis (IPAA).

Methods
Patients with anastomotic leakage after IPAA undergoing early surgical closure of the anastomotic defect after short Endo-sponge® treatment were prospectively followed and compared with a consecutive cohort of IPAA patients with an anastomotic leak treated with the creation of a loop ileostomy and occasionally drainage of the presacral cavity.

Results
A total of 15 patients were treated with early surgical closure and 29 patients were treated conventionally. In the early surgical closure group, the Endo-sponge® treatment was continued for a median of 12 days (iqr 7-15), with a median of 3 (iqr 2-4) Endo-sponge® changes. Secondary anastomotic healing was achieved in all patients (n = 15) in the early surgical closure group, which was significantly higher compared to 52% (n = 16) in the conventional treatment group (P = 0.003). Closure of the anastomotic defect was achieved after a median of 48 days (25-103) in the early surgical closure group compared to 70 days (iqr 49-175) in the conventional treatment group (P = 0.013). A functional pouch was seen in 93% and 86% of the patients respectively. No significant differences in direct medical costs were found.

Conclusion
Early surgical closure after a short period of Endo-sponge® treatment is highly effective to treat anastomotic leakage after IPAA without increasing costs.
INTRODUCTION

Restorative proctocolectomy (RPC) with ileal pouch-anal anastomosis (IPAA) is the treatment of choice in patients with ulcerative colitis (UC) and familial adenomatous polyposis (FAP). The Achilles’ heel of this procedure is anastomotic leakage. Even in the presence of a protective stoma, anastomotic leakage occurs in 4% of the IPAA patients, while the non-diverted pouches have a risk of leakage of up to 15% \(^1-3\).

Anastomotic leakage in the non-diverted pouches will most often present with pelvic sepsis. The anastomotic leak in diverted pouches often presents subclinically as a presacral abscess. The presacral abscess may develop into a presacral sinus with a chronic low grade infection, or even fistula formation to the perineal or gluteal area \(^4\). The presacral sinus may postpone or even preclude stoma reversal. If it is possible to close the stoma, pouch function might be compromised due to the chronic pelvic inflammation and its subsequent fibrosis \(^5,6\).

The goal of treating anastomotic leakage is the prevention of chronic sepsis and concomitant chronic sinus formation. Conventional management of anastomotic leakage after IPAA is faecal diversion by an ileostomy, which can be combined with transanal or percutaneous drainage of the presacral abscess cavity. Weidenhagen et al. described a novel approach to treat the presacral abscess with Endo-sponge\(^\circledR\) vacuum assisted drainage. The Endo-sponge\(^\circledR\) is endoscopically placed through the anastomotic defect into the presacral cavity and is connected to a low vacuum suction system \(^7\). By changing the Endo-sponge\(^\circledR\) two times per week and tapering the size of the Endo-sponge\(^\circledR\) systematically, the abscess cavity gradually collapses. This technique is labour-intensive, expensive and it takes several weeks until closure is achieved \(^7-13\). In addition, a small sinus may persist in the end with a risk of recurrent sinus after stoma reversal. We have proposed a modification of this technique. Instead of repetitive exchanges of the Endo-sponge\(^\circledR\) aiming at gradual collapse of the cavity, the Endo-sponge\(^\circledR\) is used to clean the cavity during two or three Endo-sponge\(^\circledR\) placements. When the cavity is clean and is surrounded by healthy granulation tissue, the anastomotic defect is closed surgically \(^14\). This innovative approach might overcome the drawbacks of the Weidenhagen technique.

The aim of this study was to determine if early surgical closure is feasible, results in a higher percentage of secondary healed anastomosis, reduces the time to anastomotic healing and leads to a higher percentage of functional pouches in patients with anastomotic leakage after IPAA for UC or FAP compared to the conventional management. In addition, we analysed the direct medical costs of both treatment modalities.
METHODS

We included all consecutive patients with anastomotic leakage after IPAA for UC or FAP in the period January 2003 – January 2014. Anastomotic leakage was defined as a symptomatic or asymptomatic leakage with an anastomotic defect confirmed by radiological imaging or during relaparotomy for abdominal sepsis. Patients undergoing early surgical closure after Endo-sponge® treatment of the anastomotic leakage between January 2010 and January 2014 were prospectively recorded and compared with a retrospectively identified cohort of IPAA patients with anastomotic leakage who underwent conventional treatment between January 2003 and December 2009. Since 2010, the anastomotic leakages were treated with a short course of Endo-sponge® followed by surgical closure of the anastomotic defect, when conservative treatment was not feasible. The Institutional Review Board (IRB) of the Academic Medical Centre in Amsterdam, the Netherlands, granted exemption from approval for this study.

