

Immunosuppressive medication is not associated with surgical site infection after surgery for intractable ulcerative colitis in children

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Summary

Pediatric ulcerative colitis (UC) sometimes progresses to an intractable condition for medical therapy. The surgical management of UC is challenging because of difficult procedures and frequent infectious complications. The aim of this study was to survey surgical procedures and infectious complications in pediatric patients with UC in Japan and to assess the relationship between preoperatively administered immunosuppressive drugs and postoperative surgical site infection (SSI). A survey of pediatric patients treated from 2000 to 2012 was sent to 683 facilities nationwide. Secondary questionnaires were sent to physicians who followed up patients with UC who had undergone surgery with the aim of assessing the relationships between postoperative SSI and selected preoperative patient characteristics, disease severity, medications, and operative procedures. Data for 136 patients (77 boys and 59 girls) were assessed. Median age at surgery was 14.1 years (range: 2.4-18.9 years). Surgery was performed in one stage in 35 cases, two stages in 57 cases, and three stages in 44 cases. SSI occurred in 36/136 patients (26%). According to multiple logistic regression analysis, there were statistically significant associations between SSI and staged surgery (three/one, OR: 6.7, 95% CI: 2.1-25.5, $p = 0.0007$; three/two, OR: 3.4, 95% CI: 1.4-8.6, $p = 0.0069$) and female sex (OR: 2.3, 95% CI: 1.0-5.4, $p = 0.0434$). Preoperative medications and incidence of SSI were not significantly associated. Preoperative immunosuppressive medication does not affect the incidence of SSI. Three-stage surgery and female sex are independent predictors of development of postoperative SSIs in pediatric patients with UC.

Keywords: Ulcerative colitis, children, colectomy, complication

1. Introduction

Inflammatory bowel diseases (IBDs), a group of chronic inflammatory gastrointestinal disorders, include Crohn disease and ulcerative colitis (UC). In recent years, the incidence of IBD has increased markedly in both adults and children. IBD's onset during childhood is in 20-30% of patients and this condition is characterized by extensive intestinal involvement and rapid early progression. IBD is more severe in children than in adults (1).

Colectomy is uncommonly performed for pediatric UC; rates have remained stable from 1983 to 2009. However, the rates of in-hospital postoperative complications have increased, particularly in patients undergoing emergency colectomy (2,3). Such complications reportedly occur in 25% of cases, gastro-intestinal (13%) and infectious (9.3%) complications being the most common (2). Independent predictors of postoperative complications were identified in these studies and it was concluded that optimizing timing of colectomy may reduce postoperative complications in pediatric patients with UC. Knod *et al.* (4) have reported that colectomy with ileoanal anastomosis does not have a greater incidence of complications in young children (≤ 11 -years-old) with UC than in older patients and achieves a good postoperative quality of life and stool patterns.

Generally, patients with UC undergoing elective colectomy have high rates of surgical site infection (SSI), specifically deep and organ/space infections (5). Uchino *et al.* (6) have also demonstrated that, in surgical patients with clean-contaminated wounds, IBD is an independent risk factor for incisional SSI.

Recently, immunomodulators and biologics that affect patients' immune systems have been increasingly used to treat steroid-dependent and -resistant pediatric UC. A European Crohn's and Colitis Organisation paper has stated that preoperative thiopurines do not increase the risk of postoperative complications in adult patients (7). Additionally, there does not appear to be a higher rate of postoperative complications after colectomy for UC performed immediately following or in the medium term after the use of cyclosporine. Two studies have demonstrated that previous exposure to azathioprine/6-mercaptopurine does not affect the rates of short term and late postoperative complications after pouch surgery for UC (8,9). However, there are few studies concerning the relationship between preoperative drugs and post-colectomy infectious complications in children.

The aim of this study was to survey surgical procedures and postoperative infectious complications in patients with pediatric UC in Japan and to assess the relationship between preoperatively administered drugs and postoperative SSI.

