

Similar outcomes for anti-tumor necrosis factor- α antibody and immunosuppressant following seton drainage in patients with Crohn's disease-related anal fistula

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Abstract. Anal fistula is common in patients with Crohn's disease (CD) and leads to significant morbidity. The efficacy of seton drainage combined with anti-tumor necrosis factor- α monoclonal antibody (anti-TNF- α) or immunosuppressant in the treatment of CD-related anal fistula remains unclear. The aim of the present study was to compare the efficacy between seton drainage combined with anti-TNF- α and seton drainage combined with immunosuppressant postoperatively on the treatment of CD-related anal fistula. A total of 65 patients with CD-related anal fistula who had received seton drainage combined with postoperative medication were divided into an antibiotics only group, anti-TNF- α group and immunosuppressant group; all patients were treated with antibiotics. Fistula closure, external orifice exudation rate and recurrence rate were assessed among these patients. The duration of follow-up ranged from 3 to 84 months with an average of 25.3 months. There were 11 (16.9%) cases of recurrence after seton drainage, 9 of which underwent a second seton drainage. In the total study group, 34 (52.3%) cases achieved complete fistula closure, and 10 (15.4%) cases showed external orifice

exudation. No significant difference was found among these three groups, regarding fistula closure rate, closure time of fistula and recurrence rate. The external orifice exudation rate was significantly higher in the anti-TNF- α group compared with the antibiotics only group and immunosuppressant group ($P=0.004$ and $P=0.026$, respectively). Seton drainage is an effective treatment for CD-related anal fistula. The efficacy is similar whether combined with anti-TNF- α or immunosuppressant.

Introduction

Perianal lesions are a common complication in Crohn's disease (CD), among which the anal fistula is the most common (1). Anal fistula develops in 13.7-50% of patients with CD, and it may be the initial presentation or develop during the course of the disease (1-6). Moreover, recurrent fistula has been reported to occur in up to 33-57% of these patients (7-10). Perianal lesions associated with CD can develop to be both painful and disabling and potentially require surgery, particularly complex anal fistula which generally denotes a more aggressive and disabling CD phenotype (1,11). Patients with CD-related anal fistula may experience anal pain, dyschezia and fecal incontinence in addition to emotional symptoms and impairment of social and sexual functioning that significantly debase the quality of their lives (12).

Treatments for CD-related anal fistula include surgery (for example, surgical incision and drainage, seton drainage, fistulotomy and fistulectomy), medical management (including antibiotics, immunosuppressant and biologics) and combined treatment. Some experts recommend a conservative surgical approach with simple seton drainage as a key treatment for anal fistula, and suggest that combining medical therapy may improve the efficacy (13). Anti-tumor necrosis factor- α (anti-TNF- α) monoclonal antibody and immunosuppressant are the first-line medicines on the treatment of CD. However, the efficacy of seton drainage combined with anti-TNF- α monoclonal antibody or with immunosuppressant on the treatment of CD-related anal fistula remains unclear. There have been few reports on CD-related anal fistula. Furthermore, no

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Abbreviations: CD, Crohn's disease; anti-TNF- α , anti-tumor necrosis factor- α ; RCT, randomized controlled trial; AGA, American Gastroenterological Association; CDAI, Crohn's disease activity index; PDAI, perianal disease activity index

Key words: Crohn's disease, anal fistula, seton drainage, anti-tumor necrosis factor- α , immunosuppressant

randomized controlled trial (RCT) results or reports of large numbers of cases are available.

In the current study, 65 patients with CD-related anal fistula who underwent seton drainage at the Sixth Affiliated Hospital of Sun Yat-Sen University (Guangzhou, China) from June 2007 to February 2014 were enrolled, with the aim of comparing the efficacy between seton drainage combined with anti-TNF- α monoclonal antibody and with immunosuppressant on the treatment of CD-related anal fistula.