Early surgical closure

In patients with anastomotic leakage after IPAA creation without ileostomy, the first Endo-sponge® placement was combined with ileostomy creation under general anaesthesia. Subsequent Endo-sponge® changes were carried out under light sedation at the endoscopy room. First, the abscess cavity was examined and rinsed with saline (0.9%) using a flexible gastroscope (GF-100 Video Gastroscope; Olympus, 9.8-mm diameter, Olympus Corp., Tokyo, Japan). Next, one or more open-pored polyurethane Endo-sponge(s)® (B. Braun Medical B.V., Melsungen, Germany) were placed via a plastic overtube under the guidance of the gastroscope into the deepest point of the abscess cavity \( \text{Figure 1} \). Thereafter, the Endo-sponge(s)® were connected to a low-vacuum suction bottle (Redyron® TRANS PLUS suction device, Melsungen, Germany). The Endo-sponge(s)® were endoscopically changed every 3-4 days to prevent tissue ingrowth or in case of vacuum depletion. When the abscess cavity was considered clean and the edges of the anastomosis were mobile, the anastomotic defect was closed surgically. Under general anaesthesia, the anastomotic dehiscence was transanally sutured with polydioxane 3-0 (PDS, Ethicon Endo-Surgery Inc., Cincinnati, Ohio, USA) over a vacuum drain by using the Lone Star Retractor System ™ (Lone Star Medical Products ®, Houston, Texas). The trans-anastomotic drain was removed on the 3rd postoperative day and antibiotics were given for 10-14 days postoperatively. All reconstructed anastomoses were evaluated by endoscopic inspection after two weeks or CT-scan with intraluminal contrast. Stoma closure was scheduled when anastomotic healing was confirmed. If there was a persisting anastomotic defect during radiological or endoscopic evaluation, continuation of Endo-sponge® treatment with a second attempt of defect closure, was considered.
Conventional treatment

After radiological confirmation of the anastomotic leakage, a diverted ileostomy was created, if not done so primarily. Depending on the size of the cavity, additional transanal or percutaneous drainage of the abscess cavity was performed, sometimes followed by regular irrigation via the drain, or a wait and see policy was adopted. During follow-up, secondary healing of the anastomosis was regularly checked endoscopically or by an x-ray with contrast enema of the pouch. Stoma closure was scheduled if anastomotic healing was confirmed.

Outcomes

Main outcome parameter was the percentage of secondary healed anastomosis at 6 months, without a persistent abscess or anastomotic defect assessed by imaging. Secondary outcome parameters were the time from diagnosis of the leakage to secondary anastomotic healing and the percentage of functional pouches at last date of follow-up. In addition, the size of the initial abscess cavity, the time to intervention, duration of Endo-sponge® treatment, the number of Endo-sponge® treatments, the number of patients with a chronic presacral sinus longer than one year, and the direct medical costs of both treatment modalities were calculated. Secondary healing of the anastomosis was defined as no signs of contrast leakage during contrast enema or abdominal CT scan with intravenous, oral and rectal contrast and an intact anastomosis during endoscopic inspection. Patients were classified as having a functional pouch when continuity was restored by ileostomy closure and no long term complications were reported (such as a persisting high defecation frequency, urgency incontinence or re-creation of a stoma).
Cost analysis

The direct medical costs per patient were calculated for both treatment groups. The direct medical costs were calculated from diagnosis of anastomotic leakage up to stoma reversal or up to 2 years of follow-up if ileostomy closure was not yet performed. The direct medical costs were calculated as the product sum of health care volumes involved and their unit costs. The direct medical costs included the costs of the index hospital admission, readmission(s), reoperation(s), visits to and telephone contacts with the outpatient departments (OPD) and the emergency room (ER), and endoscopic examination or radiological imaging from diagnosis of anastomotic leakage up to ileostomy reversal. In addition, we accounted for subsequent ileostomy care costs. For the early surgical closure group the costs of the Endo-sponge® treatment, Endo-sponge® changes, and surgical closure of the defect were incorporated as well.

The total medical cost consists of all patients that were successfully treated with early surgical closure and the successfully treated patients in the conventional treatment group. In addition, a separate cost analysis was performed up to two years after diagnosis of the leakage for the patients in whom no defect closure was observed at the end of follow-up or an ileostomy was present due to pouch failure. Unit costing was based on the Dutch costing manual for health care research or was determined in cooperation with the hospital administration and pharmacy. The unit costs are determined for the year 2010, after price-indexing (based on general consumer price indices; www.cvz.nl, access date April 20, 2013) of unit costs stemming from different calendar years.