2. Materials and Methods

This study was a retrospective analysis of data from

multiple institutions in Japan. A national survey of immunomodulators and biologics used in pediatric patients with IBD (aged < 17 years at diagnosis) between 2000 and 2012 was sent to 683 facilities treating pediatric patients with IBD in Japan from December 2012 to March 2013 (10). All participating physicians followed the Japanese diagnostic criteria for Crohn disease and UC (11). These diagnostic criteria are substantially the same as the Port criteria published by the IBD working group of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (12). This primary survey assessed the total number of pediatric patients with IBD, the number treated with immunomodulators and biologics, and the number who underwent surgery.

Secondary questionnaires were sent to physicians who followed up patients with UC who had undergone surgery, the purpose being to assess the following factors: selected patient characteristics, severity of UC, preoperative medications, operative procedure, and SSI. Patient characteristics assessed included sex, age at disease onset, age at surgery, preoperative duration of disease, indications for surgery, and preoperative blood analysis data including serum albumin, hemoglobin and C-reactive protein (CRP) concentrations.

Clinical severity of disease was evaluated according to the Pediatric Ulcerative Colitis Activity Index (PUCAI) (13) and Japanese disease severity criteria as established by the Research Committee on Inflammatory Bowel Disease of the Ministry of Health and Welfare in Japan in 1994 (11). Extent of disease at surgery was evaluated according to the Montreal classification of UC as E1 (ulcerative proctitis), E2 (left-sided UC), and E3 (extensive UC) (14).

Preoperative medical therapy assessed included systemic prednisolone (PDN), 5-aminosalicylates, azathioprine (AZA), cyclosporine A (CYA), tacrolimus (TAC), infliximab (IFX), and apheresis therapy. Patients' records were reviewed if any of these therapies had been used within 90 and 30 days prior to the first-stage operation. The dosage of PDN administered during the month before surgery was also calculated. Serum trough levels of TAC, CYA, and IFX and 6-thioguanine nucleotide concentrations in patients receiving AZA were not monitored.

Generally, operative procedures for UC both adults and children were classified as one-, two-, or three-stage procedures to complete total proctocolectomy with ileal J-pouch anal anastomosis (IPAA). The one-stage procedure is total proctocolectomy with IPAA without a diversion stoma. The two-stage procedure includes total proctocolectomy with IPAA and creation of diversion ileostomy in the first stage and closure of the ileostomy in the second stage. The three-stage procedure includes subtotal colectomy with creation of a diversion ileostomy and mucus fistula of the sigmoid colon or rectal stump in the first stage. In the second stage, remnant proctocolectomy and IPAA with recreation of diversion

ileostomy are performed. Finally, the ileostomy is closed in the third stage.

SSI was defined according to the definition of the Centers for Disease Control and Prevention as infections occurring within 30 days after surgery (15). All patients were followed up for a minimum of 30 days after the final stage of their procedures. SSI, including incisional wound infection (I-SSI), and/or organ/space infection (OS-SSI), was evaluated. Anastomotic leaks and abscesses (OS-SSI) were diagnosed by contrast imaging, computed tomography, or intraoperative findings (16).

The relationships between preoperative factors, including administered drugs, and incidence of postoperative SSI occurrence after first stage operations on pediatric patients with UC was assessed in this study.

The data were analyzed by the χ^2 and Mann-Whitney U tests and by multiple logistic regression analysis using the JMP version 7 software program (SAS Institute, Cary, NC, USA). A *p* value of less than 0.05 was considered to be statistically significant.

This study was approved by the institutional ethical committees of Juntendo University and all participating institutions.

3. Results

In the primary survey, 1,617 pediatric patients with UC were enrolled from 1 January 2000 to 31 December 2012. Data for 146 patients who had undergone surgery were collected *via* secondary questionnaires that were sent to the physicians who were following them up. Finally, we were able to assess 136 patients (77 boys and 59 girls), 10 of these patients being excluded because of incomplete data concerning surgery, medications, and SSI.

Table 1 shows the study of patients' baseline characteristics. Median age at disease onset was 12.0 years (range 0.3-17.7 years), median age at surgery 14.1 years (range: 2.4-18.9), and median preoperative duration of disease 679 days (range 16-3,611 days). Median preoperative serum albumin, hemoglobin, and CRP concentrations were 3.2 g/dL (range: 1.4-4.8 g/dL), 10.6 g/dL (range: 4.9-17.5 g/dL), and 0.33 g/dL (range: 0.0-16.11 g/dL), respectively. As to preoperative disease activity, median PUCAI score was 45 (range: 0-85). According to Japanese criteria of disease severity, 12% of patients had mild disease, 40% moderate, and 45% severe. According to the Montreal classification, 96% of patients had E3 disease (extensive UC).

