Construction of an ileocolic neosphincter — Nipple valve anastomosis for prevention of postoperative recurrence of Crohn's disease in the neoterminal ileum after ileocecal or ileocolic resection. A long-term follow-up study

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Abstract

Objective: To test the effect of an ileocolic neosphincter—nipple valve anastomosis after ileocolic resection for Crohn's disease, on the clinical and surgical recurrence-free survival, in a long-term follow-up pilot study.

Background and aims: Fifty-nine patients, with Crohn's disease were operated on with an ileocecal or ileocolic resection and a nipple valve between 1993 and 2007.

Methods: The nipple valve is constructed by everting the neoterminal ileum for a length of 4–5 cm and stabilized with 3 or 4 longitudinal stapler rows (N=36) or only in a basal zone (N=23). The nipple is telescoped with the tip pointed into the colon and the base of the nipple anastomosed to colon. Follow-up at regular intervals included clinical evaluation, Harvey–Bradshaw index, laboratory tests, colonoscopy and small bowel radiology when appropriate.

Results: The perioperative mortality was nil. Early postoperative complications were: wound infection (N=4), anastomotic leak (N=1), reoperated, nipple ischemia (N=1) reoperated, enterocutaneous fistula (N=1). Clinical recurrence in the neoterminal ileum was after 1, 3, 4 and 5 years: 11%, 20%, 23% and 24%. Eleven patients (19%) were reoperated for recurrence in the neoterminal ileum after median 96 months follow-up. The cumulative reoperation rate was after 1, 3, 4 and 5 years: 4%, 13%, 13% and 16%, respectively.

Conclusion: The low clinical and surgical recurrence rate in the neoterminal ileum may suggest a protective effect of the neosphincter on postoperative recurrence of Crohn's disease. This result should be tested in a randomized controlled trial.

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1. Introduction

About 70% of patients need surgery during the first 10 years of Crohn’s disease and about 50% are likely to need repeat resection during a time period of 15 years. The risk of postoperative recurrence, i.e. symptomatic or radiological in ileal and ileocolic disease is reported to be 18–55% at 5 years and 40–76% at 10 years. After 1 and 3 years 72–93% of the patients already have endoscopic recurrent disease.

Recurrent disease is always confined to the aboral side of the ileocolic anastomosis, even after a second and third resection. It is suggested that coloileal reflux may be a contributory factor for anastomotic recurrence and that construction of an ileocolic neosphincter–nipple valve anastomosis may have a favourable effect in preventing anastomotic recurrence. This result encouraged me to initiate a prospective, uncontrolled pilot study between 1993 and 1997 including 25 patients, to test the effect of the nipple valve anastomosis after ileocecal or ileocolic resection for Crohn’s disease, on the clinical recurrence rate in the neoterminal ileum. The results of this pilot study are previously reported. In 1997 I tried to initiate a randomized controlled multicentre study comparing the nipple valve anastomosis vs. a conventional end-to-end anastomosis. Due to unwillingness of patients to be randomized to either group, this initiative failed. I then decided to extend the pilot study including more patients with a longer follow-up time for more reliable long-term results, as a basis for a new randomized trial. All patients operated on with a nipple valve anastomosis between 1993 and 2007 are included in this extended pilot study.

2. Patients and methods

Between January 1993 and September 2007, 59 patients, 30 males and 29 females with Crohn’s disease were operated on with an ileocecal or ileocolic resection. An ileocolic neosphincter–nipple valve was constructed in the ileocolic anastomosis. In all patients the diagnosis of Crohn’s disease was verified by histologic examination of resected specimens. All patients had terminal ileal disease or clinical recurrence in the neoterminal ileum. Patients with simultaneous macroscopically active disease of the duodenum, proximal small bowel and/or distal or total colitis which was not resected, were also included. Indication for resection was small bowel obstruction and/or penetrating disease with intractable pain. Eighteen patients were previously resected once, and six patients twice for Crohn’s disease. Characteristics of patients are given in Table 1. All patients were preoperatively classified according to the Vienna classification (Table 2).

2.1. Surgical procedures

Minimal ileocecal or ileocolic resection was performed with macroscopically free resection margins of 5–10 cm. In addition resection of the small bowel, colon and stricturoplasty has been performed. Fourteen patients were operated on laparoscopically assisted with mobilization of the bowel. The resection and construction of the nipple anastomosis was performed extracorporeally (Table 3).

