Impact of Preoperative Medical Therapy for Surgical Site Infection in Children with Ulcerative Colitis: A Single-Center Experience

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ABSTRACT

Backgrounds: We aimed to investigate the relationship between preoperative immunomodulator administration and occurrence of Surgical Site Infection (**SSI**) in pediatric Ulcerative Colitis (**UC**) patients.

Methods: We evaluated **SSI** occurrence after total proctocolectomy with ileal J-pouch anal anastomosis and creation of diversion ileostomy at the first stage in pediatric **UC** 24 patients. **SSI** was defined as an infection occurring within 30 days after operation. The relationships between **SSI** occurrence and preoperative medical therapy were reviewed.

Results : SSIs were diagnosed in seven (29%) patients, including four with incisional **SSI** and one with organ/space **SSI**, and two patients had both. The total dose of preoperatively administered prednisolone and preoperative immunomodulator administration were significantly related to **SSI** occurrence (p=0.028 and p=0.046, respectively). Multivariate analysis showed that the total dose of preoperatively administrated prednisolone ≥20,000 mg (Receiver Operatorating Characteristic curve cut-off) was an independent risk factor for SSI occurrence (p=0.035). Preoperative immunomodulator administration increased the risk of SSI in patients who received high-dose prednisolone (≥7250 mg, median; p=0.028), but not in patients who received low-dose prednisolone (<7250 mg).

Conclusions: In pediatric **UC** patients who receive low-dose prednisolone, preoperative immunomodulator administration does not affect **SSI** occurrence after total proctocolectomy.

Keywords: Surgical Site Infection; Ulcerative Colitis; Children

INTRODUCTION

Colorectal surgery is associated with a high rate of surgical site infection (**SSI**), including incisional wound infection (**I-SSI**) and organ/space infection (**OS-SSI**), and such as anastomotic leakage and intraperitoneal abscess **[1].** In particular, surgery for inflammatory bowel disease, such as ulcerative colitis (**UC**) and Crohn's disease has an increased risk of occurrence of **SSI**. This increased risk is due to inflammatory or proinflammatory conditions in disease characters, infectious or contaminated conditions, patients' malnutrition, immunosuppressive status due to disease, and immunosuppressive drugs, such as corticosteroids or immunomodulators, and disturbance of tissue healing **[2].**

Several reports, especially from Japanese institutes, have shown that a high total prednisolone dose administered before surgery is related to **SSI** in patients with **UC [2–6].** Japanese **UC** surgeons have reported that total prednisolone levels ≥10,000 mg may be an additional factor for surgical indication in **UC** adult patients considering postoperative surgical complications, including **SSI [2,6].** A previous report from our institute showed that the occurrence of postoperative infectious complications was significantly correlated with the total dose, but not the monthly dose, of preoperatively administered prednisolone in pediatric **UC** patients **[4,7].**

Use of non-steroid, new drugs is preferable to prednisone in pediatric patients who have a hopeful future. However, corticosteroids remain the main drug for inducing remission in **UC** therapy. New drugs, including immunomodulators and anti-tumor necrosis factors, that are used for **UC** therapy have an immunosuppressive action in patients and may lead to infectious complications. Increasing surgical complications, including **SSI**, by using new drugs instead of prednisolone, is undesirable. Several studies investigated the relationship between preoperative administration of new drugs and postoperative **SSI** in pediatric **UC** patients. Almost all of these studies concluded there is no relationship between **SSI** and immunomodulators or infliximab

[3,8,11]. However, evaluation of the occurrence of **SSI** without the effect of corticosteroids is difficult because corticosteroids remain the main drug for inducing remission in **UC** therapy. Additionally, previous studies did not evaluate the occurrence of **SSI** by considering the total dose or monthly dose of corticosteroids that were administered before surgery.

This study aimed to investigate the relationship between preoperative immunomodulator administration and occurrence of **SSI**. Especially, we considered the effect of the total dose and monthly dose of preoperatively administered prednisolone in pediatric **UC** patients.

