



Retrospective Study

Short- and long-term outcomes of surgical treatment in patients with intestinal Behcet's disease

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Abstract

BACKGROUND

Behcet's disease (BD), a chronic vasculitic disorder affecting multiple organs, is characterized by recurrent oral and genital ulcers, arthritis, vasculitis, and intestinal ulcers. Although intestinal involvement of BD is common in East Asia, the efficacy and long-term outcomes of surgical treatment of intestinal BD still remain to be established.

AIM

To evaluate the postoperative clinical course of intestinal BD and determine factors associated with its recurrence.

METHODS

Data from patients who underwent surgical treatment for intestinal BD between January 2010 and August 2021 were retrospectively reviewed. Patients' demographics, clinical features, postoperative course, complications, and follow-up data were evaluated.

RESULTS

We analyzed 39 surgeries in 31 patients. The mean patient age was 45.1 years, and the mean interval between the diagnosis of intestinal BD and surgical treatment was 4.9 years (range 1.0-8.0 years). The most common indication for surgery was medical intractability ($n = 16$, 41.0%), followed by fistula or abscess ($n = 11$, 28.2%). Laparoscopic approaches were used in 19 patients (48.7%), and 5 patients (12.8%) underwent emergency surgeries. The most common surgical procedure was ileocecal resection ($n = 18$, 46.2%), followed by right colectomy ($n = 11$, 28.2%). A diverting stoma was created in only one patient (2.6%). During a mean

follow-up period of 45 (range 8-72) months, eight cases (20.5%) of recurrence in five patients required reoperation. The interval between operations was 12.1 months (range 6.3-17.8 mo). Four patients (10.3%) experienced recurrence within 1 year postoperatively, and all eight recurrences occurred within 2 years of the initial surgery. The reoperation rates at 1 and 3 years were 10.3% and 20.5%, respectively. A redo ileocolic anastomosis was performed in all recurrent cases. In multivariate Cox regression analysis, emergency surgery [hazard ratio (HR) 9.357, 95% confidence interval (CI): 1.608-54.453, $P = 0.013$] and elevated C-reactive protein (CRP) levels (HR 1.154, 95% CI: 1.002-1.328, $P = 0.047$), but not medication use, were predictors of recurrence.

CONCLUSION

Surgical resection is a feasible treatment option for complicated BD. Reoperation is associated with severe inflammatory conditions, reflected by increased CRP levels and the requirement for emergency surgery.

Key Words: Behcet syndrome; Intestinal; General surgery; Recurrence; Risk factors

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Core Tip: Behcet's disease (BD), a chronic vasculitic disorder impacting multiple organs, often necessitates surgical intervention due to medical intractability, fistulas, or abscesses. This study examined 31 patients who underwent surgery for intestinal BD. Recurrence occurred in 20.5% of cases, with all instances happening within two years after surgery. Emergency surgery and elevated C-reactive protein (CRP) levels were predictive of recurrence. This suggests that surgical resection is a viable option for complicated BD, but reoperation is more likely in patients with severe inflammation as indicated by elevated CRP levels and the requirement for emergency surgery.

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INTRODUCTION

Behcet's disease (BD) is a chronic multisystemic vasculitic disorder affecting the arteries and veins[1,2]. It manifests as recurrent oral and genital ulcers, skin and ocular lesions, arthritis, vasculitis, neurologic lesions, or intestinal ulcers[1,2]. The prevalence of BD is higher in East Asia and the Mediterranean than in the United Kingdom and North America[3,4].