Materials and methods

Patients. All cases of CD-related anal fistula who had received seton drainage from June 2007 to February 2014 in the Sixth Affiliated Hospital of Sun Yat-sen University were identified retrospectively. Written informed consent was obtained from all patients. All patients enrolled had been treated with seton drainage, routinely using post-operative antibiotics such as metronidazole or ornidazole. A review of the clinical data demonstrated that all patients in the immunosuppressant group were treated with azathioprine. The preferred anti-TNF- α monoclonal antibody was infliximab (94.4%) and only one patient was treated with adalimumab after seton drainage. Seton drainage is a simple surgical procedure for anal fistula. To identify the primary openings, methylthioninium chloride was injected through the secondary openings and the blue liquid was subsequently identified. Any secondary superficial tracts were opened and deep primary tracts were drained using the seton. Surgical silk or a silicone tube was loosely tied over the sphincter. All the patients had been followed up for their efficacy of fistula treatment as outpatients or by phone call up to May 2014. The patients were generally followed up at the third and sixth months for the first year and yearly thereafter. The following data were recorded: Gender, age at diagnosis, initial symptom (fistula or intestinal symptoms), combined with perianal abscess or not, previous perianal surgery history, American Gastroenterological Association (AGA) classification, Vienna classification (ABL classification), Parks' classification, previous medications, preoperative and postoperative Crohn's disease activity index (CDAI) score, and any other relevant data. A diagnosis of CD was established according to the Practice Guidelines of the World Gastroenterology Organization (14). Anal fistulas were classified according to the AGA classification as either simple or complex, and were also assessed using Parks' classification (15). Anorectal magnetic resonance imaging (MRI) had been performed on every patient and was evaluated by imaging specialists when the diagnosis of CD-related anal fistula was made. This study was approved by the scientific and ethics committees of the Sixth Affiliated Hospital, Sun Yat-Sen University.

Definitions of variables and outcomes of interest. In this study, a CD-related anal fistula was defined as an abnormal connection between the epithelialized surface of the anal canal and the perianal skin in patients with CD. Anal fistulas were classified according to Parks' classification into intersphincteric, transsphincteric and suprasphincteric. In addition, anal diseases were classified as simple or complex according to the AGA classification by the same surgeon

who performed the proctological examination. The patients were categorized according to treatment into three groups: Antibiotics only, immunosuppressant and anti-TNF- α groups. The immunosuppressant group was defined as treatment with immunosuppressive agent without other medications, with the exception of post-operative antibiotics. The anti-TNF- α group was defined as treatment with anti-TNF- α monoclonal antibody without other medications, with the exception of post-operative antibiotics. The antibiotics only group was defined as treatment only with post-operative antibiotics. In this study, the antibiotics only group served as a control to evaluate the efficacy of seton drainage combined with anti-TNF- α monoclonal antibody or with immunosuppressant on the treatment of CD-related anal fistula.

The disease activity of patients was assessed according to the CDAI score, which ranges from 0 to 600, in which higher scores indicated more severe disease activity. As the perianal disease activity index (PDAI) showed a high standard deviation due to the limited number of cases included, fistula closure and external orifice exudation were used to evaluate the efficacy of the treatment of CD-related anal fistula instead of PDAI in this study. The outcome of anal fistula was categorized as follows: i) Complete fistula closure, where improvement lasted throughout the follow-up without recurrence, and the fistula closed completely without exudate or pain; ii) incomplete fistula closure, where the fistula was not completely closed or perianal pain or exudate was not alleviated; iii) external orifice exudation, where the fistula was not completely closed and fluid exuded from an external orifice and iv) fistula recurrence, where the anal fistula reappeared after complete healing or perianal abscess was recurrent following the completion of drainage.

Statistical analysis. All statistical analyses were performed with SPSS software, version 16.0 (SPSS, Inc., Chicago, IL, USA). Quantitative data are described as means \pm standard deviations. Categorical variables are presented as frequencies and constituent ratios. Differences between quantitative data that met normality and homogeneity criteria were analyzed using Student's t-test. Enumeration data was compared using the χ^2 test. Analysis of variance was used for multiple comparisons of continuous variables with categorical variables, with Bonferroni correction for multiple comparisons, and Kruskal-Wallis test whenever the distribution was not normal. $P < 0.05$ was considered to indicate a statistically significant difference.