Statistical analysis

Descriptive data are reported as median with interquartile range (iqr) or mean ± standard deviation according to distribution. Categorical data were analysed with Fisher’s exact test or Chi-square-test. Continuous variables were analysed using the Mann-Whitney-Wilcoxon test. P < 0.05 was considered statistically significant.

For the cost analysis the costs of both treatment modalities were compared by calculating the 95% confidence intervals (CI) for the mean differences after correction for bias, because of skewed distributions. Accelerated, non-parametric bootstrapping was used with stratification for Endo-sponge® treatment, drawing 10,000 samples of the same size as the original samples separately for each group and with replacement. All analyses were performed with IBM SPSS Statistics, version 20.0 (IBM Corp., Armonk, NY, United States).

RESULTS

Between January 2003 and January 2014, 393 patients underwent RPC and IPAA. Of these patients, 46 patients were diagnosed with an anastomotic leakage (11.7%). Five patients
were referred to our hospital for treatment of an anastomotic leak after IPAA. Of these 51 patients, 15 patients underwent early surgical closure and 29 patients received conventional treatment. The remaining 7 patients were excluded because they underwent other closing techniques; the original Weidenhagen technique (n = 4) and direct suturing of the defect without preceding Endo-sponge\textsuperscript{®} therapy (n = 3). These procedures were performed in the period between the use of the conventional method and the adaptation of the early surgical closure technique.

Neither the location of the leakage nor the size of the abscess cavity differed between the study groups (Table 1). In the early surgical closure group, a diverting ileostomy was created during the RCP in four of the 15 (27\%) patients. In nine patients (60\%), an ileostomy was constructed after diagnosis of the anastomotic leakage. In two patients (13\%), early closure after Endo-sponge\textsuperscript{®} treatment was attempted without an ileostomy. In one of these two patients (7\%) the early closure failed initially. After creation of a diverting

<table>
<thead>
<tr>
<th>Table 1 Patient characteristics</th>
<th>Conventional treatment n = 29</th>
<th>Early surgical closure n = 15</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at surgery (years)</td>
<td>36 [22-47]</td>
<td>37 [25-56]</td>
<td>0.603</td>
</tr>
<tr>
<td>Sex (M)</td>
<td>15 (52)</td>
<td>12 (80)</td>
<td>0.068</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td>0.552</td>
</tr>
<tr>
<td>- UC</td>
<td>20 (69)</td>
<td>9 (60)</td>
<td></td>
</tr>
<tr>
<td>- FAP</td>
<td>9 (31)</td>
<td>6 (40)</td>
<td></td>
</tr>
<tr>
<td>Indication for surgery</td>
<td></td>
<td></td>
<td>0.764</td>
</tr>
<tr>
<td>- Refractory</td>
<td>14 (48)</td>
<td>7 (47)</td>
<td></td>
</tr>
<tr>
<td>- Dysplasia / carcinoma</td>
<td>8 (28)</td>
<td>3 (20)</td>
<td></td>
</tr>
<tr>
<td>- Preventive</td>
<td>7 (24)</td>
<td>5 (33)</td>
<td></td>
</tr>
<tr>
<td>Colectomy procedure</td>
<td></td>
<td></td>
<td>0.137</td>
</tr>
<tr>
<td>- Open</td>
<td>14 (48)</td>
<td>7 (47)</td>
<td></td>
</tr>
<tr>
<td>- Total laparoscopic</td>
<td>5 (48)</td>
<td>4 (27)</td>
<td></td>
</tr>
<tr>
<td>- Hand-assisted laparoscopic</td>
<td>10 (7)</td>
<td>4 (27)</td>
<td></td>
</tr>
<tr>
<td>Stapled anastomosis</td>
<td>26 (90)</td>
<td>11 (73)</td>
<td>0.161</td>
</tr>
<tr>
<td>Abscess size (cm\textsuperscript{3})*</td>
<td>141 [15-222]</td>
<td>161 [74-257]</td>
<td>0.291</td>
</tr>
<tr>
<td>- Length (cm)#</td>
<td>4 [2-6]</td>
<td>4 [3-6]</td>
<td></td>
</tr>
<tr>
<td>- Height (cm)&amp;</td>
<td>7 [3-8]</td>
<td>6 [5-8]</td>
<td></td>
</tr>
<tr>
<td>- Width (cm)+</td>
<td>6 [3-7]</td>
<td>6 [4-7]</td>
<td></td>
</tr>
<tr>
<td>Primary diversion</td>
<td>3 (10)</td>
<td>4 (27)</td>
<td>0.207</td>
</tr>
<tr>
<td>Mortality</td>
<td>1 (3)</td>
<td>0</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Data are presented as median [IQR] or n (%). \*Fisher’s exact test (two-tailed) / \#Mann Whitney U test
*Measurement of the abscess size was possible in 18 patients in the conventional treatment group and 11 patients in the early surgical closure group. *All dimensions of the abscess cavity were measured from an abdominal CT-scan at their maximal size. #The length of the cavity was measured on the sagittal or axial plane &The height was measured on the sagittal or axial plane +The width of the cavity was measured on the coronal or axial plane.
stoma and a second period of Endo-sponge® treatment surgical closure was successful. In the conventional treatment group, three patients were primarily diverted during the RPC (10%) and the other 26 patients (90%) underwent secondary diversion after diagnosis of the leakage.

