

ORIGINAL ARTICLE

Risk factors for complications after bowel surgery in Korean patients with Crohn's disease

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Purpose: To assess the incidence and factors predictive of early postoperative complications in Korean patients who undergo surgery for Crohn's disease (CD). **Methods:** We retrospectively assessed 350 patients (246 males, 104 females; mean age, 30 ± 9 years) who underwent surgery for primary or recurrent CD at Asan Medical Center between January 1991 and May 2010. The incidence and predictive factors of early postoperative complications were analyzed by both univariate and multivariate analyses. **Results:** Of the 350 patients, 81 patients (23.1%) developed postoperative complications, the most common being septic complications (54 patients), including 19 cases of wound infection. Thirty patients (8.6%) required re-operations, and only one patient died. Multivariate analysis showed that four factors were independently associated with a high risk of early postoperative complications; preoperative moderate to severe anemia (hematocrit concentration < 30%; odds ratio [OR], 3.1; 95% confidence interval [CI], 1.6 to 5.9), hypoalbuminemia (serum albumin level < 3.0 g/dL; OR, 2.6; 95% CI, 1.4 to 4.7), emergency surgery (OR, 4.0; 95% CI, 1.5 to 10.6), and covering stoma (OR, 2.6; 95% CI, 1.3 to 5.4). Correction of preoperative moderate to severe anemia and hypoalbuminemia decreased the incidence of postoperative complications. Mean hospital stay was significantly longer in patients with than without postoperative complications (31.3 ± 27.2 days vs. 10.3 ± 3.8 days, $P < 0.001$). **Conclusion:** Preoperative anemia, low albumin level, emergency surgery, and covering stoma significantly increased the risk of early postoperative complications in patients with CD. Correcting preoperatively deficient nutritional factors may reduce postoperative morbidities.

Key Words: Crohn disease, Surgery, Korea, Risk factors, Postoperative complications

INTRODUCTION

Despite significant progress in the medical treatment of Crohn's disease (CD), most patients eventually require surgery. For example, in a population-based cohort of 907 patients with primary ileocecal CD, the resection rates 1, 5, and 10 years after diagnosis were 66%, 77%, and 83%, re-

spectively [1]. Intestinal resection and surgery for perianal fistulas are the most common procedures. The postoperative complication rate following intestinal resection for CD is higher than for other benign diseases, despite most patients with CD being young and without significant comorbidities. Postoperative septic complications, including anastomotic leakages, enterocutaneous

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fistulae, and intraabdominal abscesses, are especially troublesome, with incidence rates ranging between 5% and 20%. Among the risk factors for postoperative septic complications are the preoperative presence of intra-abdominal abscess and/or fistula, systemic infection, impaired nutritional status, intestinal obstruction, preoperative low albumin level, and chronic therapy [2-4].

Although the incidence and prevalence of CD are much lower in Asian than in Western countries, the increasing incidence of CD in Asian countries over the past few decades indicates that more attention should be paid to the characteristics of Asian CD patients, including those in Korea [5-7]. However, the incidence and risk factors of complications after surgery for CD remain poorly understood in Asian patients, including those in Korea. We therefore retrospectively evaluated the incidence of CD and risk factors for postoperative complications in Korean patients undergoing surgery for CD.

METHODS

We retrospectively reviewed our prospectively collected database of patients with CD, identifying 350 patients who underwent abdominal surgery for histologically established primary or recurrent CD between January 1991 and May 2010 at the Asan Medical Center. The Asan Medical Center Institutional Review Board approved this study. Patients who underwent surgery for appendicitis were excluded, since minor procedure such as appendectomy could underestimate the rate of postoperative complications. And patients whose surgical procedure was limited to perianal surgery were also excluded. We excluded patients who underwent closures of loop ileostomy or colostomy, reoperations for postoperative complications because these surgeries were not surgical indication for CD itself. Only early complications that occurred within the first 30 days after surgery were examined in this study. We excluded septic complications that occurred more than 30 days postoperatively because late sepsis is mainly caused by recurrent CD.