Indications for surgery, which overlapped each other in this study, are listed in Table 2. The most frequent indications for surgery were intractable disease caused by resistance to medications, including steroid dependency and steroid resistance, in 77 % of patients. The next most frequent indications were poor quality of life in 23%, adverse effects of drugs in 12%, massive bleeding in 11%, and growth retardation in 9%.

Table 1. Baseline patients' characteristics

Characteristics	
Gender (Female/Male)	59/77
Age at disease onset (years old)	12.0 (0.3-17.7)
Age at operation (years old)	14.1 (2.4-18.9)
Preoperative disease duration (days)	679 (16-3611)
Preoperative serum albumin (g/dL)	3.2 (1.4-4.8)
Preoperative serum hemoglobin (g/dL)	10.6 (4.9-17.5)
Preoperative serum CRP (mg/dL)	0.33 (0-16.11)
PUCAI	45 (0-85)
Japanese disease severity criteria	
Mild	16 (12%)
Moderate	55 (40%)
Severe	61 (45%)
unknown	4 (3%)
Montreal classification of UC	
E1 (ulcerative proctitis)	0 (0%)
E2 (left-sided UC)	1 (1%)
E3 (extensive UC)	131 (96%)
unknown	4 (3%)

CRP, reactive protein; PUCAI, pediatric ulcerative colitis activity index; UC, ulcerative colitis. Data was shown by median (range).

Table 2. Operative indications

Indication for operation	<i>n</i>	%
Perforation	4	3
Massive bleeding	16	11
Toxic Megacolon	6	4
Colon cancer	0	0
Fluminant disease	4	3
Growth Retardation	13	9
Intractable disease	109	77
Lower QOL	33	23
Drug side effect	17	12
Extra-intestinal complications	2	1

Table 3 shows the surgical procedures and relevant patient characteristics, including preoperative medications and laboratory data. Thirty-five patients had undergone one-stage surgery, 57 two-stage surgery, and 44 three-stage surgery. Patients who had undergone three-stage surgery had a significantly shorter duration of preoperative disease than those in the other groups (*p* = 0.0147); their more severe conditions being reflected by the necessity for more complex surgery (*p* < 0.0001), worse PUCAI scores at surgery (*p* < 0.0001), lower preoperative albumin (*p* < 0.0001) and hemoglobin concentrations (*p* = 0.0059), and higher preoperative CRP concentrations (*p* < 0.0001). Preoperative medications varied by group and institution. In particular, few patients in this study received IFX.

SSI developed in 36/136 patients (26%) (Table 4). I-SSI occurred in 28/136 patients (21%) and OS-SSI in 16/136 patients (12%). SSI occurred in 11% of patients who had undergone one-stage surgery, comprising I-SSI in 9% and OS-SSI in 9%; in 19% patients who had undergone two-stage surgery, comprising I-SSI in 13% and OS-SSI in 12%; and in 48% patients who had

