Delayed surgery for acute severe colitis is associated with increased risk of postoperative complications

J. Randall[1], B. Singh[1], B. F. Warren[2], S. P. L. Travis[3], N. J. Mortensen[1] and B. D. George[1]

Departments of [1]Colorectal Surgery, [2]Cellular Pathology and [3]Gastroenterology, John Radcliffe Hospital, Oxford, UK
Correspondence to: Mr B. D. George, Department of Colorectal Surgery, John Radcliffe Hospital, Oxford OX3 9DU, UK
(e-mail: brucegeorge@doctors.org.uk)

Background: This study determined the long-term outcome after colectomy for acute severe ulcerative colitis (ASUC) and assessed whether the duration of in-hospital medical therapy is related to postoperative outcome.

Methods: All patients who underwent urgent colectomy and ileostomy for ASUC between 1994 and 2000 were identified from a prospective database. Patient details, preoperative therapy and complications to last follow-up were recorded.

Results: Eighty patients were identified, who were treated with intravenous steroids for a median of 6 (range 1–22) days before surgery. Twenty-three (29 per cent) also received intravenous ciclosporin. There were 23 complications in 22 patients in the initial postoperative period. Sixty-eight patients underwent further planned surgery, including restorative ileal pouch–anal anastomosis in 57. During a median follow-up of 5·4 (range 0·5–9·0) years, 48 patients (60 per cent) developed at least one complication. Patients with a major complication at any time during follow-up had a significantly longer duration of medical therapy before colectomy than patients with no major complications (median 8 *versus* 5 days; *P* = 0·036).

Conclusion: Delayed surgery for patients with ASUC who do not respond to medical therapy is associated with an increased risk of postoperative complications.

Introduction

Acute severe ulcerative colitis (ASUC) is defined as a bloody stool frequency of six or more times per day and at least one of the following: tachycardia over 90 beats per min, temperature exceeding 37·8°C, haemoglobin less than 10·5 g/dl or erythrocyte sedimentation rate over 30 mm/h[1]. ASUC potentially carries a high risk of death, but the introduction of intensive intravenous steroid treatment, reported in 1955, reduced acute mortality from 24 to 7 per cent[1]. Timely surgery in conjunction with intensive medical therapy further reduced the mortality rate to less than 1 per cent in specialist centres[2–6]. However, with the advent of rescue medical therapy for steroid failure with ciclosporin or infliximab, surgery is under scrutiny.

Surgery is carried out after failure of medical therapy, the standard approach being colectomy with end-ileostomy formation and preservation of the rectum. Many patients go on to have later restorative surgery with an ileal pouch–anal anastomosis (IPAA). This means that postoperative complications can accumulate. Analysis of regional and national mortality statistics suggests that the threshold for elective colectomy for inflammatory bowel disease may be too high[7]. This has raised questions about criteria for, and the optimal timing of, surgery. The aim of this study was to determine the long-term outcome after colectomy for ASUC and to assess whether the duration of medical therapy before colectomy is related to long-term morbidity.

Methods

All patients undergoing emergency colectomy for severe ulcerative colitis between January 1994 and December 2000 were identified from a prospective colorectal database.

Names were checked against stomatherapy, theatre and pathology records to ensure that no patient was omitted. ASUC was defined according to Truelove and Witts' criteria[1]. Patients undergoing elective surgery for ulcerative colitis and those undergoing colectomy for known Crohn's disease or infective colitis were excluded from the study. Patients with indeterminate colitis and those who subsequently turned out to have Crohn's colitis were analysed separately. Clinical details up to the last outpatient visit were obtained.

The following information was recorded: patient demographics, duration of colitis before index admission, medical co-morbidity, length of hospital stay before colectomy, medical treatment, indication for surgery, surgical details, complications, length of hospital stay, histopathology and subsequent surgery. Complications were defined as early if occurring within 30 days of surgery, or late if developing subsequently. Complications were identified from a prospective database and confirmed through individual retrospective chart review by two independent assessors.