Surgical outcome was determined by postoperative follow-up. Complications were classified as septic or nonsep-

tic. Septic complications included wound infections, abdominal abscesses, clinical anastomotic leakage, bowel perforation, pneumonia, and enterocutaneous fistulae. Anastomotic leakage was confirmed by re-laparotomy or percutaneous drainage. Asymptomatic radiologic anastomotic leakage was not considered because contrast enemas were not performed routinely after surgery. Intra-abdominal abscesses were confirmed by computed tomography scan and percutaneous drainage or re-laparotomy. Nonseptic complications included intestinal obstructions, postoperative hemorrhage, pulmonary edema and effusion, stoma problems, adrenal insufficiency, and cerebral infarction. CD was also classified using the Montreal classification which classified CD for clinical application according to the age of onset (A), disease location (L), and disease behavior (B) as the predominant phenotypic elements. Patients were divided into two groups, those with and without postoperative complications, and the following putative risk factors were compared in the two groups: preoperative risk factors include patient age, gender, or smoking history; preoperative treatment with steroids, American Society of Anesthesiologists (ASA) score, immunosuppressants, or infliximab; history of previous laparotomy; poor nutritional status; preoperative anemia and hypoalbuminemia; preoperative parenteral nutritional support; duration of symptoms before surgery; site of disease; or Montreal classification. And operative risk factors include indications for surgical intervention (i.e., stenosis, fistula, or failure to respond to medical treatment; emergency surgery; laparoscopic or open procedure; presence of an intra-abdominal abscess or fistula at the time of surgery; type of operation [resection, stricturoplasty, or bypass]; and covering stoma). We also assessed groups of patients who underwent elective surgery with corrected and non-corrected preoperative anemia and hypoalbuminemia.

Poor nutritional status was defined as unintentional weight loss greater than 10% of the usual body weight over a period of 6 to 12 month. We defined preoperative hematocrit concentration and serum albumin level as the last hematocrit and serum albumin measurement before the index operation. Preoperative anemia was defined as a hematocrit concentration of less than 36.0% for women

and less than 39.0% for men according to World Health Organization's sex based criteria [8]. And moderate to severe anemia was defined as a hematocrit concentration less than 30.0% [9]. Hypoalbuminemia was defined as serum albumin < 3.0 g/dL.

Table 1. Incidence and type of postoperative complications in patients with Crohn's disease

Type of complication	No. (n = 81)	Re-operation (n = 30)
Septic complications	54 (66.7)	26 (86.7)
Wound infection	19 (23.4)	9 (30.0)
Intra-abdominal abscess	17 (20.9)	2 (6.7)
Anastomotic leakage	13 (16.0)	11 (36.7)
Perforation	2 (2.4)	2 (6.7)
Enterocutaneous fistula	2 (2.4)	2 (6.7)
Pneumonia	1 (1.2)	0 (0)
Non-septic complications	27 (33.3)	4 (13.3)
Intestinal obstruction	15 (18.5)	2 (6.7)
Hemorrhage	5 (6.2)	1 (3.3)
Pulmonary edema or effusion	3 (3.7)	0 (0)
Adrenal insufficiency	1 (1.2)	0 (0)
Superior mesenteric artery syndrome	1 (1.2)	0 (0)
Cerebral infarction	1 (1.2)	0 (0)
Stoma problem	1 (1.2)	1 (3.3)

Values are presented as no. of patients (%).

Putative risk factors for postoperative complications were analyzed by univariate analyses, using the chi-squared test with Yates' correction or Student's t-test for quantitative and qualitative variables, as appropriate. Factors with a P-value < 0.05 on univariate analysis were incorporated into multivariate analysis. Statistical significance was defined as a P-value < 0.05.