2.2. Construction of the nipple anastomosis

After ileocecal or ileocolic resection, the neoterminal ileum is everted for a length of 2.5–3 cm used initially in the pilot study (9 patients) to 4–5 cm used in the remaining patients as the standard length of the nipple. The eversion is first secured with a single layer of continuous absorbable running suture (3-0 Vicryl, Ethicon). To prevent inversion or sliding, the nipple is stabilized with 3 (N=17) or 4 (N=19) longitudinal stapler rows along the whole length of the nipple used initially in the study. Based on reported experimental studies, in the last 23 patients the 3 stapler rows were applied only in a basal stabilization zone of 2–2.5 cm of the nipple, anastomosed to the colon with a distal unstabilized valve zone pointed into the colon. The stapler fork is introduced into the nipple lumen para- and antimesenterically (two and one stapler rows, respectively) after removal of the proximal staplers on the fork. Different longitudinal stapling instruments have been used (TL 455, TL 60, Knifeless Proximate–Ethicon Endosurgery, Cincinnati, Ohio, USA). The hand-sewn end-to-end anastomosis is performed by telescoping the nipple into the colon lumen and suturing the colon to the base of the nipple in a two-layer fashion. For both layers a continuous absorbable running suture is used (3-0 Vicryl, Ethicon, Norderstedt, Germany).

2.3. Postoperative prophylactic medical therapy against recurrent disease

Treatment with 5-ASA, mesalazine (Mesasa⁶, Smith Kline Beecham or Pentasa⁸, Ferring AS) was started simultaneously with intake of solid food before discharge from hospital. Initially a low dose of 0.75–1 g daily was used in three patients and increased to 2.5–3 g/daily as a standard dose for prophylaxis.

Table 1 Characteristics of patients.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>30 (51)</td>
</tr>
<tr>
<td>Female</td>
<td>29 (49)</td>
</tr>
<tr>
<td>Age at operation (years) (range)</td>
<td>Median 31 (16–71)</td>
</tr>
<tr>
<td>95% CI</td>
<td>31–37</td>
</tr>
<tr>
<td>Years with disease</td>
<td>Median 4 (0.3–33)</td>
</tr>
<tr>
<td>95% CI</td>
<td>5–9</td>
</tr>
<tr>
<td>Preoperative medical treatment for Crohn’s disease</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>8 (14)</td>
</tr>
<tr>
<td>Steroids</td>
<td>7 (12)</td>
</tr>
<tr>
<td>5-ASA</td>
<td>15 (25)</td>
</tr>
<tr>
<td>Steroids + 5-ASA</td>
<td>22 (37)</td>
</tr>
<tr>
<td>Azathioprin</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Steroids + 5-ASA + azathioprin</td>
<td>6 (10)</td>
</tr>
<tr>
<td>Extent of disease</td>
<td></td>
</tr>
<tr>
<td>Terminal ileum</td>
<td>22 (37)</td>
</tr>
<tr>
<td>Ileocolon</td>
<td>28 (48)</td>
</tr>
<tr>
<td>Upper gastrointestinal tract</td>
<td>9 (15)</td>
</tr>
</tbody>
</table>
Table 2  Classification of patients according to the Vienna classification of Crohn’s disease.

<table>
<thead>
<tr>
<th>Surgical procedure</th>
<th>No. of patients (%) (resection)</th>
<th>Surgical procedure</th>
<th>No. of patients (%) (resection)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ileocecal</td>
<td>27 (46) 10^a</td>
<td>Ileocecal + strictureplastic</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Ileocecal + small bowel</td>
<td>4 (7) 1^a</td>
<td>Ileocecal + colon</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Anastomotic recurrence</td>
<td>12 (20)</td>
<td>Right hemicolecotmy</td>
<td>6 (10) 1^a</td>
</tr>
<tr>
<td>Extended right hemicolecotmy</td>
<td>4 (7) 2^a</td>
<td>Subtotal colectomy</td>
<td>3 (5)</td>
</tr>
</tbody>
</table>