Statistical analysis

Data are presented as median (range) unless indicated otherwise. Univariable analysis was performed using Mann–Whitney U test for continuous variables, and χ^2 and Fisher's exact tests for categorical variables. Multivariable logistic regression analysis was used to identify factors associated with postoperative morbidity. All statistical analysis was performed using SPSS® version 17 (SPSS, Chicago, Illinois, USA).

Results

Eighty patients (42 male; median age 37 (range 10–80) years) were identified. Median follow-up was 5·4 (range 0·5–9·0) years; 60 patients (75 per cent) were followed up for more than 4 years.

Preoperative medical details

The median duration of colitis was 3 (range 0–30) years. The median number of hospital admissions with colitis before the index admission leading to colectomy was 1 (range 0–6). For 28 patients (35 per cent), the index admission was their first admission with severe colitis. Twenty patients had medical co-morbidity (American Association of Anesthesiologists grade II, 13; grade III, seven).

All patients received high-dose intravenous steroids, started early after admission. Twenty-three (29 per cent)

received intravenous ciclosporin (4 mg/kg for a median of 3 days). No patient had infliximab (all were treated before 2001). Patients underwent medical therapy for a median of 6 (range 1–22) days before colectomy. All underwent surgery because the colitis failed to resolve with medical therapy. Two patients had features of toxic megacolon, but none had a perforation.

Operative details and histopathology

All patients had an open colectomy with ileostomy formation. Histopathological examination of the resected colon showed ulcerative colitis in 64 patients and indeterminate colitis[8] in 16. One patient had severe dysplasia and one had a T2 N0 carcinoma. Two patients were noted to have a carcinoid tumour in the appendix. Two patients had their diagnosis revised to Crohn's disease during follow-up; both had indeterminate colitis in the colectomy specimen, with subsequent progressive perianal disease consistent with Crohn's disease. Median postoperative stay in hospital was 9 (range 4–171) days. Seven patients stayed in hospital for more than 21 days after colectomy.

Subsequent elective surgery

Further planned surgery was undertaken in 68 patients. Fifty-seven patients underwent IPAA, a median of 8 (range 3–46) months after emergency colectomy. Forty-six had a covering ileostomy, which was subsequently closed in 44 patients a median of 5 (range 2–15) months after pouch surgery. Eleven patients had a completion proctectomy and permanent ileostomy at a median of 16 (range 5–55) months after emergency colectomy. The principal reasons for choosing proctectomy rather than restorative surgery were: patient choice (seven), co-morbidity (three) and poor sphincter function (one). Twelve patients did not have an IPAA or completion proctectomy, for the following reasons: died from unrelated pathology (three), postponed at patient request (three), major complications after colectomy (two) or unclear (four).

Mortality and morbidity

The operative mortality rate was zero. Three patients died during follow-up from unrelated causes (lung carcinoma, one; ovarian carcinoma, one; stroke, one).

Forty-eight patients (60 per cent) experienced a complication during follow-up, including the initial colectomy and further planned surgery (*Table 1*). There were 23 early complications, within 30 days of surgery, in 22

Table 1 Complications at any time during follow-up after initial colectomy

	No. of patients (n = 80)
Wound infection	10 (13)
Intra-abdominal abscess	8 (10)
Pneumonia	3 (4)
Septicaemia	3 (4)
Symptomatic proctitis in rectal remnant	2 (3)
Small bowel obstruction	21 (26)
Resolved	14 (18)
Reoperated	7 (9)
Ischaemic bowel	2 (3)
Deep vein thrombosis	2 (3)
Incisional hernia	3 (4)
Anastomotic leak (pouch)	1 (2)
Pouchitis	7 (12)
High ileostomy output	4 (5)

Values in parentheses are percentages.