Table 3. Patients' characteristics among operative procedures

Items	One	Two	Three	p value
girls : boys	14 : 21	21 : 35	24 : 20	0.2055
Age at disease onset (years old)	11.4 ± 3.6	11.4 ± 3.1	11.1 ± 5.0	0.7996
Severity at onset (mild/moderate/severe)	3/21/8	5/23/20	4/16/20	
PUCAI at disease onset	52.5 ± 25.4	53.4 ± 21.5	62.2 ± 21.2	0.3496
Disease extent at onset (rectum/left side/total colitis)	0/4/30	3/5/41	1/6/35	
Age at operation (years old)	14.0 ± 2.7	13.8 ± 2.6	13.1 ± 3.6	0.8278
Preoperative disease duration (days)	951.6 ± 782	873.2 ± 635.7	657.1 ± 834.1	0.0147
Severity at operation (mild/moderate/severe)	3/22/10	11/26/16	2/8/34	< 0.0001
PUCAI at operation	38.9 ± 20.5	39.5 ± 25.8	69.0 ± 21.6	< 0.0001
Disease extent at operation (E1/E2/E3)	0/1/33	0/1/54	0/1/43	0.5627
Preoperative serum albumin (g/dL)	3.7 ± 0.8	3.7 ± 0.6	2.7 ± 0.8	< 0.0001
Preoperative serum hemoglobin (g/dL)	11.5 ± 2.3	11.2 ± 2.3	9.7 ± 2.2	0.0059
Preoperative serum CRP (mg/dL)	1.9 ± 3.7	0.8 ± 2.2	4.0 ± 4.5	< 0.0001
Preoperative 90 5ASA (y/n)	31/2	53/4	28/11	0.0064
Preoperative 90 PDN (y/n)	32/2	42/15	32/7	0.0344
Preoperative 90 APT (y/n)	13/19	15/42	8/31	0.1665
Preoperative 90 AZA (y/n)	11/21	30/27	8/31	0.0047
Preoperative 90 TAC (y/n)	3/29	17/40	5/34	0.0277
Preoperative 90 CYA (y/n)	3/29	13/44	10/29	0.1589
Preoperative 90 IFX (y/n)	1/31	9/48	1/38	0.0288
Preoperative 30 5ASA (y/n)	30/3	49/8	26/16	0.003
Preoperative 30 PDN (y/n)	31/3	39/18	38/6	0.0131
Preoperative 30 APT (y/n)	9/23	8/49	13/29	0.0935
Preoperative 30 AZA (y/n)	12/20	24/33	7/35	0.0179
Preoperative 30 TAC (y/n)	4/28	13/44	6/36	0.3762
Preoperative 30 CYA (y/n)	3/29	12/45	9/33	0.2805
Preoperative 30 IFX (y/n)	1/31	1/56	1/41	0.9182
EsPDN(g)	633.5 ± 751.0	663.7 ± 1004.7	838.2 ± 839.4	0.87
EsPDN(g)/BW (kg)	14.7 ± 15.9	21.8 ± 34.9	22.0 ± 22.5	0.1586

CRP; creative protein, PUCAI; pediatric ulcerative colitis activity index, 5ASA; 5-aminosalicylates, PDN; prednisolone, APT; apheresis therapy, AZA; azathioprine, TAC; tacrolimus, CYA; cyclosporine A, IFX; infliximab, y; yes, n; no, EsPDN; estimated PDN administered dose during 1month before operation, BW; body weight. Data was shown by mean ± standard deviation.

Table 4. SSI occurrence among operative procedures

Items	Total (136)	One (35)	Two (57)	Three (44)
SSI	36 (26%)	4 (11%)	11(19%)	21 (48%)
I-SSI	28 (21%)	3 (9%)	8 (13%)	17 (35%)
OS-SSI	16 (12%)	3 (9%)	7 (12%)	6 (14%)

SSI; surgical site infection, I-SSI; incisional wound infection, OS-SSI; organ/space infection.

undergone three-stage surgery, comprising I-SSI in 35% and OS-SSI in 14%.

Table 5 shows the relationships between development of SSI after first stage operations and selected factors. SSI occurred significantly more frequently in girls than boys ($p = 0.012$). Neither disease severity nor preoperative medications were significantly associated with development of SSI. There was a statistically significant relationship between staged surgery and development of SSI ($p = 0.0004$).

Table 6 shows the results of multiple logistic regression analysis. Staged surgery (three/one, OR: 6.7, 95% CI: 2.1-25.5, $p = 0.0007$; three/two, OR: 3.4, 95% CI: 1.4-8.6, $p = 0.0069$) and female sex (OR: 2.3, 95% CI: 1.0-5.4, $p = 0.0434$) were statistically significant predictors of development of SSI in pediatric patients with UC. Staged surgery was the sole statistically

significant risk factor for I-SSI, (three/one, OR: 6.5, 95% CI: 1.9-30.2, $p = 0.0021$; three/two, OR: 3.6, 95% CI: 1.4-9.9, $p = 0.0091$); however, no predictors of OS-SSI, such as anastomotic leakage or intraperitoneal abscess, were identified in this study.