2.4. Follow-up

After discharge from the hospital all patients were followed-up regularly by clinical and laboratory examinations at 6-month intervals and additionally if any symptom or laboratory tests indicated a possible recurrence of disease. Symptoms were graded according to the Harvey–Bradshaw index of activity in Crohn’s disease,^{12} amended in accordance with bowel action by OMGE^{13} which reduces the scores from “number of liquid stools per day” to maximum five (ten or more motions a day). Scores of 4 or higher were considered to indicate clinical recurrence of disease. In addition elevation of ESR, leucocyte- and thrombocyte counts and CRP were used additionally to verify clinical recurrence. The intention was to perform postoperative colonoscopy in all patients after 1, 3 and 5 years to check up on any invagination or retraction of the nipple and for endoscopic recurrence, but unwillingness was a great problem. Endoscopic recurrence was in this study defined as recurrent lesions on the nipple and/or in the duct verified histologically by biopsy. Patients with signs and symptoms of clinical recurrence were examined by gastroduodenoscopy, colonoscopy before schedule, barium follow-through studies of the small bowel and eventually laparotomy for surgical treatment and to verify the site of recurrence. The first patient operated on in the pilot study died from cardiac disease and was 83 years old without clinical or endoscopic recurrence after nearly 12 years follow-up. The remaining 58 patients are all alive. The end of follow-up was in February 2008.

2.5. Statistics

Values for characteristics of patients are given as mean, median, range and 95% CI intervals. The clinical recurrence-free survival till recurrence in the neoterminal ileum and the surgical recurrence-free survival were described by Kaplan–Meier plots.^{14} Comparison between groups was made by log-rank test. A statistical significance of \( p<0.05 \) was assumed. All variables which may be related to postoperative clinical recurrence were analyzed by univariate analyses (chi-square, Fisher exact test, Mann–Whitney test) or a proportional hazard (Cox) regression model when appropriate. Significant variables from the univariate analyses were tested in a multiple Cox regression model. The risk factors assessed were: gender, age at diagnosis and operation, years with disease, preoperative medication for Crohn’s disease, location of disease, behaviour of disease (stricturing, penetrating, nonpenetrating), tobacco, previous resections, laparoscopic vs. open surgery, nipple length, number of stapler rows, basal vs. longitudinal staplers, resection margin, early postoperative morbidity, postoperative medical prophylaxis and endoscopic recurrence. The calculations were performed with the Statistica program package (Statsoft, Inc, Tulsa, Okla, USA).

2.6. Ethical considerations

The study was performed in accordance with the ethical standards of the Helsinki Declaration of 1975. All patients were given full information about the nipple procedure and a conventional end-to-end anastomosis and had the option to choose either type of operation. Full and informed consent has been obtained from all patients operated on between 1993 and 2007. Included in the information after 1997 were the results of the pilot study.^{9}

3. Results

3.1. Early postoperative morbidity

The perioperative mortality was nil. One patient was re-operated for a small anastomotic leak. Postoperative bowel action was not normalized after 12 days in another patient where reoperation revealed oedema of the nipple anastomosis and ischemia by microscopic examination. Four patients had wound infections, one deep and three superficial.

3.2. Clinical recurrence — univariable and multivariable analyses

The clinical recurrence rates according to site of recurrence are given in Table 4. The clinical recurrence-free survival till
recurrence in the neoterminal ileum is given in Fig. 1. The median and mean times to clinical recurrence of neoterminal ileal disease were 84 months and 79 months, respectively.

The clinical recurrence-free survival in the neoterminal ileum did not differ according to age (<40 years vs. ≥40 years), between stricturing and penetrating disease or between location of disease (terminal ileum, ileocolon, upper GI-tract).

Colonoscopy of the nipple valve anastomosis with biopsy was performed in 32 patients after a median time of 17 months. A second and third colonoscopy was performed only in 23 and 14 patients, respectively. Endoscopic recurrence in the nipple valve anastomosis was found in 7 of 32 patients (22%). All inspected nipples were intact without any sign of invagination or retraction. The colonoscope could not pass through the nipple duct to the neoterminal ileum in any case. Of patients with endoscopic recurrence four of seven patients (57%) had clinical recurrence in the neoterminal ileum vs. 5 of 25 (20%) with normal endoscopy after 17 months (p=0.05).