RESULTS

Of the 350 included patients (246 males, 104 females; mean age, 29 ± 9 years; range, 14 to 74 years), 81 patients (23.1%) experienced postoperative complications (Table 1). One patient (0.29%) died due to small bowel perforation after a total colectomy and end-ileostomy, with septicemia being the primary cause of death. Of the 81 patients who experienced postoperative complications, 54 patients (66.7%) and 27 patients (33.3%) experienced septic and non-septic complications, respectively. Thirty patients with major complications, most with septic complications, required reoperations. Reoperation rate was significantly higher in patients with septic complication com-

Table 2. Demographic and clinical characteristics of patients with Crohn's disease

Characteristic	Without complications (n = 269)	With complications (n = 81)	P-value
Mean age (yr)	29.67 ± 9.58	31.35 ± 10.86	0.184
Male gender	192 (71.4)	54 (66.7)	0.410
Smoking	18 (6.7)	5 (6.2)	0.857
Weight loss (>10%)	84 (31.2)	27 (33.3)	0.785
Previous laparotomy	95 (35.3)	28 (33.3)	0.902
Mean duration of symptoms (mo)	60.0 ± 77	47.8 ± 52	0.364
Preoperative steroid (>3 mo)	145 (54.9)	49 (61.3)	0.306
Immunosuppressive agents	102 (37.9)	38 (46.9)	0.196
Infliximab	27 (10.0)	12 (14.8)	0.234
Parenteral nutrition	195 (72.4)	63 (77.8)	0.469
Preoperative anemia	218 (81.0)	71 (87.7)	0.169
Moderate to severe (hematocrit <30%)	79 (29.4)	41 (50.6)	<0.001
Preoperative hypoalbuminemia (<3.0 g/dL)	78 (29.0)	39 (48.1)	0.002
Site of disease			0.873
Proximal small bowel	29 (10.8)	9 (11.3)	
Distal small bowel	120 (44.8)	32 (40.0)	
Large bowel	21 (7.8)	6 (7.5)	
Small and large bowel	98 (36.6)	33 (41.3)	

Values are presented as mean \pm SD or no. of patients (%).

pared with non-septic complication (48.1% vs. 14.8%, $P = 0.004$). Seventeen patients developed intra-abdominal abscesses, with two requiring surgical intervention, whereas the other 15 improved with antibiotic treatment and percutaneous catheter drainage of purulent fluid from a drainage site. Thirteen patients developed anastomotic leakage, with 11 requiring re-operation due to generalized peritonitis. Fifteen patients developed intestinal obstructions, with two requiring reoperations. Mean postoperative hospital stay was significantly longer in the group with than without postoperative complications (31 days vs. 10 days, $P < 0.001$).

The relationships between postoperative complications and clinical factors are shown in Table 2. Univariate analysis showed that postoperative complications were significantly associated with preoperative hypoalbuminemia ($P = 0.002$) and moderate to severe anemia ($P < 0.001$). No other preoperative factor was associated with an increased risk of postoperative complications, including patient age, gender, or smoking history; previous laparotomy; weight loss; preoperative anemia; preoperative parenteral nutritional support; duration of symptoms; preoperative treatment with steroids, immunosuppressive agents or infliximab; site of disease; abscess or fistula detected at the time of surgery; or Montreal classification (Table 3). Among operative factors, indication for surgery ($P = 0.032$), emer-

Table 3. Characteristics of Crohn's disease according to the Montreal classification

Characteristic	Without complications (n = 269)	With complication (n = 81)	P-value
Age at diagnosis (yr)			0.252
A1 (<17)	56 (20.8)	11 (13.6)	
A2 ($\geq 17, \leq 40$)	190 (70.6)	60 (74.1)	
A3 (>40)	23 (8.6)	10 (12.3)	
Location			0.873
L1 (ileal)	120 (44.8)	32 (40.0)	
L2 (colonic)	21 (7.8)	6 (7.5)	
L3 (ileocolic)	98 (36.6)	33 (41.3)	
L4 (isolated upper disease)	29 (10.8)	9 (11.3)	
Behavior			0.168
B1 (non-stricturing)	46 (17.1)	7 (8.6)	
B2 (stricturing)	65 (24.2)	23 (28.4)	
B3 (penetrating)	158 (58.7)	51 (63.0)	