Table 2 Complications within 30 days after colectomy

	No. of patients (n = 80)
Wound infection	2 (3)
Intra-abdominal abscess	4 (5)
Pneumonia	3 (4)
Septicaemia	3 (4)
Small bowel obstruction	
Resolved	3 (4)
Reoperated	2 (3)
Wound dehiscence	2 (3)
Deep vein thrombosis	2 (3)
High ileostomy output	2 (3)

Values in parentheses are percentages.

Table 3 Emergency operations at any time during follow-up after colectomy

	No. of patients
Laparotomy for adhesions	7
Laparotomy for ischaemic bowel	2
Repair of parastomal herniation of small bowel loops	2
Refashioning ileostomy	2
Incisional hernia repair	2
Laparotomy for anastomotic leak	1
Abscess drainage	4
Examination under anaesthetic	7
Below-knee amputation	1

Fig. 1 Rate of major complications in relation to preoperative hospital stay
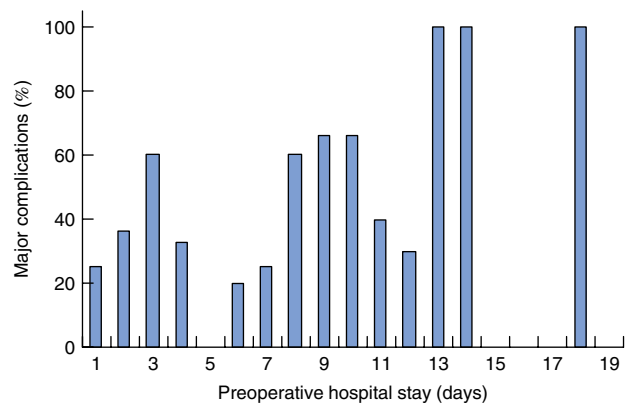
patients (28 per cent) following initial subtotal colectomy and ileostomy formation (*Table 2*).

Following IPAA, one (2 per cent) of 57 patients developed an anastomotic leak. One patient subsequently developed pouch–anal stenosis requiring dilatation, and one patient developed an intra-abdominal abscess, requiring radiological drainage following ileostomy closure. Pouchitis was recorded in seven patients; this was diagnosed on a clinical, endoscopic and histological basis[9]. Two of 11 patients developed early complications following completion proctectomy: extensive venous gangrene leading to below-knee amputation in one and wound infection in another.

During a total follow-up of up to 9 years, 40 patients (50 per cent) had an unplanned emergency readmission to hospital. Small bowel obstruction was the most common complication requiring readmission, occurring in 21 (26 per cent) of 80 patients after initial surgery. Further laparotomy for small bowel obstruction was required in two patients within 30 days of colectomy and in five patients later in the follow-up period. Reoperations during follow-up are summarized in *Table 3*.

Analysis of factors associated with postoperative morbidity

In univariable analysis, the only preoperative factor significantly associated with postoperative morbidity during follow-up was the interval between admission and surgery ($P = 0.036$); age ($P = 0.389$), sex ($P = 0.660$), duration of symptoms ($P = 0.924$), ciclosporin therapy ($P = 0.553$), preoperative bowel frequency ($P = 0.681$), histopathology (ulcerative *versus* indeterminate colitis; $P = 1.000$) and rectal stump closure technique ($P = 0.541$) showed no association. When major complications were defined as those prolonging hospital stay or necessitating readmission, preoperative duration of admission was significantly longer in patients who developed major complications than in those who did not (median (range)

8 (2–14) *versus* 5 (0–22) days; $P = 0.036$). Multivariable analysis showed that duration of in-hospital medical treatment was the only factor associated with increased postoperative complications (odds ratio 1·12 (95 per cent confidence interval 1·00 to 1·24); $P = 0.044$). *Fig. 1* shows the incidence of complications in relation to preoperative hospital stay.