METHODS

Our study included 24 children and adolescents who were younger than 20 years old with **UC** who underwent total proctocolectomy by the two-stage procedure from 2003 to 2012 in Mie University Hospital, Japan. And, we evaluated the occurrence of **SSI** after total proctocolectomy with **IPAA** and creation of diversion ileostomy at the first stage in 24 patients. At our institute, patients underwent one-, two-, or three-stage procedures for **UC**. The one-stage procedure included total proctocolectomy with ileal J-pouch anal anastomosis (**IPAA**) by the hand-sewn procedure without a diversion stoma. The two-staged procedure included total proctocolectomy with **IPAA** and creation of diversion ileostomy at the first stage, and closure of ileostomy after 2-3 months at the second stage. The three-stage procedure included subtotal colostomy with creation of diversion ileostomy and a mucous fistula of the sigmoid colon at the first stage. At the second stage, remnant proctocolectomy and **IPAA** with recreation of diversion loop ileostomy were performed. Finally, loop ileostomy was closed at the third stage.

The diagnosis of UC at onset and during the clinical course was based on clinical features, laboratory test results indicating inflammation, and on endoscopic and Histopathological findings. Disease severity was defined according to the diagnostic criteria for determination of the severity of **UC** as established by the Research Committee of Inflammatory Bowel Disease of the Ministry of Health and Welfare in Japan in 1994 **[12]**. A diagnosis of mild disease satisfied all of the following six criteria: occurrence of up to four stools per day, presence of blood in the stool less than once per day, body temperature <37.5°C, no tachycardia of more than 90 beats/min, hemoglobin level of >10 g/dl, and an erythrocyte sedimentation rate of less than 10 mm/h for men and 15 mm/h for women. The six criteria for severe disease were as follows: occurrence of six or more stools per day, daily presence of blood in the stool, body temperature elevation to 37.5°C, tachycardia of more than 90 beats/min, hemoglobin level of <10 g/dl, and an erythrocyte sedimentation rate of less than 30 mm/h. The diagnosis of severe disease satisfied at least four of the following six criteria including the occurrence of both six or more stools per day and daily presence of blood in the stool, as well as either body temperature elevation to 37.5°C or tachycardia of more than 90 beats/min. Moderate disease was defined as intermediate severity between the mild and severe disease states. Final diagnosis of UC was confirmed by histological examination of resected specimens.

For treating **SSI**, standard procedures were used in all of the patients as follows. Antimicrobial prophylaxis was administered 30 min before the procedure. The hair in the operative field was shaved using electric clippers following induction of general anesthesia. The surgical site was wiped with 10% povidone-iodine solution before surgery and draped with a disposable towel. Absorbable synthetic sutures were used to close the fascia and peritoneum. Intra-abdominal drainage tubes were passed through a stab incision that was separate from the wound. The skin was closed using stainless steel staples, and the wound was then wiped with normal saline. No local irrigation of tissues with solutions containing antimicrobial agents was used. The site was covered with a film dressing until removal of the staples. Routine postoperative care was provided to each patient.

The patients were identified using a postoperative infection database or hospital records. The data were recorded prospectively for each patient in the database immediately after the operation by the operating surgeon. The patients were assessed for postoperative SSI by the surgeon or attending doctor. The presence of SSI was determined as an infection that occurred within 30 days after operation according to the definition by the Centers for Disease Control and Prevention **[13].** Each patient was followed up for a minimum of 30 days after the final stage of procedure. **SSI**, including superficial or deep **I-SSI**, and/or **OS-SSI**, was evaluated. Anastomotic leaks and abscesses in **OS-SSI** were diagnosed by contrast imaging, computed tomography, or intraoperative findings.