Values are presented as no. of patients (%).

gency surgery ($P = 0.013$) and covering stoma ($P = 0.027$) were associated with postoperative complications, but perioperative blood transfusion, laparoscopic vs. open procedures and type of operation were not (Table 4).

Multivariate analysis showed that postoperative complications were significantly associated with preoperative moderate to severe anemia (odds ratio [OR], 3.1; 95% confidence interval [CI], 1.6 to 5.9) and hypoalbuminemia (OR, 2.6; 95% CI, 1.4 to 4.7), emergency surgery (OR, 4.0; 95% CI, 1.5 to 10.6), and covering stoma (OR, 2.6; 95% CI, 1.4 to 4.7) (Table 5).

Patients with CD found to have poor nutritional status and anemia were administered parenteral or enteral nutrition before surgery, including iron supplementation or blood transfusion to patients with moderate to severe anemia and albumin solution to patients with hypoalbumi-

Table 4. Operative characteristics of patients with Crohn's disease

Characteristic	Without complications (n = 269)	With complications (n = 81)	P-value
Indication for surgery			0.032
Stenosis	65 (24.0)	23 (28.4)	
Abscess	51 (19.0)	14 (17.3)	
Fistula	93 (34.6)	25 (30.9)	
Perforation	10 (3.7)	10 (12.3)	
Intractability	46 (17.1)	7 (8.6)	
Emergency surgery	11 (4.1)	10 (12.3)	0.013
Perioperative transfusion	81 (30.1)	33 (40.7)	0.074
Laparoscopic procedure	37 (13.9)	7 (8.6)	0.256
Type of operation (resection)	259 (96.3)	79 (97.5)	0.740
Covering stoma	31 (11.6)	18 (22.2)	0.027

Values are presented as no. of patients (%).

Table 5. Multivariate analysis of risk factors associated with major complications after surgery for Crohn's disease

	Relative risk	95% Confidence interval	P-value
Male gender	0.952	0.502-1.808	0.882
Age (≥ 30 yr)	1.069	0.592-1.930	0.824
Moderate to severe anemia	3.108	1.620-5.964	0.001
Hypoalbuminemia	2.637	1.454-4.782	0.001
Covering stoma	2.687	1.315-5.490	0.007
Indication of surgery	0.986	0.98-1.218	0.896
Emergency surgery	4.079	1.557-10.688	0.004

Table 6. Outcomes of preoperative replacement therapy in patients with anemia and hypoalbuminemia after elective surgery for Crohn's disease

Complication	Moderate to severe anemia			Hypoalbuminemia		
	Correction (n = 70)	No correction (n = 38)	P-value	Correction (n = 40)	No correction (n = 64)	P-value
Overall	15 (21.4)	19 (50.0)	0.002	6 (15.0)	26 (40.9)	0.006
Septic	10 (14.3)	13 (34.2)	0.016	5 (12.5)	18 (28.1)	0.062

Values are presented as no. of patients (%).

nia. Preoperative anemia was corrected in 70 patients and not corrected in 38, whereas preoperative hypoalbuminemia was corrected in 40 patients and not corrected in 64. When we compared the overall and septic complications of these corrected and non-corrected groups, we found that correction of both preoperative anemia and hypoalbuminemia significantly reduced the incidence of overall complications, whereas correction of anemia, but not hypoalbuminemia, significantly reduced the rate of septic complications (Table 6).