Results

General information. A total of 65 patients with CD that were treated with immunosuppressant or anti-TNF- α monoclonal antibody following seton drainage were included over the 7-year period. Baseline characteristics of the patients are described in Table I. Among them, 49 (75.4%) were male and 16 (24.6%) were female, aged from 10 to 59 years with a mean age of 25.3 ± 9.2 years. At the time of diagnosis with CD-related anal fistula, 29.2% of patients had been previously exposed to previous medications at some time, 23.1% had been treated with immunosuppressant, and 6.1% had received anti-TNF- α monoclonal antibody. The most common ABL classifications were A1 (90.8%), B1 (80.0%) and L3 (56.9%) in this study.

Table I. Baseline characteristics of 65 patients with CD-related anal fistula.

Baseline characteristics	Values
Gender	
Male	49/65 (75.4)
Female	16/65 (24.6)
Male/female	3.06
Age at diagnosis, years	25.3±9.2
A classification	
A1	59/65 (90.8)
A2	6/65 (9.2)
B classification	
B1	52/65 (80.0)
B2	57/65 (7.7)
B3	9/65 (12.3)
L classification	
L1	15/65 (23.1)
L2	13/65 (20.0)
L3	37/65 (56.9)
L4	0/65 (0)
Previous perianal surgery history	33/65 (50.8)
Initial symptom	
Anal fistula before CD diagnosis	35/65 (53.8)
Anal fistula after CD diagnosis	20/65 (30.8)
Concurrent with CD diagnosis	10/65 (15.4)
Combined with perianal abscess	32/65 (49.2)
AGA classification	
Simple anal fistula	16/65 (24.6)
Complex anal fistula	49/65 (75.4)
Parks' classification	
Intersphincteric	46/65 (70.8)
Transsphincteric	16/65 (24.6)
Suprasphincteric	3/65 (4.6)
Previous medications	
No previous medications	46/65 (70.8)
Immunosuppressant	15/65 (23.1)
Anti-TNF- α monoclonal antibody	4/65 (6.1)
Preoperative CDAI score	74.0±38.0
Postoperative CDAI score	26.0±18.6

Quantitative data are presented as the mean \pm standard deviation. Categorical variables are presented as frequencies (percentages). CD, Crohn's disease; AGA, American Gastroenterological Association; anti-TNF- α , anti-tumor necrosis factor- α ; CDAI, Crohn's disease activity index.

Anal fistula characteristics. Among the 65 patients with CD-related anal fistula, complex anal fistula (75.4%) and intersphincteric anal fistula (70.8%) were the most common type of anal lesion. The majority of patients (53.8%) had developed anal fistula prior to experiencing intestinal symptoms. In addition, 49.2% of patients also had a perianal abscess.

Table II. Overall efficacy of treatment in 65 patients with CD-related anal fistula.

Efficacy measure	Value
Fistula closure	34/65 (52.3)
External orifice exudation	10/65 (15.4)
Fistula recurrence	11/65 (16.9)
Follow-up period, months	25.3±17.9
Time to recurrence, months	5.5±6.5
Repeated seton drainage	9/11 (81.8)

Quantitative data are presented as means \pm standard deviations. Categorical variables are presented as frequencies (percentages). CD, Crohn's disease.

Overall efficacy of CD-related anal fistula treatments. The overall efficacy of CD-related anal fistula treatments in patients who received seton drainage is shown in Table II. All participants had been followed up at outpatient clinic or by phone call. The duration of follow-up ranged from 3 to 84 months with an average of 25.3±17.9 months. A total of 11 patients (16.9%) relapsed in an average of 5.5±6.5 months after seton drainage following comprehensive medication therapy. Among these 11 patients, 9 (81.8%) received seton drainage again. During the follow-up, 34 cases (52.3%) completely closed. As post-operative pelvic MRI was not routinely performed, it was not possible to eliminate the possibility of internal orifice closure. There were 10 cases who continued to exhibit exudate from the external orifice (15.4%) at the end of follow-up.

Postoperative medications. Postoperative medications administered to the patients are described in Table III. There were 26 patients treated with post-operative antibiotics only, 21 patients treated with immunosuppressant and 18 patients treated with anti-TNF- α monoclonal antibody in addition to antibiotics. All patients enrolled had been treated with seton drainage, routinely using post-operative antibiotics such as metronidazole or ornidazole. Following a review of the patients' clinical data, it was found that all patients in immunosuppressant group were treated with azathioprine. The preferred anti-TNF- α monoclonal antibody was infliximab (94.4%) and only 1 patient was treated with adalimumab.