Intestinal BD is a subtype of BD predominantly characterized by gastrointestinal symptoms, such as abdominal pain, hematochezia, diarrhea, abdominal masses, and intestinal ulcerations[5]. The incidence of gastrointestinal involvement varies across different countries, ranging from 0% to 60%[6,7]. Intestinal BD is more frequent in East Asia (including Korea and Japan) than in Mediterranean countries[6,7]. However, the appropriate treatments for this disorder are yet to be established. Intestinal BD is primarily treated empirically due to the scarcity of well-designed studies on this topic, the rarity of the disease, and the heterogeneity of disease patterns[8]. Medical treatment of BD entails using corticosteroids, 5-aminosalicylic acid, sulfasalazine, azathioprine, and 6-mercaptopurine. However, intestinal BD often requires surgical treatment because of poor response to medical treatment and high frequency of complications, such as intestinal perforation, fistula, or bleeding[9,10]. Some patients with intestinal BD experience frequent recurrences despite surgical treatment and require repeated surgeries[11]. Although surgical treatment is performed in many patients with intestinal BD, its clinical efficacy and long-term outcomes still need to be fully understood.

In this study, we aimed to evaluate the postoperative clinical course of intestinal BD and determine factors associated with reoperations due to recurrences.

MATERIALS AND METHODS

Patients and clinical variables

We conducted a retrospective review of data from patients with intestinal BD who underwent surgical resection between January 2010 and August 2021 at Asan Medical Center, Seoul, South Korea. Intestinal BD was diagnosed by gastroenterologists based on colonoscopic criteria and clinical manifestations through a modified Delphi process[5]. Patients were classified as having definite, probable, or suspected intestinal BD. Patients with any evidence of other gastrointestinal diseases, such as Crohn's disease, intestinal tuberculosis, or ischemic enteritis, during the follow-up period were excluded. Patient demographics and clinical characteristics, including age, sex, BD symptoms, medical treatments, laboratory findings, and indications for surgery, were compared. Collected surgical data included surgery type (open *vs* laparoscopy), surgical procedure, number of emergency surgeries, number of cases with a diverting stoma, expected

blood loss, and duration of the surgery. The postoperative course was evaluated based on postoperative complications, mortality within 30 days of surgery, and reoperation related to the recurrence of intestinal BD symptoms. The study protocol was approved by the institutional review board of Asan Medical Center (approval No. 2022-0238).

Definitions of variables

Recurrence was defined as a relapse of intestinal BD symptoms, reappearance of ulcers at the anastomosis site, and newly developed fistula or abscess near the anastomosis associated with the reappearance of ulcers. If there were only other BD symptoms such as oral ulcer and genital ulcer other than the intestinal BD symptoms, they were excluded from recurrence. Reoperation was defined as a surgical intervention related to intestinal BD during the follow-up period after the initial surgery.

Outcomes

The primary outcome of this study was the recurrence rate of intestinal BD after surgical treatment. The secondary outcomes were factors associated with recurrence after the initial surgery.

Statistical analysis

Categorical variables are expressed as numbers and percentages and were compared using the chi-square test. Continuous variables are expressed as medians with interquartile ranges (IQRs) or mean $\pm$ SD values and were compared using the Student's *t*-test. Cumulative recurrence rates were calculated using the Kaplan-Meier method, and factors associated with recurrence were compared using log-rank tests. All statistical analyses were performed using SPSS for Windows (version 25.0; SPSS Inc., Chicago, IL, United States), with *P* value of < 0.05 considered statistically significant.

RESULTS

A total of 39 surgeries in 31 patients with intestinal BD were performed between January 2010 and August 2021. The demographics and clinical characteristics of the patients are summarized in Table 1. The median age at the time of diagnosis of BD was 36 (IQR 29-49) years. The median age at the time of diagnosis of intestinal BD was 38 (IQR 30-49) years, and the median age at the time of initial surgery was 49 (IQR 31-57) years. The median interval between intestinal BD diagnosis and surgical treatment was 3 (IQR 1-8) years. The proportions of male and female patients were equivalent (51.3% *vs* 48.7%, respectively). The most common symptom of systemic BD was oral ulcers (35.9%), and the most common indication for surgical treatment of intestinal BD was medical intractability and the development of perforation or fistula (41.0% each). Patients who underwent surgery for intestinal BD had mildly elevated preoperative C-reactive protein (CRP) levels and erythrocyte sedimentation rates.