Early surgical closure

The Endo-sponge® was placed after a median of 2.0 days (iqr 0-8) following the diagnosis of anastomotic leakage. The Endo-sponge® treatment was continued for a median of 12 days (iqr 7-15), with a median of three (iqr 3-4) Endo-sponge® changes. After a median of 15 days (iqr 11-31) the anastomotic defect was surgically closed (Table 2). In two patients the surgical closure after Endo-sponge® treatment failed initially. A second period of Endo-sponge® treatment followed by surgical closure was successful in both of them.

Table 2 Treatment of anastomotic defect after IPAA

<table>
<thead>
<tr>
<th></th>
<th>Conventional treatment n = 28*</th>
<th>Early surgical closure n = 15</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time between diagnosis of leakage and surgical closure of defect (days)</td>
<td>15 [11-31]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time between diagnosis of leakage and observed closure of defect (days)</td>
<td>70 [49-175]</td>
<td>48 [25-103]</td>
<td>0.013</td>
</tr>
<tr>
<td>Time between pouch surgery and observed closure of defect (days)</td>
<td>84 [59-183]</td>
<td>59 [39-137]</td>
<td>0.081</td>
</tr>
<tr>
<td>Ileostomy reversed at end of follow-up</td>
<td>25 (89)</td>
<td>14 (93)</td>
<td>1.000†</td>
</tr>
<tr>
<td>Long term pouch dysfunction (%)</td>
<td>4 (14)</td>
<td>1 (7.1)</td>
<td>1.000†</td>
</tr>
</tbody>
</table>

Data are presented as median [IQR] or n (%). *Fisher’s exact test (two-tailed) / †Mann-Whitney test. *In one patients the pouch was excised due to adenocarcinoma

Anastomotic healing

Secondary anastomotic healing after 6 months was achieved in all 15 patients in the early surgical closure group compared to 16 out of the 29 patients (52%) in the conventional treatment group (P = 0.003). Secondary anastomotic healing was achieved in the early surgical group after a median of 48 days (iqr 25-103) compared to 70 days (49-175) in the conventional treatment group (P = 0.013). A chronic presacral sinus was present in none of the patients in the early surgical closure group versus two patients (7%) in the conventional treatment group (P = 0.542). Patients in the early surgical closure group were followed for a median of 25 months (iqr 12-39) versus a median 104 months (iqr 60-122) in the conventional treatment group (P < 0.001).

One pouch in the early surgical closure group had to be diverted again, due to persisting high defecation frequency and urgency incontinence. Therefore, early surgical closure of the anastomotic defect resulted in a functional pouch in 14 of the 15 patients (93%), in the conventional treatment group, the pouch was excised in one FAP patient.
due to the development of an adenocarcinoma, this patient was therefore excluded for the functional analysis. In the remaining 28 patients in the conventional treatment group, a presacral sinus persisted in four of the 28 patients (14%) after reversal of the ileostomy. Of these four patients, the persisting leakage resolved after extensive surgical treatment in one patient. The presacral sinus in the other three patients were observed during endoscopy but appeared to be not clinically relevant. Therefore, no treatment was instigated. In addition, one patient developed a dysfunctional pouch after stoma reversal in the conventional treatment group due to high defecation frequency. No diversion was performed in this patient. Thus, 24 of 28 patients (86%) in the conventional treatment group had a functional pouch at the end of follow up.