The three treatment groups were similar with respect to gender, age, Vienna classification (ABL classification), history of perianal surgery, time the anal fistula developed in relation to the CD diagnosis, AGA classification, Parks' classification, previous medications and preoperative and postoperative CDAI scores. However, there are more patients having anal fistula combined with perianal abscess in the immunosuppressant group compared with the antibiotics only group ($P=0.043$).

Comparison of efficacy between the anti-TNF- α group and the immunosuppressant group. The final efficacy rates (complete fistula closure) of the antibiotics only, immunosuppressant and anti-TNF- α groups were 61.5, 47.6 and 44.4%, respectively, and the recurrence rates were 7.7, 28.6 and 16.7% for the three groups, respectively. The present study showed that there

Table III. Baseline characteristics of 65 patients with CD-related anal fistula treated with different postoperative medications.

Baseline characteristics	Antibiotics only (n=26)	Immunosuppressant (n=21)	Anti-TNF- α (n=18)	P-value
Gender				0.215
Male	21/26 (80.8)	13/21 (61.9)	15/18 (83.3)	
Female	5/26 (19.2)	8/21 (38.1)	3/18 (16.7)	
Age at diagnosis, years	25.5 \pm 9.2	25.9 \pm 9.5	24.4 \pm 9.4	0.879
A classification				
A1	23/26 (88.5)	20/21 (95.2)	16/18 (88.9)	0.690
A2	3/26 (11.5)	1/21 (4.8)	2/18 (11.1)	
B classification				
B1	23/26 (88.5)	13/21 (61.9)	16/18 (88.9)	0.169
B2	1/26 (3.8)	3/21 (14.3)	1/18 (5.6)	
B3	2/26 (7.7)	5/21 (23.8)	1/18 (5.6)	
L classification				0.241
L1	5/26 (19.2)	5/21 (23.8)	5/18 (27.8)	
L2	8/26 (30.8)	1/21 (4.8)	4/18 (22.2)	
L3	13/26 (50.0)	15/21 (71.4)	9/18 (50.0)	
Previous perianal surgery history				0.521
Yes	13/26 (50.0)	12/21 (57.1)	7/18 (38.9)	
No	13/26 (50.0)	9/21 (42.9)	11/18 (61.1)	
Initial symptom				0.134
Anal fistula before CD diagnosis	17/26 (65.4)	12/21 (57.1)	6/18 (33.3)	
Anal fistula after CD diagnosis	8/26 (30.8)	5/21 (23.8)	7/18 (38.9)	
Concurrent with CD diagnosis	1/26 (3.8)	4/21 (19.0)	5/18 (27.8)	
Combined with perianal abscess	8/26 (30.8)	14/21 (66.7)	10/18 (55.6)	0.041
	8/26 (30.8)	14/21 (66.7)		0.043
	8/26 (30.8)		10/18 (55.6)	0.304
		14/21 (66.7)	10/18 (55.6)	1.000
AGA classification				0.562
Simple anal fistula	8/26 (30.8)	5/21 (23.8)	3/18 (16.7)	
Complex anal fistula	18/26 (69.2)	16/21 (76.2)	15/18 (83.3)	
Parks' classification				0.937
Intersphincteric	20/26 (76.9)	14/21 (66.7)	12/18 (66.7)	
Transsphincteric	5/26 (19.2)	6/21 (28.6)	5/18 (27.8)	
Suprasphincteric	1/26 (3.8)	1/21 (4.8)	1/18 (5.6)	
Previous medications				0.309
No previous medications	21/26 (80.8)	15/21 (71.4)	10/18 (55.6)	
Immunosuppressant	5/26 (19.2)	4/21 (19.0)	6/18 (33.3)	
Anti-TNF- α monoclonal antibody	0/26 (0)	2/21 (9.5)	2/18 (11.1)	
Preoperative CDAI score	63.2 \pm 44.2	75.8 \pm 27.1	87.5 \pm 36.4	0.110
Postoperative CDAI score	21.5 \pm 23.7	27.5 \pm 16.4	30.6 \pm 10.0	0.260
Follow-up period, months	31.5 \pm 19.8	21.6 \pm 16.5	20.8 \pm 14.4	0.074