DISCUSSION

Relatively high rates of postoperative morbidity and septic complications have been reported in patients who undergo operations for CD. These rates have been reported to range from 2.3 to 38% for wound sepsis, 2.6 to 14% for abdominal abscess, 1 to 17% for anastomotic leakage, and as high as 7% for postoperative death [2,3,10-13]. Of our 350 patients who underwent surgery for CD, only one (0.3%) died, a rate that compares favorably with the 0 to 2% mortality rates reported in recent Western studies [1-3]. Our overall postoperative complication rate of 23.1% also compared favorably with the ranges reported in Western patients [2,11,12,14]. Among them, 8.6% of our patients experienced major complications requiring reoperation, and patients developing postoperative complications had a significantly longer mean hospital stay. In our study, septic complications including wound infection, intra-abdominal abscess and anastomotic leakage were most common postoperative complications, and anastomotic leakage was the most serious postoperative complication in patients with CD. About two third of pa-

tients with wound infection and intra-abdominal abscess has been resolved by conservative treatment or non-surgical intervention, but majority of patients with anastomotic leakage developed peritonitis requiring laparotomy.

Several studies have investigated the risk factors associated with the development of complications after surgery for CD [2,3,11,15,16]. Most of these risk factors were associated with preoperative patient condition. For example, one study found that preoperative albumin concentration, preoperative steroid treatment, and abscess and fistula at the time of laparotomy were significant risk factors for intra-abdominal septic complications [3]. Another study reported that preoperative weight loss >10%, intra-abdominal abscess, steroid use for more than 3 months, and recurrent clinical episodes of CD were significantly associated with poor postoperative outcomes [15]. Other studies have found that preoperative hemoglobin concentration <10 g/mL, steroid use, intra-abdominal abscess, low albumin concentration, extensive resections, and multiple previous operations were significantly associated with postoperative morbidity [2,11,16].

We found that preoperative moderate to severe anemia and hypoalbuminemia were significantly associated with a higher incidence of postoperative complications after surgery for CD. We also found that preoperative correction of moderate to severe anemia and hypoalbuminemia significantly decreased the incidence of postoperative complications.

Poor nutrition has been associated with increased rates of surgical morbidities, due perhaps to a depressed immune system [17]. These patients are physiologically impaired, are prone to septic complications, and may benefit from timely and appropriate institution of preoperative enteral or parenteral nutrition [18]. Low albumin concen-

tration and weight loss are two variables used as criteria of poor nutritional status [3,11,15]. Among our patients, however, weight loss was not an apparent risk factor. This may reflect difficulties in assessing patients' nutritional status by preoperative weight loss alone, in that patients' weight may fluctuate during the preoperative period. Thus, we may have underestimated the number of CD patients who were malnourished, even if their weight was stable.

A meta-analysis of 90 cohort studies and nine prospective controlled studies showed that hypoalbuminemia was an independent predictor of postoperative poor outcome in critically ill patients [19], an association apparently independent of both nutritional status and inflammation. We also found that hypoalbuminemia was an independent risk factor for complications after bowel surgery in patients with CD. Multivariate analysis of the relationship of serum albumin and postoperative complications showed that preoperative serum albumin <3.0 g/dL increased the risk of postoperative complication by 2.6 folds.

Although hypoalbuminemia is a well known marker of malnutrition or a risk factor of postoperative complications, the benefit of albumin replacement to correct preoperative hypoalbuminemia in patients with CD are unclear. Several studies have shown that albumin replacement therapy did not decrease the rates of death or major complications [20,21]. However, others found that treatment of hypoalbuminemic patients with exogenous human albumin solution resulted in a greater than twofold decrease in major complications [22,23]. A recent meta-analysis of 71 randomized trials showed that albumin administration significantly reduced overall morbidity among acutely ill hospitalized patients [24]. Few studies, however, have assessed the clinical relevance of these properties, especially in CD patients who underwent surgery. Nevertheless, characteristics of albumin contributing normal oncotic pressure, innate immune response may help to explain the possible benefits observed after correction of hypoalbuminemia