The evaluated surgical data are presented in Table 2. Emergency surgeries were performed in five patients. The laparoscopic and open surgery rates were similar (51.3% *vs* 48.7%, respectively). The most common surgical procedure was ileocecal resection (48.7%), followed by right hemicolectomy (28.2%). A diverting stoma was created in only one case. The median duration of surgery was 116 (IQR 95-740) min.

Data on the postoperative course are presented in Table 3. Five patients experienced post-operative complications, and no case of mortality was recorded. Eight (20.5%) cases and five patients required reoperation due to recurrence, all of which were performed within 2 years after the previous surgery. In five (12.8%) of these eight cases, reoperation was performed within 1 year after the previous surgery (Figure 1A). The cumulative recurrence rates after the initial surgery are 7.7% in 1 year, 12.8% in 2 years, 17.9% in 3 years and 20.5% in 4 years (Figure 1B). The most common causes of recurrence were medical intractability and the presence of perforation or fistula. A diverting stoma was created in one of the eight patients, and a redo anastomosis was performed in the other seven patients. The median interval between the previous surgery and reoperation due to recurrence was 12 (IQR 6.25-17.75) months.

Univariate analyses demonstrated that elevated CRP levels and emergency surgeries were significantly associated with the recurrence of intestinal BD. In multivariate analysis, emergency surgery remained significantly associated with the recurrence of intestinal BD (Table 4).

DISCUSSION

Intestinal BD is characterized by deep ulcers, most commonly found in the ileocecal area or terminal ileum[12]. Many patients with intestinal BD require emergency surgeries because deep ulcers tend to penetrate the intestinal wall[13]. However, only a few studies have explored the long-term clinical outcomes and related prognostic factors in surgical patients with intestinal BD. Therefore, in this study, we aimed to investigate the long-term outcomes of surgical treatment for intestinal BD and identify the predictive factors for recurrence and reoperation.

In this study, 8 of the 39 surgical cases (20.5%) of intestinal BD required reoperation due to recurrence during the follow-up period. The complicated recurrences that required reoperation were confirmed through CT, endoscopy, and physical examination. When no findings other than BD-related complications observed as a result of physical examination and CT scan were identified, it was considered as a symptom of BD recurrence. The 5-year cumulative reoperation rate was 20.5%, and all reoperations were performed within 2 years after the previous surgery. The cumulative reoperation rates were 12.8% and 20.5% at 2 and 5 years after the initial surgery. A previous study in Japan reported a

Table 1 Patient characteristics and clinical variables

	Cases (<i>n</i> = 39)
Age (yr) at the time of diagnosis of BD, median (IQR)	36 (29-49)
Age (yr) at the time of diagnosis of intestinal BD, median (IQR)	38 (30-49)
Age (yr) at the time of surgery, median (IQR)	49 (31-57)
Interval (yr) between intestinal BD diagnosis and surgical treatment, median (IQR)	3 (1-8)
Sex, <i>n</i> (%)	
Male	20 (51.3)
Female	19 (48.7)
Symptoms and signs of BD, <i>n</i> (%)	
Oral ulcer	14 (35.9)
Genital ulcer	7 (18.0)
Ocular lesion	1 (2.6)
Skin lesion	0 (0.0)
Arthritis	0 (0.0)
Vascular lesion	1 (2.6)
Neurologic lesion	0 (0.0)
Location of ulceration, <i>n</i> (%)	
Ileocecal	35 (89.7)
Ascending colon	3 (7.7)
Rectum	1 (2.6)
Medications, <i>n</i> (%)	
Steroids	28 (71.8)
Colchicine	31 (79.5)
5-ASA or sulfasalazine	27 (69.2)
Azathioprine or 6-MP	23 (59.0)
TNF- α inhibitor	15 (38.5)
Antibiotics	13 (33.3)
Indication for operation, <i>n</i> (%)	
Medical intractability	16 (41.0)
Perforation or fistula	16 (41.0)
Stricture	4 (10.3)
Bleeding	3 (7.7)
Preoperative CRP (mg/L), median (IQR)	3.9 (0.92-6.41)
Preoperative ESR (mm/h), median (IQR)	30.0 (15.0-49.5)
Preoperative neutrophil (%), median (IQR)	66.1 (59.0-73.8)
Preoperative lymphocyte (%), median (IQR)	18.1 (11.8-27.2)
Preoperative procalcitonin, median (IQR)	0.0 (0.0-0.1)
Preoperative albumin (g/dL), median (IQR)	3.0 (2.6-3.3)

