

Effects of Intravenous Cyclosporin on the Surgical Treatment for Acute Severe Ulcerative Colitis

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ABSTRACT

AIM: The aim of the study is to evaluate postoperative morbidity after treatment with intravenous cyclosporine A (iv CsA) for acute severe ulcerative colitis (UC) patients.

METHODS: We assessed 33 UC patients and divided them into three groups. Group 1 consisted of 6 patients who underwent restorative proctocolectomy with ileal pouch anal anastomosis (IPAA) and ileostomy with preoperative iv CsA and prednisolone. Group 2 consisted of 18 patients who underwent subtotal colectomy and ileostomy with preoperative iv CsA and prednisolone. Group 3 consisted of 9 patients who underwent subtotal colectomy and ileostomy with preoperative prednisolone alone. Perioperative laboratory data and postoperative complications were compared. In addition, risk factors for postoperative complications were evaluated with univariate and multivariate analysis.

RESULTS: All of Group 1 patients responded to CsA treatment, and their daily steroid use were reduced to approximately 20 mg. Although Group 1 patients had higher incidence of postoperative complications than the other groups, no patients died or underwent a re-operation. Aging was the only independent risk factor for postoperative complications following CsA treatment.

CONCLUSION: All the patients in Group 1 safely underwent IPAA for severe UC. Younger CsA responding UC patients were supposed to be good candidates for IPAA.

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Key words: Cyclosporin A; Ulcerative colitis; Surgical treatment; Postoperative complications

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INTRODUCTION

Ulcerative colitis (UC) is a remitting and relapsing, chronic inflammatory bowel disease which is characterized by inflammation and ulceration of the colon and rectum. Symptoms of UC usually consist of abdominal pain, bloody and/or mucous diarrhea. Environmental factors, genetic factors and immune responses have been considered as major etiology of UC. The age-standardized prevalence in 2005 was reported to be 63.6 per 100000 individuals in Japan, which was much lower than in Western countries but steadily increasing with time^[1]. Steroids are the agents that firstly choiced in the treatment of patients with acute, severe UC, but, intravenous cyclosporine A (iv CsA) has been shown to reduce the need for emergent surgery in steroid-resistant UC. Studies suggest that the short-term response rate of iv CsA is 60-80% and that the long-term response rate is about 40%^[2-5]. Several studies assessed postoperative complications following CsA treatment, but most studies focused on patients receiving subtotal colectomy. We performed restorative proctocolectomy with ileal pouch anal anastomosis (IPAA) on acute severe UC patients those who responded to CsA treatment. The aim of the present study is to evaluate the postoperative morbidity after treatment with iv CsA in our series of patients who underwent IPAA or subtotal colectomy and assess good candidates for IPAA following iv CsA.

METHODS

Patients

Between August 1995 and March 2004, fifty one patients underwent surgery for UC at the Department of General Surgery, Chiba University. Excluded chronic cases, we retrospectively reviewed the case notes of 33 patients of acute severe UC among them. The definition of severe condition was based on that of Truelove and Witts^[6]. We divided them in three groups. Group 1 consisted of 6 patients who underwent restorative proctocolectomy and ileostomy following iv CsA and prednisolone treatment. Group 2 consisted of

18 patients who underwent subtotal colectomy and ileostomy after iv CsA and prednisolone. Group 3 consisted of 9 patients who underwent subtotal colectomy and ileostomy after iv prednisolone alone.

Methods

In Group 1 and 2, CsA was given as a 24-hour continuous intravenous infusion at a dose of 2-4 mg/kg per day. The surgical procedure was performed in either three or two steps. In the three-step procedure, the initial operation was subtotal colectomy, the section of colon being at the rectosigmoid junction, allowing the mucous fistula to be sutured at the distal end of the abdominal incision. At this time a Brooke ileostomy was raised. In the two-step procedure, the first operation was restorative proctocolectomy and ileal pouch anal or anal canal anastomosis with a loop ileostomy. Depended on surgeon's decision, the two-step procedure was employed to the CsA responded patients whose daily dose of prednisolone was reduced to 20 mg.

Preoperative and postoperative laboratory data such as hemoglobin (Hb), white blood cell counts (WBC), C-reactive protein (CRP), albumin (Alb), total bilirubin (T-bil), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were compared. Preoperative data were measured on the day or one day before the surgery and postoperative data were measured on the next day of the operation. Postoperative early complications, which occurred within 30 postoperative days, were compared between the three groups. In addition, risk factors for perioperative complications were evaluated by a univariate and a multivariate analysis.