Discussion

This study quantified the postoperative mortality and surgical morbidity following emergency colectomy and ileostomy for ASUC. Although the operative mortality rate was zero, the combined rate of short- and long-term surgical morbidity was 60 per cent. This is undoubtedly high, but represents the cumulative morbidity encountered over an extended follow-up (median more than 5 years) after emergency surgery. While acknowledging the significant risks of surgery for ASUC, this study also highlights the dangers of delayed surgery; patients with major postoperative complications had a significantly longer duration of preoperative medical therapy.

Before interpreting the data as providing evidence to support medical rather than surgical therapy for ASUC, physicians should consider that there are no published reports of the cumulative complication rate of medical therapy after treatment of ASUC and that some of the complications of medical therapy may be fatal (three of 86 deaths in patients treated with ciclosporin in one series[10], one of 83 deaths after infliximab in another[11]) or of long duration (steroid-induced diabetes or osteoporosis[4]). This study helps explore the limits beyond which medical therapy of ASUC is associated with a higher risk of complications in those who eventually require surgery. This is not to question the value of medical therapy, which should be pursued vigorously in an effort to avoid surgery. However, if continued for 8 days or more, there is a higher complication rate if surgery becomes necessary. Although this study did not examine the outcome for those who avoided surgery on that admission, long-term follow-up over more than a decade from this centre showed that the colectomy rate in incomplete responders to medical therapy was 80 per cent[12].

The association between duration of medical therapy in hospital and postoperative complications does not prove a causal relationship but is consistent with epidemiological statistics from the Oxford region (rather than just the John Radcliffe Hospital) and nationally, which have shown improved 3-year mortality rates for patients admitted for inflammatory bowel disease who underwent elective surgery compared with those who had emergency

colectomy or no colectomy[7]. It is possible that the threshold for surgery may be too high, given that the UK national audit of inflammatory bowel disease in 2006 identified a mortality rate of 2·1–4·7 per cent after emergency colectomy for ASUC[13], which is appreciably higher than the rate of less than 1 per cent reported from specialist centres, or zero in this series. The present study was conducted before infliximab became widely used as rescue therapy for ASUC failing to respond to intravenous steroids. Far from decreasing the relevance of the findings, the implications are yet more pertinent. This is because the median time to respond to infliximab is longer than that for ciclosporin. This not only adds to a potential delay before necessary surgery, but also adds to the potential risk should septic complications occur after emergency surgery in the presence of infliximab, which continues to have a biological effect for many weeks. There is controversy about whether infliximab alone increases postoperative complications in patients with ulcerative colitis[14,15].

The cumulative morbidity rate at a median 5 years after surgery was, however, significant. Half of the patients had an unplanned readmission to hospital at some stage during follow-up, including the period after definitive pouch surgery or proctectomy. Small bowel obstruction was the most common major complication, occurring in 26 per cent of patients and requiring reoperation in a third of these (9 per cent overall). These figures are similar to the 8 per cent reoperation rate reported for small bowel obstruction following colectomy[16] and 23 per cent rate of small bowel obstruction in 1178 patients undergoing ileoanal pouch formation[17]. Laparoscopic approaches[18] and the use of antiadhesion strategies (such as Seprafilm® (Genzyme, Cambridge, Massachusetts, USA) and Adept® (Baxter, Deerfield, Illinois, USA)) may reduce the rates of small bowel obstruction in the future. None of the patients in this series underwent laparoscopic surgery or received chemical barriers.

The lack of laparoscopic surgery is a notable feature in this series as the data relate to patients treated before the recent increase in laparoscopic surgery. It has yet to be established whether laparoscopic techniques reduce the long-term (obstructive) complication rate for colectomy or other operations[19]. An early study demonstrated the feasibility of laparoscopic colectomy, but showed no benefit over conventional open surgery[20]. Subsequent studies in acute colitis comparing laparoscopic colectomy with case-matched controls or same-institute controls have shown (in all but one study) that laparoscopic colectomy takes longer than open colectomy, but is associated with a significantly shorter hospital stay[21–24]. Short-term complication rates were similar between laparoscopic and open procedures in

each study, but a trend towards fewer complications always favoured laparoscopic colectomy.