In spite of advice not to smoke tobacco, 27 patients (46%) continued tobacco smoking after surgery. Twenty-seven (46%) were nonsmokers and in five patients (8%), the use of tobacco was unknown. The clinical recurrence rate in the neoterminal ileum was higher in smokers vs. non smokers, 37% vs. 11% (p=0.03).

Table 4 Clinical recurrence in the neoterminal ileum, upper GI-tract and colon after ileocecal or ileocolic resection.

<table>
<thead>
<tr>
<th>Year after surgery</th>
<th>No. of patients (%)</th>
<th>Neoterminal ileum</th>
<th>Small bowel</th>
<th>Colon</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 N=55</td>
<td>6 (11)</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>2 N=47</td>
<td>8 (17)</td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>3 N=40</td>
<td>8 (20)</td>
<td>4</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>4 N=39</td>
<td>9 (23)</td>
<td>5</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>5 N=37</td>
<td>9 (24)</td>
<td>5</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>6 N=34</td>
<td>10 (29)</td>
<td>5</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>10 N=20</td>
<td>11</td>
<td>5</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>15 N=2</td>
<td>13</td>
<td>5</td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1 Clinical recurrence-free survival till recurrence in the neoterminal ileum after ileocecal or ileocolic resection of Crohn’s disease.

Figure 2 Surgical recurrence-free survival including all recurrences and recurrence in the neoterminal ileum.

Forty-one patients (70%) have used 5-ASA as long-term treatment. Eighteen patients (30%) refused to use 5-ASA due to pregnancy (N=2) or unwillingness. Compliance with 5-ASA prophylaxis has been fairly well even after long-term follow-up without clinical recurrence. The clinical recurrence-free survival did not differ by using 5-ASA prophylactically or not, 20% vs. 28%, (p=0.4).

The single risk factor for clinical recurrence in the neoterminal ileum was: tobacco smoking (p=0.03). Endoscopic recurrence in the nipple valve anastomosis may have an effect (p=0.05: power=0.5). A laparoscopic procedure had no effect on the clinical and surgical recurrence rate.

3.3. Surgical recurrence

In all twenty-one patients (36%) were reoperated, 16 patients (27%) for clinical recurrence in all locations. The site of recurrence was finally judged at the reoperation. In all eleven patients (19%) were reoperated for recurrence in the neoterminal ileum during a median of 96 months follow-up. The median time to reoperation for recurrent neoterminal ileal disease was 58 months. The cumulative 1, 3, 4, 5 and 6 year recurrence rates in the neoterminal ileum requiring surgery were: 4%, 13%, 13%, 16% and 24%, respectively. The surgical recurrence-free survival including all recurrences and recurrence in the neoterminal ileum is given in Fig. 2.

4. Discussion

4.1. Early postoperative morbidity

Mortality rates of 2–2.7% after resection of Crohn’s disease are previously reported from Sweden and Norway.15,16 The mortality was nil in this study. Two postoperative complications required reoperation. One had a minor anastomotic leak and one patient had ischemia of the nipple anastomosis. High complication rates are reported in Crohn’s disease with anastomotic leaks of 2–17% and wound infections of 2–37%.17–20 The corresponding results of the present study were 2% and 7%. Yamamoto et al.21 found a lower rate of anastomotic leak after a stapled end-to-end anastomosis vs. sutured end-to-end anastomosis (2% vs. 8%) and recommend use of stapled anastomosis. The leak rate of this study with sutured anastomosis is comparable with his stapled group.
4.2. Clinical and endoscopic recurrence

The recurrence rate in the neoterminal ileum in this study was after 1, 3, 4 and 5 years, 11%, 20%, 23% and 24%. Rutgeerts et al.4 and Olaison et al.5 found clinical anastomotic recurrence of 20–37% after 1 year and 34–86% after 3 years. In a recent study 49% of the patients developed clinical recurrence within 3 years.22 Muñoz-Juárez et al.23 reported after conventional end-to-end anastomosis 57% clinical recurrence after median 70 months follow-up and 24% after wide-lumen stapled anastomosis —median follow-up 46 months. The clinical recurrence rate in the neoterminal ileum of the present study is low compared with these reports4,5,22 and comparable with the results of the wide-lumen-stapled anastomosis group.23