BD: Behcet's disease; IQR: Interquartile range; 5-ASA: 5-Aminosalicylic acid; 6-MP: 6-Mercaptopurine; TNF: Tumor necrosis factor; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate.

Table 2 Surgical data

	Cases (n = 39)
Emergency surgery, n (%)	5 (12.8)
Surgery type, n (%)	
Open surgery	20 (51.3)
Laparoscopy	19 (48.7)
Surgical procedure, n (%)	
SB segmental resection	3 (7.7)
Ileocecal resection	19 (48.7)
Right hemicolectomy	11 (28.2)
Other	6 (15.4)
Diverting stoma, n (%)	1 (2.6)
Expected blood loss, n (%)	
Minimal	14 (35.9)
10-100 mL	16 (41.0)
> 100 mL	1 (2.6)
NA	8 (20.5)
Duration of surgery (min), median (IQR)	116 (95-740)

SB: Small bowel; IQR: Interquartile range; NA: Not assessed.

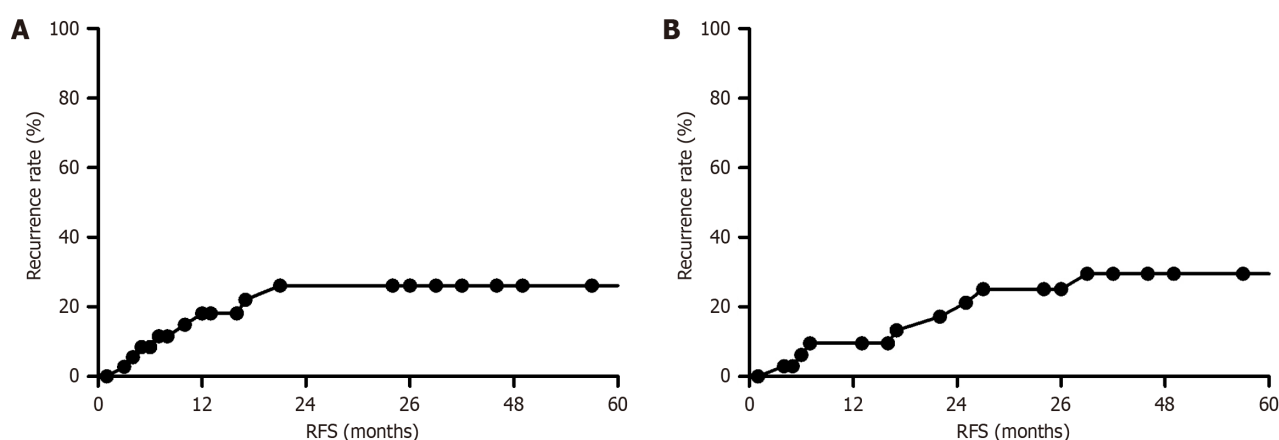


Figure 1 Recurrence-free survival after surgical treatment and initial surgical treatment in patients with intestinal Behcet's disease. A: After surgical treatment; B: After initial surgical treatment.