Significant differences ($P < 0.05$) are highlighted in bold. Quantitative data are presented as means \pm standard deviations. Categorical variables are presented as frequencies (percentages). CD, Crohn's disease; AGA, American Gastroenterological Association; anti-TNF- α , anti-tumor necrosis factor- α ; CDAI, Crohn's disease activity index.

was no significant difference in fistula closure, recurrence rate and the number of patients who received repeated seton drainage among three groups. The anal fistulas of patients in

the anti-TNF- α group were closed slightly faster compared with those in the antibiotics only group (2.2 vs. 3.6 months) and immunosuppressant group (2.2 vs. 3.4 months). However,

Table IV. Comparison of efficacy between the anti-TNF- α group and the immunosuppressant group.

Efficacy measure	Antibiotics only (n=26)	Immunosuppressant (n=21)	Anti-TNF- α (n=18)	P-value
Fistula closure	16/26 (61.5)	10/21 (47.6)	8/18 (44.4)	0.468
Fistula closure (remission) time, months	3.6 \pm 4.8	3.4 \pm 3.2	2.2 \pm 1.6	0.534
External orifice exudation	1/26 (3.8)	2/21 (9.5)	7/18 (38.9)	0.004
	1/26 (3.8)	2/21 (9.5)		1.000
	1/26 (3.8)		7/18 (38.9)	0.004
		2/21 (9.5)	7/18 (38.9)	0.026
Fistula recurrence	2/26 (7.7)	6/21 (28.6)	3/18 (16.7)	0.165
Time to recurrence, months	3.3 \pm 3.9	7.2 \pm 8.4	3.5 \pm 2.8	0.680
Repeated seton drainage	2/2 (100.0)	5/6 (83.3)	2/3 (66.7)	0.632

Significant differences ($P<0.05$) are highlighted in bold. Quantitative data are presented as means \pm standard deviations. Categorical variables are presented as frequencies (percentages). Anti-TNF- α , anti-tumor necrosis factor- α .

no significant difference was shown in the fistula closure time ($P=0.534$). In addition, anti-TNF- α monoclonal antibody treatment was associated with a significantly higher rate of external orifice exudation compared with the antibiotics only group (38.9 vs. 3.8%; $P=0.004$) and immunosuppressant group (38.9 vs. 9.5%; $P=0.026$) (Table IV).

Discussion

Anal fistula is one of the most common complications and main surgical indications of CD (1). According to an expert consensus on inflammatory bowel disease by the Chinese Medical Association (16), perianal symptoms are an indication of surgical treatment for CD-related anal fistula. Surgical intervention is not necessary for an asymptomatic simple fistula, and the use of antibiotics is recommended. Azathioprine or 6-mercaptopurine can be a second choice, while anti-TNF- α monoclonal antibody is not recommended as a routine treatment. The comprehensive therapy is not necessary until the symptoms of anal fistula arise. According to the experts' recommendations, appropriate surgical treatments combined with antibiotics or azathioprine as a maintenance treatment can promote fistula healing in complex anal fistula.

Surgical treatments, including abscess drainage and seton drainage, are irreplaceable for complex anal fistula. However, whether to conduct fistulotomy and fistulectomy should be considered carefully, as a big wound area will increase the risk of fecal incontinence. In comparison with those treatments, seton drainage for CD-related anal fistula ensures sufficient drainage and enables the functions of the anal sphincter to be preserved, so as to reduce the incidence of postoperative fecal incontinence. In the present study, 65 patients underwent seton drainage. During the average 25.3 month follow-up, anal fistula completely closed in 34 cases (52.3%) and 31 cases (47.7%) showed an unclosed external orifice. There were 10 cases who continued to exhibit an exudate from the external orifice at the end of follow-up. The overall treatment efficacy for CD-related anal fistula is known to be worse than that of the common anal fistula (17). In the present study, it was found that the cure rate for patients receiving seton drainage reached 50%. As some

patients achieved internal orifice closure, exudation from the external orifice of the fistula appears to be a better indication of prognosis compared with complete fistula closure.