4. Discussion

The major findings of this study were that female sex and three-stage surgery are independent predictors of development of SSI after surgery for UC in pediatric patients. Three-stage surgery was an independent predictor of development of I-SSI occurrence; female sex was not. No predictors of OS-SSI were identified. Preoperative medications, including 5-ASA, AZA, TAC, and CYA, did not significantly affect the incidence of SSI.

SSI is the most frequent complication of colorectal surgery. In adult colorectal surgery, dirty or contaminated surgery, open ileostomy or colostomy placement, emergency surgery, and multiple procedures are reportedly associated with increased risk of SSI (17,18). Segal *et al.* (19) reported that risk factors for I-SSI and OS-SSI differ in patients who undergo colon resection.

The surgical management for UC is challenging because the procedure of IPAA is difficult; additionally,

Table 5. The relationship between SSI occurrence and several factors in patients who received first stage operation

Items	SSI (+)	SSI (-)	p value
girls : boys	22 : 14	37 : 63	0.0125
Age at disease onset (years old)	11.4 ± 4.3	11.3 ± 3.7	0.6570
Severity at onset (mild/moderate/severe)	2/15/16	6/49/32	0.5065
PUCAI at disease onset	58.3 ± 26.2	54.9 ± 20.3	0.5956
Disease extent at onset (rectum/left side/total colitis)	366/74	4/10/78	0.2459
Age at operation (years old)	13.9 ± 2.2	13.5 ± 3.2	0.7962
Preoperative disease duration (days)	864.9 ± 980.6	811.0 ± 642.9	0.4544
Severity at operation (mild/moderate/severe)	5/14/16	12/41/44	0.9492
PUCAI at operation	53.7 ± 28.6	45.0 ± 26.1	0.1828
Disease extent at operation (E1/E2/E3)	0/0/35	1/2/95	0.3952
Preoperative serum albumin (g/dL)	3.2 ± 0.8	3.4 ± 0.9	0.1087
Preoperative serum hemoglobin (g/dL)	10.4 ± 2.7	11.0 ± 2.2	0.1998
Preoperative serum CRP (mg/dL)	2.4 ± 4.0	1.9 ± 3.5	0.0927
Preoperative 90 5ASA (y/n)	27/6	85/12	0.4716
Preoperative 90 PDN (y/n)	26/7	80/17	0.6412
Preoperative 90 APT (y/n)	9/24	27/68	0.8992
Preoperative 90 AZA (y/n)	12/21	37/58	0.7921
Preoperative 90 TAC (y/n)	6/27	19/76	0.8194
Preoperative 90 CYA (y/n)	6/27	20/75	0.7216
Preoperative 90 IFX (y/n)	1/32	10/85	0.1453
Preoperative 30 5ASA (y/n)	25/9	80/18	0.3226
Preoperative 30 PDN (y/n)	29/7	79/20	0.9223
Preoperative 30 APT (y/n)	8/26	21/76	0.8211
Preoperative 30 AZA (y/n)	9/25	32/65	0.4761
Preoperative 30 TAC (y/n)	6/28	17/80	0.9872
Preoperative 30 CYA (y/n)	5/29	21/76	0.3706
Preoperative 30 IFX (y/n)	0/34	3/94	0.1764
EsPDN(g)	843.5 ± 869.9	652.0 ± 915.9	0.0917
EsPDN(g) / BW (kg)	24.8 ± 29.4	18.6 ± 27.3	0.1800
Stage operation (one/two/three)	4/11/21	31/46/23	0.0004

SSI; surgical site infection, CRP; creactive protein, PUCAI; pediatric ulcerative colitis activity index, 5ASA; 5-aminosalicylates, PDN; prednisolone, APT; apheresis therapy, AZA; azathioprine, TAC; tacrolimus, CYA; cyclosporine A, IFX; infliximab, y; yes, n; no, EsPDN; estimated PDN administered dose during 1month before operation, BW; body weight. Data was shown by mean ± standard deviation.

