Long-term prevention of post-operative recurrence in Crohn's disease cannot be affected by mesalazine

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Received 13 October 2008; received in revised form 10 December 2008; accepted 11 December 2008

KEYWORDS
Crohn's disease; Post-operative recurrence; Clinical recurrence; Surgical recurrence; Mesalazine

Abstract

Background: Prevention of post-operative recurrence has a central role in the management of Crohn's Disease (CD). Many drugs have been evaluated in prospective randomised controlled trials (RCTs) but the results are disappointing. Mesalazine, the drug more extensively investigated, has been shown to be effective for preventing recurrence in the short-term; however, the overall benefit is small and no data are available on the long-term effectiveness.

Aim: To compare the long-term occurrence of post-operative recurrence in patients who received regular prophylactic treatment with mesalazine with patients who did not receive prophylaxis after the first radical resection for ileo-caecal CD.

Patients and methods: The records of 216 patients with ileo-caecal CD at their first resection were reviewed: 146 patients (67.6%) received post-operative prophylaxis with mesalazine while 70 patients (32.4%) received no prophylaxis. Allocation of patients in the two groups was determined by patients' preferences and by different policies in the post-operative prophylactic approach. The mean follow-up after surgery was 153.7 months (range 12–544). The co-primary endpoints were post-operative clinical and surgical recurrence. Statistical analysis: Kaplan–Meier survival method, Chi-square, Student t-test.

Results: The two groups were comparable with regard to gender, age at surgery, smoking habits, pattern of CD (perforating/not perforating), and disease duration before surgery. One year after surgery, a small, not statistically significant, risk reduction in clinical recurrence was observed in mesalazine treated group (−7.6%; 95% CI −18.0% to 2.8%). Within 10 years after surgery, the cumulative probability of clinical recurrence and surgical recurrence were similar in the two groups (Log Rank test p=0.9 and p=0.1 respectively).

Conclusion: Mesalazine prophylaxis is not effective for preventing the long-term post-operative recurrence in ileo-caecal Crohn's disease.

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do:10.1016/j.crohns.2008.12.001
1. Introduction

Most patients with Crohn’s disease (CD) will require surgery during the course of their disease. However, surgery is not curative and post-operative recurrence is quite inexcusable. It has been reported that one year after resection, 60–80% of patients have new lesions at the neo-terminal ileum (endoscopic recurrence), 10–20% will develop symptoms (clinical recurrence) and 5% will need further intestinal resection (surgical recurrence).1,2 After 10 years, approximately 50% of patients will experience clinical recurrence and 35% will need re-operation.3

Prevention of post-operative recurrence is therefore considered to be a central problem in the management of CD.4 Several drugs have been evaluated as prophylactic treatment in randomised controlled trials (RCTs) and meta-analysis: these include mesalazine,5–12 antibiotics (metronidazole and ornidazole),13,14 budesonide,15–17 azathioprine or mercaptopurine,18,19 interleukin-10,20 and, more recently, probiotics.21–23

Mesalazine is the drug more extensively evaluated. Several RCTs have been published from 1994 to 2000.5–9 A meta-analysis published in 1997,10 and subsequently updated in 200011 and 2002,12 showed a little but significant effect of mesalazine for reducing clinical recurrence. The overall risk difference (RD) is –10% (95% CI – 16.9% to –3.2%; p=0.0041), and the number of patients needed to treat (NNT) to prevent one recurrence is 10. A more relevant effect has been reported for preventing endoscopic recurrence and, in particular, severe endoscopic recurrence, with an overall reduction of risk of 18% and of 20%, respectively.2,12 A meta-regression of all the studies published has shown that prolonged disease duration and ileal location are predictors of better response.10 It is not clear which is the optimal dose of mesalazine for maintaining remission in CD, it has been shown that pH 7-dependent mesalazine seems to be more effective than pH 6-dependent and controlled release formulations.25

Based on the available evidence (evidence grade A), major guidelines from the British Society of Gastroenterology26 the European Crohn’s and Colitis Organisation,27 and the American College of Gastroenterology28 recommend post-operative prophylactic treatment with mesalazine for at least 18–24 months after surgical resection. Nevertheless, some authors continue to not recommend regular post-operative prophylaxis for all patients.29,30 The efficacy of prophylactic treatment with mesalazine has been extensively investigated in the short-term after surgery (1–3 years) while no data are available on the long-term.