Cost analysis
The total treatment costs per patient were €27,627 (95% per cent c.i. €23,239 to €32,690) for the early closure group and €33,441 (95% per cent c.i. €24,955 to €46,728) for the conventional treatment group (P = 0.529). When patients with no observed secondary healed anastomosis and patients without ileostomy reversal are added with a follow-up of two years, the total direct medical costs were €27,879 (95% per cent c.i. €23,716 to €32,580) for the early surgical closure group, and €37,687 (95% per cent c.i. €27,592 to €51,007) for the conventional treatment group (P = 0.304).

DISCUSSION
Early surgical closure of a leaking IPAA following a short Endo-sponge® treatment resulted in a significantly higher percentage of secondary healed anastomosis at 6 months compared to the conventional treatment. Furthermore, early surgical closure significantly reduced the time to anastomotic healing with a median of 22 days compared to the conventional treatment. Early surgical closure resulted in a high percentage of functional pouches at the end of follow-up. Treatment costs per patient in both study groups were assessed and compared. This showed no differences in treatment costs.

Closing anastomotic leakage surgically is a paradigm shift, because traditionally this has been considered to fail by definition. The success of early surgical closure of the anastomotic defect as shown in the present study is probably explained by the preceding Endo-sponge® treatment, which resolves the pelvic sepsis behind the anastomosis. Subsequent surgical closure of the anastomotic defect is of great importance to prevent influx of mucus and debris in the cleaned cavity jeopardizing closure of the cavity. The short period of negative pressure via a vacuum drain is thought to be useful for drainage of contaminated fluids in the cavity enabling expansion of the pouch with collapse of the presacral cavity. Diversion of the pouch might be an essential component of this
treatment strategy, because if the anastomotic repair is not perfect the cavity will expand again due to the pressure of the intestinal contents. Closure failed initially in one of two patients without faecal diversion. The first results of early anastomotic reconstruction after a short period of Endo-sponge® treatment are very promising and compare favourably to the alternative strategies. Endo-sponge® treatment until closure as propagated by Weidenhagen has a mixed rate of success (56-94%)\(^7\). The median time of closure is more than 340 days in both patients undergoing low anterior resection and patients undergoing RPC\(^4\). Prolonged treatment using the Weidenhagen technique is associated with high costs due to a lot of Endo-sponge® exchanges and stoma materials\(^7\), and is a logistic burden. No statistical significant difference in direct medical costs in both treatment strategies was found. However, early surgical closure seems to be less expensive than the conventional treatment. This is most likely due to the higher costs in stoma materials and outpatient clinic visits.

The early surgical closure treatment was successful in all patients after 6 months but resulted in a non-functional pouch in one patient (7%) due to high defecation frequency and urge incontinence. In the conventional treatment group the treatment was only successful in 52% of the patients after 6 months and in four patients (14%) a dysfunctional pouch was present at the end of follow-up. A chronic presacral abscess or presacral sinus formation after leakage is held responsible for delayed anastomotic healing or the inability for ileostomy reversal\(^5\). If eventually the defect has healed and the stoma is closed, the function of the pouch can be compromised due to fibrosis and scarring. Therefore, we think that the time interval between diagnosis of anastomotic leakage and the duration of subsequent treatment is essential and effects long term functional outcome. Endo-sponge® treatment according to Weidenhagen showed to be more successful if the treatment was started within six weeks after initial surgery with colo-anal or ileo-anal anastomosis, which is significantly higher than a 38% success rate if started after six weeks\(^1\).

Ideally, pouch function was assessed with validated questionnaires to determine whether the pouch function of the early closure group is better preserved when the anastomotic leak is treated aggressively. We considered comparison with respect to function difficult due to the many confounders effecting pouch function e.g. the small group size, pouchitis, temporary ileostomy, mucosectomy and initial diagnosis.

This study is limited by the partially retrospective design. Definition of the moment of anastomotic healing in both groups was therefore difficult. In the prospective group all closures were checked endoscopically two weeks after surgical closure, while in the conventional group intermittent imaging was done to see whether the cavity was healed. This could have caused an overestimation of the time to heal.

Due to the difference in length of follow up the pouch failure rate of the early closure group might have shown more favourable, because it is well known that failure rates
increase over time. However, most of the failures were caused by the persistent sinuses that were prevented in the early closure group.

In conclusion, this study shows that early surgical closure after a short period of Endo-sponge® treatment is effective to treat anastomotic leakage after IPAA preventing chronic sinuses and permanent stomas.
REFERENCES