Data analysis

This was a retrospective analysis of collected data. Quantitative and categorical variables were analyzed with a 2-tailed, unpaired Student *t* test and the chi-square or Fisher exact probability test, respectively. Logistic regression was used to identify independent predictors of postoperative complications. In addition, univariate logistic regression analyses were performed to determine candidate variables such as those found to be significant at the level of $p < 0.20$ for subsequent multivariate logistic regression analysis, which was conducted to identify variables with significant independent effects. Statistical significance was designated as a probability value of less than 0.05.

RESULTS

Each group was well matched for age, gender, extent of disease and duration of illness. Fulminate colitis were seen in no patients in Group 1, and 4 in Group 2 and 3. Group 1 patients required more past hospitalization than the other groups. Preoperative daily dose of corticosteroid of Group 1 patients was significantly lower than that of the other groups ($p < 0.05$) (Table 1).

Table 1 Patients characteristics.

	Group1 (n=6)	Group2 (n=18)	Group3 (n=9) (Mean±SE)	P value
Median Age (at operation)	47.7±7.2	36.5±3.9	37.3±4.3	NS
Gender(M/F)	3/3	14/4	5/4	NS
Extent of Disease (Total/Left/Others)	5/1/0	17/1/0	7/1/1	NS
Indication for operation	Fulminant type 0 Bleeding 6	Fulminant type 4 Bleeding, fever abdominal pain 17 Parenteral cystic pneumatosis 1	Fulminant type 4 Bleeding, fever abdominal pain 6 Toxic megacolon 2 Perforation 1	
Age (at on set)	39.7±6.6	34.2±3.9	33.3±4.5	NS
Duration of illness (years)	6.6±1.2	3.0±0.9	3.6±2.5	NS
Number of past hospitalization	3.7±0.9	1.7±0.2	1.9±0.5	<0.05 ¹
Duration of preoperative hospitalization at internal medicine (months)	2.9±0.5	2.5±0.4	1.6±0.5	NS
Days from transfer to operation	9.2±1.5	4.2±1.7	2.6±1.0	NS
Daily dosage of prednisolone (mg)	22.5±4.0	45.9±3.0	56.7±6.6	< 0.01 ¹
Total dose of prednisolone (mg)	8800±1240	5051±734	6523±2808	NS

¹: G1 vs G2, G3.

Patients in Group 1 received an average of 24.2 (range, 6-60) days of iv CsA. CsA treatment was terminated on the day of surgery in 2 patients and within 10 days before surgery in the others. In Group 1, 3 patients were reconstructed with ileo-anal canal anastomosis and the other 3 patients with ileo-anal anastomosis. Patients in Group 2 received an average of 24.7 (range, 4-40) days of CsA. CsA treatment was terminated on the day of surgery in 7 patients and within 10 days before surgery in the others. Fourteen patients in Group 2 had CsA efficacy, but 4 of them terminated CsA therapy due to liver dysfunction or pneumonia. The other 4 patients had their infusions terminated for lack of efficacy. Preoperative CRP in Group 1 patients is slightly lower than that of the other groups without significant difference. Perioperative WBC, Alb, T-bil, AST, ALT had no significant differences among the three groups (Table 2).

Table 2 Perioperative laboratory data.

		Group1 (n=6)	Group2 (n=18)	Group3 (n=9) (Mean±SE)	P value
Pre-operation	Hb	9.4±0.4	9.4±0.3	9.8±0.5	NS
	WBC	8683±1336	8706±965	10300±1516	NS
	CRP	1.7±0.6	2.6±0.7	5.3±2.4	NS
	ALB	2.9±0.2	2.7±0.1	2.7±0.2	NS
	T-Bil	0.63±0.27	0.49±0.06	0.71±0.1	NS
Post-operation	AST	36.3±12.6	38.3±6.3	31.1±4.2	NS
	ALT	49.3±17.3	70.1±21.9	105.1±37.3	NS
	Hb	10.0±1.5	10.1±1.0	10.0±0.4	NS
	WBC	15233±4505	12983±623	13900±1789	NS
	CRP	6.97±4.77	6.59±4.78	7.9±1.8	NS
	AST	37.7±40.2	21.9±10.0	21.4±4.3	NS
	ALT	52.3±64.3	44.8±29.9	41.0±11.6	NS

Postoperative complications were seen in 4 patients in Group 1, 7 in Group 2 and 3 in Group 3, respectively. Although Group 1 patients had higher incidence of postoperative complications than the other groups, no patients died or underwent a re-operation. All of the four patients who had postoperative complications in Group 1 were over 40 year-old with a diabetes mellitus or cardiovascular diseases, such as a chronic pulmonary embolism, a hypertension, and a cardiac valves regurgitation. The other 2 patients in Group 1 who were less than 40 year-old with no co-morbidity had no postoperative complications. These 2 younger patients received iv CsA until the day of surgery. In Group 2 patients, one patient died due to acute respiratory distress syndrome and 3 patients required re-operations for postoperative rectal bleeding or small bowel obstruction. Seven of Group 2 patients were over 40 year-old, and five of them had postoperative complications. One patient in Group 3 died disseminated intravascular coagulation due to bone marrow carcinomatosis from rectal cancer (Table 3).