Patients' characteristics, including sex, disease onset, age at operation, duration of the disease before surgery, clinical disease severity, disease extension at surgery, preoperative endoscopic severity, surgical approach, such as open or laparotomy, operation time, and perioperative blood transfusion, were evaluated. Preoperative endoscopic findings were evaluated by Matt's grade as close as possible to the time of surgery **[14].** Matts grade was defined as follows: grade 1, normal appearance; grade 2, mild granularity of the mucosa with mild contact bleeding; grade 3, marked granularity and edema of the mucosa with contact bleeding or spontaneous bleeding; and grade 4, severe ulceration of the mucosa with hemorrhage. Preoperative medical therapy included systemic prednisolone, 5-aminosalicylates, immunosuppressants (azathioprine, cyclosporine A, and tacrolimus), infliximab, and cytapheresis. We reviewed the patients' records if these therapies were used within 30 days prior to the first-stage operation. Patients with steroid dependency were defined as those who were unable to reduce steroids below the equivalent of prednisolone 10 mg/day within 3 months of starting steroids, those without recurrent active disease, or those who had a relapse within 3 months of stopping steroids **[15].** Patients with steroid resistance were defined as those who had active disease, despite prednisolone administration up to 0.75 mg/kg/day over a period of 4 weeks **[15].**

The study design was approved by the ethics review board of Mie University Hospital, Japan. All patients or guardians provided written informed consent to allow the collection and use of

their tissues for this study. The data were analyzed by the chi-squared test and the Mann–Whitney U test using the JMP version 7 software programs (**SAS** Institute Inc., Cary, **NC, USA**). A p value of less than 0.05 was considered to be statistically significant.

RESULTS

In this study, 24 patients who underwent the two-stage procedure were included in data analysis. The occurrence of SSI was evaluated after total proctocolectomy with IPAA and creation of diversion ileostomy at the first-stage operation. **SSIs** were diagnosed in seven (29%) patients, including four with **I-SSI** and one with **OS-SSI**, and two patients had both. No mortality was observed. Table 1 shows the patients' characteristics according to the occurrence of **SSI**.

Table 1: Patients' characteristics and preoperative medications according to **SSI** occurrence.

Factors	SSI positive (n=7)	SSI negative (n=17)	P value
Gender (Male/Female)	5 / 2	10 / 7	0.557
Disease onset (years, mean±SD)	12.6 ± 2.9	12.5 ± 4.9	0.975
Age at operation (years old, mean±SD)	14.4 ± 2.7	14.4±4.1	0.823
Disease duration before surgery (years, mean±SD)	2.0 ± 1.1	2.4 ± 1.8	1
Clinical Disease Severity (mild/moderate/severe)	3/3/1	5/9/3	0.821
Disease extension at surgery (Left colitis/pancolitis)	1/6	1/16	0.517
Preoperative endoscopic findings (Matts grade 1/2/3/4)	1/4/2/0	1/6/6/4	0.29
Surgical approach (open/laparoscopy)	6/1	15/2	0.865
Operation time (min, mean±SD)	285 ± 91	296 ±72	0.548
Periopeartive Blood transfusion (Y/N)	1/6	1/16	0.517
Total dose of preoperatively administered prednisone (mg, mean±SD)	14393 ± 8522	6543 ± 4956	0.0284
Preoperative systemic prednisolone (Y / N)	5/2	14/3	0.5577
Preoperative systemic prednisolone (mg, mean±SD)	300 ± 249	473 ± 593	1
Preoperative Oral 5-ASA (Y / N)	5/2	16/1	0.147
Preoperative IM (Y/N)	7 / 0	12/5	0.0464
Preoperative AZA (Y/N)	6/1	9/8	0.1135
Preoperative CNI (Y/N)	2/5	8/9	0.397
Preoperative CYA (Y/N)	2/5	6/11	0.7489
Preoperative TAC (Y/N)	0/7	2/15	0.2281
Preoperative IFX (Y/N)	0/7	3/14	0.1344
Preoperative CAP (Y/N)	1/6	3/14	0.8389
Preoperative Steroid Dependent (Y / N)	5/2	11/6	0.7489
Preoperative Steroid Resistant (Y / N)	2/5	6/11	0.7489

5-ASA: 5-Aminosalicylates, **IM**: Immunomodulator Including Tacrolimus, Cyclosporine, Azathioprine, **AZA**: Azathioprine, **CYA**: Cyclosporine A, **TAC**: Tacrolimus, **CNI**: Calcinurin Inhibitor Including **CYA** and **TAC, IFX:** Infliximab, **CAP**: Cytapheresis.