Anemia is a common and important complication of CD. A systemic review on anemia in CD found the reported prevalence of anemia varied between 6.2% and

73.7% [25]. Some studies reported that anemia was associated with postoperative complication in patients with CD [16,26]. In the recent large cohort study, Musallam et al. [27] suggested that even mild degrees of preoperative anemia were associated with an increased risk of 30-day postoperative mortality and morbidity in patients undergoing non-cardiac surgery. Although preoperative any anemia was not apparent in the present study, we show that moderate to severe anemia is independently associated with an increased risk of morbidity and also found that correction of preoperative anemia significantly reduced the incidence of overall complications in CD patients underwent surgery.

Our study should lead to careful consideration of appropriate interventions aimed at correction of preoperative anemia in the most patients. Present guidelines recommend measurement of hematocrit concentration as close to 28 days before the scheduled surgical procedure as possible, and subsequent investigation and intervention in patients with anemia [28]. Our study supports these guidelines because anemia is most significant preoperative risk factor of morbidity. At least in elective surgical cases, the treatment of preoperative anemia before surgical intervention should be strongly considered.

Our study did not find that perioperative blood transfusion was associated with a high incidence of morbidity. Nonetheless, it seems reasonable to limit blood transfusion in patients with preoperative serum hemoglobin level more than 7 g/dL. The high morbidity and mortality reported with the use of blood transfusion [4,29]. Alternative interventions including preoperative iron and vitamin supplementation or administration of erythropoietin therapy should be considered.

It is unclear whether corticosteroid treatment impairs healing of intestinal anastomoses or increases the risks of septic complications. Although two studies found that preoperative steroid treatment was associated with a high incidence of postoperative septic complications [2,3], other studies found that steroids did not increase this risk [11,30]. In agreement with the latter, we found no significant association between preoperative steroid use and the occurrence of postoperative sepsis.

Unexpected intra-abdominal abscess or fistula has been

associated with an increased risk of postoperative septic complications [3]. We found that emergency surgery, which is associated with pre-existing septic complications, was associated with a 4.0-fold higher morbidity rate than elective surgery. Most of the patients in our study who underwent emergency surgery were septic.

A covering stoma has been reported to reduce the incidence of leakage or septic complications after surgery for CD [4,11]. We found that the incidence rates of septic complications, including intra-abdominal abscess (33.3%), wound infection (27.8%) and anastomotic leakage (11.1%) were higher in patients who did than did not require covering ileostomy. The higher incidence of septic complications in these patients may be attributed to the severity of preoperative intra-abdominal sepsis and the inflammatory condition of the intestine. However, due to the limitations of our retrospective study, we could not reflect and classify precisely how severe these were. Nevertheless, we believe that covering stoma may help to protect more severe septic postoperative complications which may result in general peritonitis and reoperation.

This study had several limitations. Owing to its retrospective design, we could not be sure whether other factors may have influenced the rate of complications, including fecal spillage and tension on the anastomosis. Moreover, the surgeon's assessment of the state of inflammatory tissue at the time of surgery is important when deciding how much intestine should be resected and whether to perform an anastomosis. This assessment is subjective and difficult to quantify. However, all patients in this study were followed-up in the same unit by the same group of physicians, who used similar guidelines and made decisions collectively.

In conclusion, we found that the incidence and characteristics of complications after bowel surgery in Korean patients with CD are comparable to those in Western CD patients. Preoperative anemia and hypoalbuminemia, emergency surgery, and covering stoma significantly increased the risks of early complications after surgery in patients with CD. A deeper understanding of the relation between these risk factors and postoperative complications may lead to the evolution of management strategies. Especially the effort to support preoperative nutritional

care, including correction of preoperative anemia and hypoalbuminemia in malnourished patients with CD may help to improved postoperative outcomes.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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