The aim of the present study was, therefore, to evaluate the long-term occurrence of post-operative recurrence comparing patients who received regular mesalazine treatment with patients who did not receive any prophylactic treatment after the first radical resection for ileo-caecal CD.

2. Patients and methods

The records of 679 patients with established diagnosis of CD referred to our two GI Units in Rome (Gastroenterology Unit, San Filippo Neri Hospital, Rome, Italy and Department of Clinical Sciences, University of Rome “La Sapienza”, Rome, Italy) were retrospectively reviewed. Patients who had undergone at least one radical surgical resection for ileal disease (with or without right colon involvement), and with at least one year of post-operative follow-up, were included in the study. According to mesalazine prophylactic treatment of post-operative recurrence patients were divided into two groups:

- Group 1: patients who had received continuation post-operative prophylactic treatment with mesalazine;
- Group 2: patients who had not received any post-operative prophylactic treatment.

Allocation of patients in the two groups was determined by patients’ preferences and by different policies in the post-operative prophylactic approach. In our current clinical practice, after ileo-caecal resection for CD, we encourage all patients to stop smoking and start mesalazine 2.4 g/day within 2 weeks after operation. Prophylactic treatment is maintained for at least 2 years, but generally it is continued indefinitely or until severe endoscopic recurrence or clinical recurrence occurs. This strategy is discussed with each patient and information concerning the little benefit of mesalazine is given. As a consequence, some patients prefer to be off tablets in the post-operative setting, after a long pre-operative history of medical treatment. In addition, some patients were referred to our institutions months or years after operation performed in other hospitals where post-operative prophylactic treatment was not applied. Few patients that were started on mesalazine and did not tolerate the medication were allocated in group 2. Clinical and demographic characteristics of all patients were recorded: gender, age at the time of surgery, smoking habits, pattern of CD according to the surgical specimen (penetrating/not penetrating), disease duration (from diagnosis to surgery) and timing of surgery (before or after 3 years from diagnosis).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Flow chart of the study.</th>
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<tbody>
<tr>
<td>Patients reviewed</td>
<td>679</td>
</tr>
<tr>
<td>Ileo-caecal CD with at least 1 “radical” resection (eligible population)</td>
<td>222/679 (33%)</td>
</tr>
<tr>
<td>Complete follow up data: at least 1 year of follow up (included in the analysis)</td>
<td>216/222 (97%)</td>
</tr>
<tr>
<td>Post-operative 5-ASA prophylaxis (group 1)</td>
<td>146 (67.6%)</td>
</tr>
<tr>
<td>No post-operative 5-ASA prophylaxis (group 2)</td>
<td>70 (32.4%)</td>
</tr>
<tr>
<td>Mean post-operative follow up months (range)</td>
<td>153.7 (12–544)</td>
</tr>
</tbody>
</table>
The post-operative course of all patients was retrospectively evaluated. Two primary end points were considered: clinical recurrence and surgical recurrence. Clinical recurrence was defined as the reappearance of symptoms requiring steroids (systemic corticosteroids or budesonide) in the presence of endoscopic and/or radiologic recurrence; surgical recurrence was defined as the need of re-operation.

2.1. Statistical analysis

The two groups were compared according to the clinical variables. Categorical and continuous variables were analysed using Chi-square test and Unpaired t test, respectively. Odds ratio (OR) was given with 95% confidence intervals (95%CI) and two-sided p-values. A p-value <0.05 was considered statistically significant.

The Kaplan–Meier survival method was used to estimate the cumulative probability of a post-operative course free of clinical recurrence and surgical recurrence. Differences between curves were tested using the Log-Rank test. Stats Direct statistical tools (Copyright © 1990–2001) was used for all calculations. Results were also checked using Epistat (copyright © Epistat Services, 1991).