reoperation rate of 44% (40 out of 91 cases)[13]. Iida *et al*[11] reported a higher recurrence rate (12 out of 15 surgical cases, 80%) than that observed in our study. In Korea, Lee *et al*[14] reported that 12 out of 26 patients (46.1%) experienced recurrences after the initial surgery, with 50% of them occurring within 2 years. Choi *et al*[15] reported a cumulative reoperation rate of 18.0% and 38.0% at 2 and 5 years, respectively, after the primary surgery in patients with intestinal BD [16]. Another study demonstrated that the cumulative probability of reoperation was 16.9% at 2 years and 36.0% at 5 years. The results of the present study are similar to those of previous studies, although the observed cumulative reoperation rate was slightly lower. This difference could be attributed to early diagnosis and treatment of intestinal BD based on medical knowledge and through advanced colonoscopy procedures.

A key finding of the present study is that the timing of surgery for intestinal BD may be an important prognostic factor for reoperation. In this study, patients underwent surgery approximately 3 years after being diagnosed with intestinal BD. Furthermore, > 80.0% of patients underwent surgery after the disease had become refractory to medical treatment or after complications, such as perforation, fistula, or obstruction had developed. As a result, > 12.0% of the patients required emergency surgery, which was identified as a significant prognostic factor in our multivariate analysis. A previous study reported that patients with intestinal BD who underwent surgery earlier exhibit better prognoses in terms

Table 3 Postoperative course and recurrence data

	Cases (n = 39)
Postoperative complications, n (%)	
Anastomosis leakage	1 (2.6)
Intra-abdominal abscess	0 (0.0)
Fistula	0 (0.0)
Wound infection	3 (7.7)
Bleeding	1 (2.6)
Ileus	0 (0.0)
Mortality, n (%)	0 (0.0)
Clavien-Dindo classification, n (%)	
1	2 (5.2)
2	0 (0.0)
3	3 (7.7)
4	0 (0.0)
Cause of reoperation, n (%)	
Medical intractability	4 (50.0)
Perforation or fistula	4 (50.0)
Stricture	0 (0.0)
Bleeding	0 (0.0)
Reoperation procedure, n (%)	
SB segmental resection	0 (0.0)
Redo anastomosis	7 (87.5)
Diverting stoma	1 (12.5)
Follow-up period (mo), median (IQR)	42.0 (8.0-72.0)
Time to recurrence (mo), median (IQR)	12.0 (6.25-17.75)

SB: Small bowel; IQR: Interquartile range.

of recurrence risk and reoperation rate than those of patients who underwent surgical treatment at a later stage^[17]. In addition, the higher preoperative CRP level was significant with higher reoperation risk. Therefore, it can be expected that the more severe systemic inflammation which cause an increasing in CRP level before operation, the more affected the reoperation. In approximately 90% (35/39) of cases, intra-venous antibiotics were administered postoperatively. Most of the antibiotics administered were metronidazole and ciprofloxacin, and carbapenem was also administered. Since most of the patients were administered similar antibiotics, antibiotics would not have had significant effects on changes of patients' inflammatory markers and risk of recurrence.

This study had several limitations. First, although our study included patients who were followed up for a sufficient period, the inclusion of more patients and surgeries is needed to make a definitive conclusion. Second, a selection bias might have been present because of the retrospective study design.

CONCLUSION

Surgical resection is a feasible treatment option for complicated BD, although this condition is associated with poor clinical courses and high reoperation rates. Furthermore, reoperation is associated with severe inflammatory conditions, as reflected by the requirement for emergency surgery or elevated CRP levels at the time of surgery. Therefore, a timely surgical treatment is essential to reduce the reoperation rate.