There were no differences in sex, disease onset, age at operation, duration of disease before surgery, clinical disease severity, disease extension at surgery, preoperative endoscopic severity, surgical approach, such as open or laparotomy, operation time, and perioperative blood transfusion between the **SSI**-positive and **SSI**-negative groups. The total dose of preoperatively administered prednisolone and preoperative immunomodulator administration were significantly related to occurrence of **SSI** (p=0.028and p=0.046, respectively). Multivariate analysis showed that the total dose of preoperatively administrated prednisolone ≥20000 mg (receiver operating characteristic cut-off) was an independent risk factor for occurrence of SSI (p=0.036, Table 2).

Table 2: Multivariate analysis in the relationship between **SSI** occurrence and preoperative medications.

Factors	Pvalue
Total dose of preoperatively administered prednisolone ≧20000 mg (ROC cut-off)	0.0357
Preoperative immunomodulators (Y/N)	0.0840

We excluded two patients who received a total dose of preoperatively administrated prednisone ≥20,000 mg to avoid the influence of prednisolone, and investigated the relationship between immunomodulators and occurrence of **SSI** in 22 patients. Twenty-two patients were divided into two groups by the median value (7250 mg) of the total dose of preoperatively administrated prednisolone. Table 3 shows the relationship between occurrence of SSI and preoperative immunomodulator administration in patients who received high-dose (≥7250 mg) prednisolone.

Table 3: The relationship between SSI occurrence and preoperative medications in patients who received high dose prednisone administration.

Factors	SSI positive (n=4)	SSI negative (n=7)	P value
Total dose of preoperatively administered prednisolone (mg, mean±SD)	11438 ± 3537	11658 ± 2719	0.7048
Preoperative IM (Y/N)	4 / 0 (100%)	3 / 4 (43%)	0.0275
Preoperative AZA (Y/N)	4 / 0 (100%)	4/ 3 (57%)	0.0680
Preoperative CNI (Y/N)	1 / 3 (25%)	2 / 5 (29%)	0.8978
Preoperative CYA (Y/N)	1 / 3 (25%)	2 / 5 (29%)	0.8978
Preoperative TAC (Y/N)	0 / 7(0%)	0 / 4 (0%)	
Preoperative IFX (Y/N)	0 / 7 (0%)	0 / 4 (0%)	
Preoperative CAP (Y/N)	1 / 3 (25%)	0 / 7 (0%)	0.1377

IM: Immunomodulator Including Tacrolimus, Cyclosporine, Azathioprine, **AZA**: Azathioprine, **CYA**: Cyclosporine A, **TAC**: Tacrolimus, **CNI**: Calcinurin Inhibitor Including **CYA** And **TAC**, **IFX**: Infliximab, **CAP**: Cytapheresis.

There was no difference in the total dose of preoperatively administered prednisone between the SSI-positive and **SSI**-negative groups. Preoperative immunomodulator administration increased the risk of SSI in patients who received high-dose prednisolone (p=0.028). However, in patients who received low-dose (<7250 mg) prednisolone, preoperative immunomodulators did not affect the occurrence of SSI (Table 4).

Table 4: The relationship between SSI occurrence and preoperative medications in patients who received low dose prednisone administration.

Factors	SSI positive (n=1)	SSI negative (n=10)	Pvalue
Total dose of preoperatively administered prednisolone (mg, mean±SD)	5000	2963 ± 2037	0.3428
Preoperative IM (Y/N)	1 / 0 (100%)	9 / 1 (90%)	0.6545
Preoperative AZA (Y/N)	1 / 0 (100%)	5/ 5 (50%)	0.2551
Preoperative CNI (Y/N)	0 / 1 (0%)	6 / 4 (60%)	0.1926
Preoperative CYA (Y/N)	0 / 1 (0%)	4/ 6 (40%)	0.3271
Preoperative TAC (Y/N)	0 / 1 (0%)	2 / 8 (20%)	0.5154
Preoperative IFX (Y/N)	0 / 1 (0%)	3/ 7 (30%)	0.4118

IM: Immunomodulator Including Tacrolimus, Cyclosporine, Azathioprine, **AZA**: azathioprine , **CYA**: cyclosporine A, **TAC**: Tacrolimus, **CNI**: Calcinurin Inhibitor Including **CYA** and **TAC**, **IFX**: Infliximab , **CAP**: Cytapheresis.