By univariate analysis in all patients, CsA treatment was not an independent risk factor for the postoperative complications. In the CsA treated patients with univariate and multivariate analyses, aging was

the only independent risk factor for the postoperative complications. Among the Group 3 patients, no independent risk factor was detected (Table 4).

Table 3 Early postoperative complications.

Group1 (n=6)	Group2 (n=18)	Group3 (n=9)
Cholecystitis 1	Rectal bleeding 2 (reope 2)	DIC 1 (dead)
MRSA colitis 2	Pneumoniae 1 (dead)	Ileus 1
Subcutaneous abscess 1	Ileus 2 (reope1)	Pancreatitis 1
	Pelvic abscess 1	
	Subcutaneous abscess 1	Cholecystitis

Table 4 Univariate and multivariate analysis for postoperative complications.

		Odds ratio (95%CI)	P value
Total patients	CsA treatment	1.094 (0.365-3.277)	0.8731
CsA treated patients			
Univariate analysis	Age	1.095 (1.024-1.172)	0.0013
	Male	0.808 (0.169-3.858)	0.7894
	Preoperative complications	4.857 (0.718-32.873)	0.0933
	Preoperative daily PSL dosage	0.983 (0.940-1.028)	0.4435
Multivariate analysis	Age	1.107 (1.011-1.212)	0.0058
	Preoperative complications	0.602 (0.040-9.108)	0.7114

DISCUSSION

Several reports have noted a significantly higher leak rate in patients taking steroids versus those who are not^[7,8]. One study suggested that patients taking more than 20 mg of prednisone per day had a significantly higher incidence of anastomotic leaks^[9]. Based on these reports, patients taking high dose of steroids usually avoid anastomosis and undertake a three-stage procedure to IPAA, involving initial total abdominal colectomy and ileostomy, followed in three to six months by interval IPAA with a diverting stoma, with final stoma closure done several months later. Steroid dose of all of Group 1 patients, who responded to CsA treatment, could be reduced to less than 20 mg per day. We were able to perform anastomosis with covering ileostomy on these 6 patients without any anastomotic complications.

Cyclosporin is a fungal metabolite and a potent immunosuppressant. Potential side effects include opportunistic infections, e.g., Pneumocystis pneumonia, renal failure, neural dysfunctions such as palsy, tremor, headache, hypertension^[10]. Half of Group 1 patients had postoperative infections, such as MRSA enteritis, cholecystitis. We cannot deny high infection rate in Group 1 patients, but all of them promptly recovered by appropriate antibiotic administration. Several studies reported that iv CsA is not associated with an increased incidence of perioperative complications compared with the use of iv steroids alone and is therefore a safe adjunctive therapy^[11,12].

On the other hand, two of Group 2 patients suffered massive bleeding from the residual rectum, which was caused by uncontrolled severe inflammation. Medical treatment in the department of internal medicine in our institution took relatively longer periods. Group 3 patients treated more than one and a half months and Group 2 patients, who were uncontrolled by CsA treatment, took more than two and a half months (Table 1). Most of these patients had insufficient enteral nutrition during the treatment, therefore these patients were supposed to be in a severe malnutrition condition. This may imply the reason for higher postoperative complications in our patients.

Multivariate analyses in the CsA treated patients showed that aging was the only independent risk factor for the postoperative complications. Two Group 1 patients whose age were less than forty had no postoperative complications, therefore two staged operations after CsA treatment had a benefit for such younger patients. Patients those who were able to avoid urgent surgery may have an option for elective laparoscopic surgery, which offers smaller skin incision and less postoperative pain and may provide huge benefits on especially younger patients. One mortality case in Group 2 was a 68 year-old male with diabetes mellitus who suffered Pseudomonas aeruginosa infection and died of subsequent acute distress syndrome. The CsA treatment for the older patients needs further evaluations.

CONCLUSIONS

Six patients who responded to CsA treatment and reduced daily steroids safely underwent IPAA for severe UC. Younger steroid refractory UC patients might be a good candidate for IPAA following CsA treatment. Further investigations will be needed for the evaluation of the safeness of CsA treatment for older severe UC patients.

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