3. Results

The records of 679 CD patients were reviewed. Out of these, 222 (33%) underwent at least one surgical resection for ileal disease with or without right colon involvement, and were eligible to be included in the study. Six patients were excluded for incomplete data regarding post-operative follow-up (less than 12 months). Therefore 216 patients were included in the analysis (97.3% of the eligible population). Out of these 216 patients, 146 (67.6%) received post-operative mesalazine prophylactic treatment (group 1), and 70 (32.4%) did not receive any prophylactic treatment (group 2). Mean follow-up after surgical resection was 153.7 months (range 12–544) (Table 1).

The clinical characteristics of patients are shown in Table 2. The two groups were comparable as the gender, age at surgery, smoking habits, pattern of CD according to surgical specimen (perforating or not perforating), disease duration and timing of surgery.

3.1. Short term post-operative course

Within one year after surgery, a clinical recurrence occurred in 29 of 216 patients (13.4%; 95%CI 9.2%–18.7%); 16 of 146 in group 1 (11%; 95%CI 6.4%–17.2%) and in 13 of 70 in group 2 (18.6%; 95% CI 10.2%–29.6%). The risk reduction (RR) of clinical recurrence within 1 year in group 1 was −7.6% (95% CI −18.0% to 2.8%) with an odds ratio (OR) of 0.52 (95%CI 0.23–1.20). Only 1 patients (group 1) required re-operation within 1 year after the first resection.

3.2. Long term post-operative course

Within 120 months after surgery, 86 of 216 patients (39.8%; 95% CI 33.2%–46.6%) had clinical recurrence and 38 (17.6%; 95%CI 12.7%–23.3%) had surgical recurrence. The cumulative probability of a post-operative course without clinical recurrence, in the whole patient population, was 78.5%, 69.8%, 58.8%, 50.7% after 30, 60, 90, 120 months respectively. The cumulative probability of a post-operative course without surgical recurrence was 97.0%, 96.4%, 85.8%, 71.8% after 30, 60, 90, 120 months respectively (Fig. 1).

The cumulative probability of a post-operative course without clinical and surgical recurrence, in groups 1 and 2, is

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Clinical characteristics of patients.</th>
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<tbody>
<tr>
<td></td>
<td>All pts</td>
</tr>
<tr>
<td></td>
<td>n. 216</td>
</tr>
<tr>
<td>Age at surgery (years) mean (range)</td>
<td>35.6 (12–78)</td>
</tr>
<tr>
<td>Sex (F/M)</td>
<td>96/120</td>
</tr>
<tr>
<td>Smoking habits</td>
<td>126/90</td>
</tr>
<tr>
<td>Yes/no or ex</td>
<td>(58%/42%)</td>
</tr>
<tr>
<td>Disease duration (months) Diagnosis-surgery: mean (range)</td>
<td>34.7 (0–438)</td>
</tr>
<tr>
<td>Time of surgery (&lt;3 years/&gt;3 years from diagnosis)</td>
<td>154/62 (71%/29%)</td>
</tr>
<tr>
<td>Perforating/non perforating</td>
<td>101/115 (47%/53%)</td>
</tr>
<tr>
<td>Post-operative 5-ASA (yes/no)</td>
<td>146/70 (68%/32%)</td>
</tr>
</tbody>
</table>

a Unpaired t-test.
A total of 28 patients (13%) received also immunomodulators (azathioprine or mercaptopurine) during the post-operative course. No difference was observed between group 1 and group 2 regard immunomodulators treatment.

The long term impact of prophylactic treatment with mesalazine was analysed stratifying patients according to five clinical variables at the time of first resection: gender, age at surgery (<40 years vs ≥40 years), smoking habits, duration of disease before surgery (<3 years vs ≥3 years), and pattern of CD according to surgical specimen (penetrating or not penetrating). No statistically significant difference in the cumulative probability of clinical and surgical recurrence was observed between the two groups. No difference was observed between the two groups regarding the cumulative probability of clinical and surgical recurrence within 120 months after surgery (Log Rank test \( p = 0.9 \) and \( p = 0.1 \) respectively).