Only a few studies have focused on the efficacy of antibiotics for perianal lesion of CD. A meta-analysis indicated that antibiotics are not a better choice than placebo in reducing or curing the exudation from a fistula (18). A randomized, double-blind, placebo-controlled pilot study evaluating antibiotics for the treatment of CD-related anal fistula found that remission and response occurred more frequently in patients treated with ciprofloxacin compared with placebo, but the differences were not significant in this pilot study and the study population was probably too small (19). Using antibiotic alone may be effective in improving the symptoms, but rarely in increasing remission rate. A double-blind RCT assessed the efficacy of antibiotics combined with anti-TNF- α monoclonal antibody and concluded that the effect of comprehensive therapy was better than that of anti-TNF- α monotherapy (20).

Regarding the timing of use of the anti-TNF- α monoclonal antibody, there is considerable controversy. Some experts consider that biological agents should be used as a first-line treatment for complex anal fistula (21,22). However, anti-TNF- α therapy may not be effective in all patients; MRI analysis demonstrated that fistula still existed after therapy, and thus additional draining was required (23-25). Combined treatment may be more beneficial. In a large retrospective cohort study, 218 patients underwent surgery alone or surgery following biological therapy. The clinical response was 35.9% in the surgery-treated group and 71.3% in the combined treatment group ($P=0.001$), suggesting that combined treatment offered a better curative effect (26).

Hotokezaka *et al* (27) reviewed 20 cases of combined treatment with seton drainage and infliximab for complex perianal lesions associated with CD. After an average follow-up of 31 months, 40% patients achieved complete remission. In the present study, 18 cases received combined therapy with seton drainage and anti-TNF- α monoclonal antibody, and 44.4% of these cases achieved complete closure of fistula subsequently, which is similar to the findings of previous studies. In an ACCENT II trial, 306 patients with CD received infliximab

through venous infusion at the exact times of 0, 2 and 6 weeks. As a consequence, 14 weeks later, 69% of the patients were in remission. The patients were then randomized to receive maintenance infliximab or placebo, and it was observed that 19% of patients in the placebo maintenance group had a complete remission of fistulas compared with 36% in the infliximab maintenance group (21). Therefore, there appears to be a consensus that surgical drainage combined with anti-TNF- α therapy is a good choice for perianal CD lesions. However, anti-TNF- α maintenance therapy requires further investigation. In the present study, the average duration of anti-TNF- α therapy was 5 courses. However, there is a risk of sepsis when anti-TNF- α agents are used in the presence of a perianal abscess. Therefore, conducting surgical drainage prior to the use of anti-TNF- α agents is of great significance for the treatment of patients with CD and perianal symptoms.

A previous study suggested a temporary fecal diversion may improve the quality of life in patients with CD and severe perianal lesions (28). However, colostomy alone cannot change the natural course of CD-related anal fistula or reduce the relapse rate. In a study conducted by Yamamoto *et al* (13), 31 patients with CD-related perianal lesions underwent colostomy. Only eight of them achieved long-term remission. In the present study, because of the limited number of cases, no patient had received a colostomy as treatment for a complex anal fistula, and thus the efficacy cannot be evaluated.

In the present study, it was found that the anti-TNF- α group had a significantly higher rate of external orifice exudation compared with the other antibiotics only and immunosuppressant groups. However, this result may be unreliable because of the limited number of cases, and medical management was determined by the degree of active drainage and complexity of the fistulas instead of selection at random.

In conclusion, the overall efficacy between post-operative use of anti-TNF- α monoclonal antibody and immunosuppressant was retrospectively compared in patients with CD-related anal fistula. However, the following limitations exist in this study: Firstly, postoperative pelvic MRI was not routinely performed to objectively assess the healing of the anal fistula in all patients. Secondly, the number of cases was probably too small, so the conclusions require further research. Therefore, RCTs with a larger sample size are necessary to determine the clinical effect of seton drainage combined with anti-TNF- α monoclonal antibody or immunosuppressant. In conclusion, seton drainage is an effective treatment for CD-related anal fistula. It shows the same efficacy whether combined with anti-TNF- α monoclonal antibody or with immunosuppressant.

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