4.3. Type of anastomosis, anastomotic recurrence and reoperations

After ileocecal or ileocolic resection different anastomotic configurations have been used, i.e. sutured or stapled end-to-end, end-to-side, side-to-end or side-to-side. A recent meta-analysis revealed no significant difference between the different anastomotic configurations in anastomotic recurrence and reoperations due to recurrence.24 The reoperation rate for clinical recurrence in the neoterminal ileum in this study was 16% after 5 years follow-up. In recent studies comparing laparoscopic and open resection, Eshuis et al.25 and Stocchi et al.26 report reoperation rates for recurrent disease of 22% and 26% in the laparoscopic group and 23% and 28% in the open group. Median and mean follow-up was 8.5 and 10.5 years, respectively. Lowney et al.27 reports surgical recurrence in 9.5% in the laparoscopic group and 24% after open resection. The mean follow-up of this study was 63 and 82 months, respectively. The median times to recurrence were 60 and 62 months, respectively. The median time to surgical recurrence in the present study was 58 months. A laparoscopic procedure in the present study had no effect on the clinical and surgical recurrence rates. Muñoz-Juárez et al.23 report reoperation rates of 26% after conventional sutured end-to-end anastomosis and 4% after wide-lumen stapled anastomosis. Median follow-up was 70 and 46 months, respectively. The results of the present study were 24% and 13% after 72 and 48 months, respectively. The clinical recurrence rate in the wide-lumen stapled anastomosis group in this study21 was comparable with the present study (24% vs. 23%), but the reoperation rate is substantially lower. The narrow duct of the nipple valve anastomosis may explain the discrepancy between the clinical and surgical recurrence rates. But the meta-analysis reported by Simillis et al.24 including all comparative studies published between 1992 and 2005 including 259 patients with stapled side-to-side anastomosis, revealed comparable clinical and surgical recurrence rates compared to end-to-end anastomosis. The ileocolic valve is a true sphincter28 and resection of this sphincter shortens the small intestinal transit time with about 3 h independent of an additional resection of the distal ileum.29 Kellogg30 was the first surgeon to construct an artificial ileocolic sphincter. Resection of the ileocolic sphincter combined with resection of small bowel results in coloileal reflux and colonization of the small bowel with colonic microorganisms which increase small intestinal permeability and precede clinical relapse of Crohn’s disease.31–37 The hypothesis of the present study is that prevention of coloileal reflux by construction of a neosphincter may prevent recurrence in the neoterminal ileum. Experimental studies in dogs comparing conventional ileocolic anastomosis and nipple valve anastomosis for prevention of short bowel syndrome, has revealed a significant decrease in bacterial contamination in the neoterminal ileum proximal to the nipple valve, one and ten millionfold lower concentration of aerobic and anaerobic bacteria, respectively.31–34,38,39 The Nipple valve anastomosis increased intestinal transit time and improved diarrhoea and malnutrition.32 For patients with Crohn’s disease with surgical recurrence and short bowel after previous resections, this additional effect of the nipple valve may be valuable. In addition to coloileal reflux and bacterial contamination of the neoterminal ileum, there is an aboral factor in the fecal stream for recurrence.30,41 We found no difference in the clinical or surgical recurrence rates between stricturing and penetrating disease in accordance with others.2 Tobacco smoking was also found in this study as an independent significant risk factor for recurrence.41 Postoperative prophylaxis with 5-ASA was not found in this study to have any effect on the recurrence rate in accordance with other reports.2,42 In a recent study Pallotta et al.43 detected coloileal reflux in 59% of investigated patients after ileocecal resection of patients with Crohn’s disease with a side-to-side anastomosis. Reflux was found in 75% of patients with recurrence in the neoterminal ileum vs. 36% in patients without recurrence, judged by endoscopy and SICUS (contrast ultrasound). This study supports the hypothesis that coloileal reflux is related to recurrence.

5. Conclusion

Construction of an ileocolic neosphincter–nipple valve anastomosis is a safe procedure with low early postoperative morbidity and low clinical and surgical recurrence rates. The results of this extended long-term study suggest that the nipple valve anastomosis with three basal stapler rows, now should be tested against a conventional anastomosis, e.g. an end-to-end sutured anastomosis and a wide-lumen side-to-side stapled anastomosis in a randomized controlled trial.

6. Sources of support

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References