The high morbidity rate in the present series probably reflects the severity of the underlying condition, but may have been compounded by steroids. All patients in this study were receiving high-dose intravenous steroids at the time of colectomy. In a report of 159 patients, of whom 71 had surgery for ulcerative colitis, the odds ratio for major septic complications in all patients taking steroids was 5·54 compared with those not receiving steroids at the time of surgery[25]. In the present study, use of ciclosporin did not increase the surgical morbidity, confirming a previous report from this unit in an overlapping cohort of patients[26].

The principle of joint medical and surgical management of ASUC remains true more than ever before, but clinicians need to be proactive. This reflects not only new medical therapy but also structural changes in healthcare delivery in the UK and elsewhere, which make it more difficult to achieve. The challenge for surgeons is to reduce perioperative morbidity, principally related to small bowel adhesions and the rectal remnant. The challenge for physicians is to develop more effective treatments for severe colitis. The challenge for both teams is to monitor patients closely and make the decision to operate at an appropriate time. Larger-scale reporting and work from the UK national audit of inflammatory bowel disease may further elucidate the factors affecting outcome after colectomy for ulcerative colitis.

Acknowledgements

References

1 Truelove SC, Witts LJ. Cortisone in ulcerative colitis; final report on a therapeutic trial. *Br Med J* 1955; **2**: 1041–1048.

2 Carter MJ, Lobo AJ, Travis SP; IBD Section, British Society of Gastroenterology. Guidelines for the management of inflammatory bowel disease in adults. *Gut* 2004; **53**(Suppl 5): V1–V16.

3 Kornbluth A, Sachar DB; Practice Parameters Committee of the American College of Gastroenterology. Ulcerative colitis practice guidelines in adults (update): American College of Gastroenterology, Practice Parameters Committee. *Am J Gastroenterol* 2004; **99**: 1371–1385.

4 Stange EF, Travis SPL for the European Crohn's and Colitis Organisation (ECCO). European evidence-based consensus on the diagnosis and management of ulcerative colitis. *J Crohns Colitis* 2008; **2**: 63–92.

5 Brown S, Haboubi N, Hampton J, George B, Travis SP; ACPGBI. The management of acute severe colitis: ACPGBI position statement. *Colorectal Dis* 2008; **10**(Suppl 3): 8–29.

6 Travis SPL, Farrant JM, Ricketts C, Nolan DJ, Mortensen NM, Kettlewell MG *et al.* Predicting outcome in severe ulcerative colitis. *Gut* 1996; **38**: 905–910.

7 Roberts S, Williams J, Yeates D, Goldacre M. Mortality in patients with and without colectomy admitted to hospital for ulcerative colitis and Crohn's disease: record linkage studies. *BMJ* 2007; **335**: 1033–1036.

8 Geboes K, Van Eyken P. Inflammatory bowel disease unclassified and indeterminate colitis: the role of the pathologist. *J Clin Pathol* 2009; **62**: 201–205.

9 Shepherd NA, Jass JR, Duval I, Moskowitz RL, Nicholls RJ, Morson BC. Restorative proctocolectomy with ileal reservoir: pathological and histochemical study of mucosal biopsy specimens. *J Clin Pathol* 1987; **40**: 601–607.

10 Arts J, D'Haens G, Zeegers M, Van Assche G, Hiele M, D'Hoore A *et al.* Long-term outcome of treatment with intravenous cyclosporin in patients with severe ulcerative colitis. *Inflamm Bowel Dis* 2004; **10**: 73–78.

11 Kohn A, Daperno M, Armuzzi A, Cappello M, Biancone L, Orlando A *et al.* Infliximab in severe ulcerative colitis: short-term results of different infusion regimens and long-term follow-up. *Aliment Pharmacol Ther* 2007; **26**: 747–756.