Table 6. Multiple logistic regression analysis

Items	Chi square	Multiple logistic regression analysis			
	p value	OR	95% CI	p value	
SSI					
female	0.0141	two/one	2.3	1.0-5.4	0.0434
staged operation	0.0004	three/one	2	0.6-7.7	0.272
		three/two	6.7	2.1-25.5	0.0007
			3.4	1.4-8.6	0.0069
I-SSI					
female	0.0460				0.132
staged operation	0.0012	two/one	1.8	0.5-8.9	0.3888
		three/one	6.5	1.9-30.2	0.0021
		three/two	3.6	1.4-9.9	0.0091
OS-SSI					
none					

SSI; surgical site infection, I-SSI; incisional wound infection, OS-SSI; organ/space infection.

patients with UC tend to be in poorer condition than patients with other colorectal diseases requiring surgery because of infection or contamination, pro-inflammatory factors characteristic of UC, anemia and malnutrition, and immunosuppression, including that induced by immunosuppressive medication. Patients with UC undergoing elective colectomy reportedly have

significantly higher rates of SSI, especially OS-SSI (5,6). Araki *et al.* (20) have reported that poor general physical status is a significant independent risk factor for OS-SSI in adult patients with UC. In a comparison of colorectal surgery for colorectal cancer versus IBD in patients with clean-contaminated wounds, IBD was shown to be an independent risk factor for I-SSI (6).

In this study, surgery for UC was performed in one stage in 35 cases, two stages in 57 cases, and three stages in 44 cases. We found three-stage surgery to be a statistically significant independent predictor of SSI, likely because of risk factors such as dirty or contaminated surgery, creation of ileostomies, and the characteristically poor condition of patients requiring three-stage surgery compared with that of those requiring only one- or two- stage surgery.

We found that female sex is a predictor of SSI, as shown by two other studies (17,21) of colorectal surgery for adult patients. In contrast, Morikane *et al.* (18) found an association between male sex and increased risk of SSI in adult patients undergoing colorectal surgery. The reasons for SSI being more common in female than male patients in three of these four studies is unclear; however, Pedroso-Fernandez *et al.* (17) proposed in a personal communication that the procedure for extracting the resected tissue and size of incision may differ in female patients for cosmetic reasons.

Until ten years ago, high total PDN doses were administered before surgery and this was strongly associated with incidence of SSI in patients with UC, especially in Japanese institutes (22-25). Use of non-steroid drugs, including immunomodulators and anti-tumor necrosis factor, has recently been increasing in pediatric patients with a hopeful future, though corticosteroids remain the main drug for inducing remission of UC. If the medications used instead of PDN for treating UC have immunosuppressive effects that may lead to infectious complications, such drugs could increase the incidence of surgical complications. Thus far, several studies have concluded that there is no relationship between preoperatively administered medications and postoperative SSI in pediatric patients with UC (25-29). Regarding use of immunomodulators, preoperative exposure to thiopurines or calcineurin inhibitors is reportedly not associated with increased postoperative complications in pediatric patients with UC who undergo colectomy (27,29). Patton *et al.* (28) found that preoperative IFX was not associated with postoperative complications in pediatric patients with UC. However, Kennedy *et al.* (26) reported that postoperative small bowel obstruction occurred more frequently in children who had been treated with IFX prior to proctocolectomy than in those who had not; however, this relationship is unclear. Because too few patients in our study had received IFX, our results did not allow us to draw a conclusion about any relationship between preoperative IFX administration and SSI occurrence.

This study has some limitations. Three-stage surgery was selected for pediatric patients with perforation, toxic megacolon, and IBD-unclassified whereas selection of one- or two-stage surgery was dependent on the policy and judgement within each surgical institute and the obtaining of informed consent for proposed procedures.

Additionally, precautions taken to prevent SSI, surgical indications and procedures, and length and positions of incisions differed between the surgical institutes. Concerning the relationship between preoperatively administered medications and SSI, we did not monitor 6-thioguanine nucleotide concentrations in patients receiving AZA (30) or trough serum con/ss in those receiving TAC (31), CYA (32), or IFX (33) in this study; we therefore could not investigate the relationship between serum concentrations of drugs and postoperative infectious complications.

In conclusion, three-stage surgery is an independent predictor of development of SSI after surgery in pediatric patients with UC. In this study, preoperative medication, including 5-ASA, AZA, TAC, and CYA, did not affect the overall incidence of SSI, or that of I-SSI or OS-SSI. An immediate correct diagnosis, appropriate medical therapy without using high total doses of PDN, optimal timing of surgery, and avoidance of three-stage surgery may result in better surgical outcomes and quality of life.

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