Table 4 Risk factors for recurrence

	Univariate analysis		Multivariate analysis	
	HR (95%CI)	P value	HR (95%CI)	P value
Sex	0.358 (0.084-1.518)	0.163	2.372 (0.370-15.186)	0.362
Age at the time of surgery	0.979 (0.923-1.039)	0.487		
Use of steroid	1.922 (0.386-9.566)	0.425		
Use of colchicine	1.901 (0.232-15.552)	0.549		
Use of azathioprine or 6-MP	0.919 (0.219-3.848)	0.908		
Use of 5-ASA or sulfasalazine	1.195 (0.241-5.930)	0.828		
Use of TNF- α inhibitor	1.485 (0.371-5.945)	0.577		
Use of antibiotics	0.279 (0.034-2.267)	0.232		
Preoperative CRP level	1.129 (1.031-1.236)	0.009	0.988 (0.868-1.125)	0.855
Preoperative ESR	1.001 (0.978-1.025)	0.925		
Preoperative neutrophil	0.973 (0.080-1.172)	0.774		
Preoperative lymphocyte	0.898 (0.650-1.240)	0.514		
Preoperative procalcitonin	28.659 (0.290-2832.482)	0.152		
Preoperative albumin level	0.336 (0.081-1.394)	0.133	0.220 (0.028-1.739)	0.151
Emergency surgery	12.216 (2.669-55.910)	0.001	10.746 (1.486-77.686)	0.019
Open surgery	1.423 (0.340-5.961)	0.629		
Postoperative complication	2.051 (0.248-16.962)	0.505		

5-ASA: 5-Aminosalicylic acid; 6-MP: 6-Mercaptopurine; TNF: Tumor necrosis factor; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; HR: Hazard ratio; CI: Confidence interval.

ARTICLE HIGHLIGHTS

Research background

Behcet's disease (BD) is a chronic vasculitic disorder that impacts various organs, presenting with recurring oral and genital ulcers, arthritis, vasculitis, and intestinal ulcers. Despite the frequent occurrence of intestinal complications in BD, the effectiveness and long-term results of surgical interventions for intestinal BD are yet to be definitively established.

Research motivation

Despite the frequent occurrence of intestinal complications in BD, the effectiveness and long-term results of surgical interventions for intestinal BD are yet to be definitively established.

Research objectives

To assess the postoperative clinical outcomes of intestinal BD and identify factors associated with its recurrence.

Research methods

A retrospective review of patients with intestinal Behcet's disease undergoing surgical resection at Asan Medical Center in Seoul, South Korea, between January 2010 and August 2021 was conducted. The study focused on patient demographics, clinical characteristics, surgical data, and postoperative outcomes, with the diagnosis of intestinal BD determined through a modified Delphi process, excluding patients with evidence of other gastrointestinal diseases during follow-up.

Research results

In a study involving 31 patients who underwent 39 surgeries for intestinal Behcet's disease, the mean patient age was 45.1 years, with a mean interval of 4.9 years between the diagnosis and surgical treatment. The primary indications for surgery were medical intractability (41.0%) and fistula or abscess (28.2%). Laparoscopic approaches were used in 48.7% of cases, and eight recurrences (20.5%) requiring reoperation were observed during a mean follow-up of 45 months, with a recurrence rate of 10.3% at 1 year and 20.5% at 3 years. Emergency surgery and elevated C-reactive protein levels were identified as predictors of recurrence in multivariate analysis.

Research conclusions

Surgical resection is a viable treatment for complicated BD, despite its association with challenging clinical courses and elevated reoperation rates, emphasizing the importance of timely surgical intervention to mitigate reoperation risk, particularly in the presence of severe inflammatory conditions.

Research perspectives

It is necessary to identify factors, including specific biomarkers, that may influence recurrence through a larger number of patients with intestinal BD and make efforts to reduce recurrence rates using this information.

FOOTNOTES

Author contributions: Park MY designed and performed the research and wrote the paper; Yoon YS designed the research and supervised the report; Park JH collected the data; Lee JL and Yu CS provided clinical advice and supervised the report.

Institutional review board statement: The study protocol was approved by the institutional review board of Asan Medical Center (approval No. 2022-0238).

Informed consent statement: This study is retrospective study and use anonymous data, and Institutional Review Board of Asan Medical Center approved study and waived informed consent.

Conflict-of-interest statement: All authors have no conflict of interest related to the manuscript.

Data sharing statement: No additional data are available.

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