12 Bojic D, Radojicic Z, Nedeljkovic-Protic M, Al-Ali M, Jewell DP, Travis SP. Long term outcome after admission for acute severe ulcerative colitis in Oxford: the 1990–91 cohort. *Inflamm Bowel Dis* 2009; **15**: 823–828.

13 http://www.rcplondon.ac.uk/clinical-standards/ceeu/Current-work/IBD/Pages/Audit-Work-Programme.aspx [accessed 28 December 2009].

14 Salvasekar C, Cima R, Larson D, Dozois EJ, Harrington JR, Harmsen WS *et al.* Effect of infliximab on short-term complications in patients undergoing operation for chronic ulcerative colitis. *J Am Coll Surg* 2007; **204**: 956–962.

15 Ferrante M, D'Hoore A, Vermeire S, Declerck S, Noman M, Van Assche G *et al.* Corticosteroids but not infliximab increase short-term infectious complications in patients with ulcerative colitis. *Inflamm Bowel Dis* 2009; **15**: 1062–1070.

16 Alves A, Panis Y, Bouhnik Y, Maylin V, Lavergne-Slove A, Valleur P. Subtotal colectomy for severe acute colitis: a 20-year experience of a tertiary care center with an aggressive and early surgical policy. *J Am Coll Surg* 2003; **197**: 379–385.

17 MacLean AR, Cohen Z, MacRae HM, O'Connor BI, Mukraj D, Kennedy ED *et al.* Risk of small bowel obstruction after the ileal pouch–anal anastomosis. *Ann Surg* 2002; **235**: 200–206.

18 Marcello PW, Milsom JW, Wong SK, Brady K, Goormastic M, Fazio VW. Laparoscopic total colectomy for acute colitis: a case–control study. *Dis Colon Rectum* 2001; **44**: 1441–1445.

19 Eshuis EJ, Polle SW, Slors JF, Hommes DW, Sprangers MA, Gouma DJ *et al.* Long-term surgical recurrence, morbidity, quality of life, and body image of

laparoscopic-assisted *vs.* open ileocolic resection for Crohn's disease: a comparative study. *Dis Colon Rectum* 2008; **51**: 858–867.

20 Wexner SD, Johansen OB, Nogueras JJ, Jagelman DG. Laparoscopic total abdominal colectomy. A prospective trial. *Dis Colon Rectum* 1992; **35**: 651–655.

21 Dunker MS, Bemelman WA, Slors JF, van Hogezand RA, Ringers J, Gouma DJ. Laparoscopic-assisted *vs* open colectomy for severe acute colitis in patients with inflammatory bowel disease (IBD): a retrospective study in 42 patients. *Surg Endosc* 2000; **14**: 911–914.

22 Seshadri PA, Poulin EC, Schlachta CM, Cadeddu MO, Mamazza J. Does a laparoscopic approach to total abdominal colectomy and proctocolectomy offer advantages? *Surg Endosc* 2001; **15**: 837–842.

23 Pokala N, Delaney CP, Senagore AJ, Brady KM, Fazio VW.

Laparoscopic *vs* open total colectomy: a case-matched comparative study. *Surg Endosc* 2005; **19**: 531–535.

24 Marceau C, Alves A, Ouaissi M, Bouhnik Y, Valleur P, Panis Y. Laparoscopic subtotal colectomy for acute or severe colitis complicating inflammatory bowel disease: a case-matched study in 88 patients. *Surgery* 2007; **141**: 640–644.

25 Aberra FN, Lewis JD, Hass D, Rombeau JL, Osborne B, Lichtenstein GR. Corticosteroids and immunomodulators: postoperative infectious complication risk in inflammatory bowel disease patients. *Gastroenterology* 2003; **125**: 320–327.

26 Hyde GM, Jewell DP, Kettlewell MGW, Mortensen NJ. Cyclosporin for severe ulcerative colitis does not increase the rate of perioperative complications. *Dis Colon Rectum* 2001; **44**: 1436–1440.