DISCUSSION

This study showed that occurrence of **SSI** after total proctocolectomy with **IPAA** and creation of diversion ileostomy at the first stage for pediatric **UC** was strongly associated with the total high dose of prednisolone that was preoperatively administered. Preoperative immunomodulator administration significantly increased the risk of occurrence of **SSI** in patients who received high-dose prednisone. However, in patients who received low-dose prednisone, preoperative immunomodulator administration had no effect on the occurrence of **SSI**.

When the effect of immunomodulators is evaluated for infectious complications after proctocolectomy in pediatric **UC** patients, eliminating or considering the adverse effect of corticosteroids is important. In Japanese adult **UC** patients who underwent **UC** surgery, the risk of postoperative infectious complications was significantly greater in those receiving a total dose >10,000 mg of systemic corticosteroids during medical therapy **[6].** Mahadevan *et al.* **[17]** reported the relationship between postoperative complications and immunomodulators while considering the preoperative prednisolone dose. They reported that early complications after restorative proctocolectomy for adult **UC** patients are associated with high-dose steroids (intravenous or oral >40 mg) and severe disease by Truelove and Witts' criteria, but not the use of thioprine. In their study, early complications included not only **SSIs**, such as anastomotic leak, wound dehiscence, pelvic sepsis, and abscess formation, but also remote infections, perineal fistula, small bowel obstruction, anastomotic strictures, and death within 30 days of colostomy.

In the pediatric population, a few studies have reported the relationship between immunomodulators or infliximab and postoperative complications, including **SSI [8-10].** With regard to use of immunomodulators, Schaufler *et al*. [9] reported that preoperative exposure to thioprines or calcineurin inhibitors (within 30 days), or infliximab (within 90 days) was not associated with increased postoperative complications in their cohort undergoing colectomy

for pediatric **UC**. With regard to use of infliximab, Kennedy et al. **[8]** demonstrated that children who were treated with infliximab prior to proctocolectomy suffered twice as many postoperative complications compared with children who were not treated with infliximab. In their study, occurrence of small bowel obstruction in patients who received infliximab was significantly increased compared with controls who did not receive infliximab; however, this relationship is unclear. Patton et al. **[10]** also i found that preoperative medications were not associated with postoperative complications in 31 pediatric **UC** patients. All of these three studies **[8-10]** evaluated the use of corticosteroids, calcineurin inhibitors, thioprines, and infliximab, but they did not evaluate the dose of corticosteroids that is strongly associated with the occurrence of SSI postoperatively. Our data are consistent with the study conducted by Mahadevan et al. in adult populations **[17].** Supporting the findings that high-dose, but not low-dose, corticosteroid use is associated with increased occurrence of **SSI**.

This study has some limitations. First, the level of immunosuppressive status achieved by patients who took immunomodulators was unclear. Second, infliximab-treated patients are rare because its use covered by medical insurance in Japan is delayed compared with other countries, and pediatricians worry about the occurrence of malignancy in pediatric patients in Japan. The third limitation of our study is that the number of patients is smaller compared with studies on adult **UC** patients. However, we were still able to evaluate the occurrence of SSI after the first-stage operation of a two-stage procedure for pediatric **UC** patients at a single center under the same standard procedure for prevention of **SSI**, as described above.

In conclusion, preoperative administration of the total high dose of prednisolone is strongly associated with occurrence of **SSI** after total proctocolectomy for pediatric **UC**. Preoperative immunomodulator administration may increase the risk of occurrence of **SSI** in patients who receive a high dose of prednisone. In patients who receive low-dose prednisone, preoperative immunomodulator administration has no effect on the occurrence of **SSI**. A medical approach with administration of immunomodulators with a low dose of prednisolone before surgery is required for avoiding **SSI**.

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