Indication for re-operation (i.e. not penetrating or penetrating disease) was the same of that of first resection in 71.4% of the entire patient population. The same figure was observed in group 1 and group 2 (61% and 77% respectively; \( p = 0.5 \)).

Figure 1  Cumulative probability of a post-operative course without clinical and surgical recurrence within 10 years in the entire patient population. The cumulative probability of a course without clinical recurrence is 78.5%, 69.8%, 58.8%, 50.7% after 30, 60, 90, 120 months respectively. The cumulative probability of a course without surgical recurrence is 97.0%, 96.4%, 85.8%, 71.8% after 30, 60, 90, 120 months respectively.

Figure 2  Cumulative probability of a 10 years post-operative course without clinical and surgical recurrence in patients who had received prophylactic treatment with mesalazine (group 1) and in patients who had not received any prophylaxis (group 2). No difference is observed between the two groups.
4. Discussion

While data on the prevention of short-term (1–3 years) post-operative recurrence are numerous but conflicting, data on long-term are entirely lacking. The aim of this study was, therefore, to assess the impact of mesalazine prophylactic treatment on the long-term post-operative recurrence of CD, comparing patients who had received with patients who had not received mesalazine after surgery. Although this study is limited by its retrospective and non-randomised design, some important aspects should be taken into consideration. The patient population studied was homogeneous, including only patients with ileal or ileo-caecal CD who had undergone their first radical resection. These inclusion criteria allowed us to select a specific patient population in which a better response to mesalazine prophylaxis could be expected.\textsuperscript{9,10} The mean post-operative follow-up was considerably long (153.7 months; range 12–544), and complete data (at least one year follow-up) were available for 97% of the eligible patient population. This reduced the common source of bias due to loss to follow-up. Primary end points (clinical recurrence and surgical recurrence) were well defined and clinically relevant. The two groups of patients (receiving and not receiving mesalazine) were comparable as the gender, age at surgery, smoking habits, pattern of CD according to surgical specimen (perforating or not perforating), and disease’s duration before surgery, and timing of surgery (<3 years or ≥3 years from diagnosis).

The short-term overall clinical recurrence rate in the whole patient population (patients receiving or not receiving mesalazine) was 13.4% (95%CI 9.2%–18.7%), a figure similar to that reported in the literature.\textsuperscript{1,2} We have defined clinical recurrence as the need of steroids to treat symptomatic disease in the presence of documented morphological (endoscopic or radiological) recurrence. This definition, although restrictive, appears to be clinically relevant as it takes into account only patients with a moderate to severe recurrence requiring a steroid course.

Patients receiving mesalazine had a small RR of clinical recurrence within 1 year after surgery (−7.6%; 95% CI −18.0% to 2.8%). The RR is not statistically significant, but, as an absolute value, it is similar to the RR reported in the meta-analysis which is, conversely, statistically significant (RR −10%; 95% CI −16.9% to −3.2%; p = 0.0041).\textsuperscript{11} Considering the NNT as a measure of the therapeutic effect, we can calculate a NNT of 13 in our patient population that is very close to the NNT of 10 reported in the meta-analysis.\textsuperscript{11} The lack of statistical significance in our study can be explained by the small sample size (216 patients) compared to the sample size of the meta-analysis which includes more than 700 patients enrolled in 5 RCTs.\textsuperscript{11}

As far as concern the long term post-operative course, approximately 50% of the whole patients population are free of clinical recurrence over 10 years, and more than 70% will not require re-operation. These figures are similar to those recently reported by others and confirm that surgery alone is an excellent treatment for patients with isolated ileo-caecal CD.\textsuperscript{31} In the long-term, no protective effect of mesalazine could be detected regarding the cumulative probability of clinical and surgical recurrence within 10 years. In other words, patients receiving and not receiving mesalazine prophylaxis after surgery have the same probability of experiencing a moderate to severe clinical recurrence requiring steroids within 10 years after resection, and have the same probability of developing refractory or complicated disease requiring re-operation. Considering that CD is currently not a curable disease, and patients are faced with a lifetime disease course, we should conclude that mesalazine prophylaxis has no long-term impact on the post-operative recurrence.

References


