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Treatment of complex perianal fistulas with seton and infliximab in adolescents with Crohn's disease

Maria Hukkinen ^{a,*}, Mikko P. Pakarinen ^a, Maija Piekkala ^b, Antti Koivusalo ^c, Risto Rintala ^c, Kaija-Leena Kolho ^b

^a Pediatric Liver and Gut Research Group, Section of Pediatric Surgery, Children's Hospital, University of Helsinki, Finland

^b Section of Pediatric Gastroenterology, Children's Hospital, University of Helsinki, Finland

^c Section of Pediatric Surgery, Children's Hospital, University of Helsinki, Finland

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KEYWORDS

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Anti-TNF- α therapy

Abstract

Background and aims: Treatment of complex perianal fistulas associated with Crohn's disease is challenging. In adults, seton drainage combined with infliximab therapy has proven to be more effective than either one alone. Results following such treatment among pediatric patients have not been reported previously. The aim of this study was to describe outcomes after combined seton and infliximab treatment for complex perianal fistulas in adolescents with Crohn's disease. **Methods:** We performed a retrospective medical record review of all consecutive Crohn's disease patients treated for perianal fistulas with seton drainage and infliximab between 2007 and 2013 (n = 13). A follow-up interview was conducted at median of two years.

Results: Median age at fistula diagnosis was 14 years. Following seton placement in fistula tracks, infliximab induction was administered at weeks 0, 2, and 6 and maintenance therapy at 8-week intervals. Over 90% responded to seton drainage and infliximab induction. Final fistula response was obtained at median of 8 weeks, being complete in 77% and partial in 15%. Setons were kept in place for median of 8 months. Fistulas recurred in 23% over a year after the final response. At last follow-up, 85% still had a response and 70% were free from perianal symptoms. Most were still on anti-TNF- α therapy, but one third had switched to adalimumab. Patients' anorectal function was well preserved and overall satisfaction with the treatment was high.

Conclusions: The results suggest that combining seton drainage with infliximab therapy improves the perianal fistula response rates in pediatric patients.

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Abbreviations: CD, Crohn's disease; Anti-TNF- α , anti-tumor necrosis factor- α ; IFX, infliximab; PCDAI, Pediatric Crohn's Disease Activity Index; ATI, anti-infliximab-antibodies; PDAI, Perianal Crohn's Disease Activity Index; QoL, quality of life; UC, ulcerative colitis; RPC, restorative proctocolectomy; AZA, azathioprine; IBD, inflammatory bowel disease.

* Corresponding author at: Section of Pediatric Surgery, Children's Hospital, University of Helsinki, Finland.

E-mail address: maria.hukkinen@helsinki.fi (M. Hukkinen).

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1. Introduction

Perianal manifestations of Crohn's disease (CD), although uncommon at time of diagnosis, will affect one third of patients over time and cause significant functional impairments and social restrictions.^{1–3} CD-associated perianal fistulas are frequently complex and refractory to treatment, with one third of patients having recurrent lesions.^{1–3} Fistulas are increasingly encountered also among children as the overall incidence of CD in pediatric population is rising.^{3,4} Fistulizing perianal disease is present in 10 to 15% of children with CD.^{3,5,6}

Anti-tumor necrosis factor (TNF)- α agent infliximab (IFX) is effective in closing and maintaining closure of perianal fistulas in adults, and current guidelines recommend its use as the initial medical treatment for complex fistulas.^{1,7,8} Up to 40% of patients, however, lose response to IFX over time.^{9–11} Although fistulas usually improve rapidly after IFX induction, only about half of treated adults still show response after one year of maintenance therapy.^{1,11} In addition, fistulas recur frequently following treatment discontinuation. Because persisting fistula tracks after premature skin closure predispose to abscess formation,^{11,12} it is recommended to place non-cutting setons in fistula tracks to maintain drainage prior to IFX regimen.^{1,5,13} Combining seton drainage with the medication seems to reduce fistula recurrences, prolong the time for recurrence, and associate with a better treatment response.^{8,12,14,15}

Various small studies have demonstrated IFX to be effective in the treatment of luminal and fistulizing CD also among children, although no large clinical trials or long-term follow-ups in pediatric populations exist.⁵ Perianal fistula healing rates are superior to adults, with over 70% responding after IFX maintenance therapy.^{10,11,16,17} However, loss of response to treatment and fistula recurrences are as common as among adults.^{10,18,19} Although no reports on combined seton and IFX therapy among children exist, seton drainage is used with the same indications as in grown-ups.^{5,8}

2. Materials and methods

This retrospective study describes outcomes after IFX therapy combined with seton placement for complex perianal fistulas in pediatric CD patients. Medical records of all consecutive CD patients who had setons placed in perianal fistula tracks and were treated with IFX between 2007 and 2013 in Helsinki University Children's Hospital were reviewed ($n = 13$). The CD diagnosis was based on upper and lower gastrointestinal endoscopies and histopathological biopsies in all cases. An experienced pediatric colorectal surgeon assessed the perianal lesions under anesthesia and placed loose noncutting seton silicone bands in fistula tracks after their revision and careful drainage of associated abscesses. Pelvic MRI for detailed evaluation of fistula tracks at time of diagnosis was performed in eight, whereas four patients underwent MRI in a later phase. Fistulas were assessed according to Parks classification.^{1,5,20}

IFX (5 mg/kg) was initiated after proper evacuation of possible perianal abscesses. The induction regimen was administered at weeks 0, 2, and 6 and infusions were continued as a maintenance therapy at 8-week intervals. All

but one had setons inserted before the induction therapy. None had been previously treated with anti-TNF- α agents. Patients were followed up regularly at outpatient clinic at time of IFX infusions, or more often when necessary. Reduction in the size, number, or drainage of the fistulas was considered as partial response, whereas cessation of drainage for at least four weeks was considered as complete response. Appearance of active drainage from the fistula track after initial response or development of a new fistula was considered as recurrence.

The medical patient records were reviewed for disease presentation, diagnostic studies, medications, and surgical procedures. Pediatric Crohn's Disease Activity Index (PCDAI) (0–100 scale)²¹ as well as weight and height were registered at time of seton placement and during follow-up. Fecal calprotectin levels were assessed as described previously, with values $< 100 \mu\text{g/g}$ considered as normal.^{22,23} Serum IFX trough levels as well as the presence of anti-IFX antibodies (ATIs) were tested by using enzyme immunoassay when considered necessary.²⁴ Possible adverse events during IFX therapy were documented. At last follow-up, a five-item Perianal Crohn's Disease Activity Index (PDAI) (0–19 scale)^{7,25} was recorded and a researcher not involved with patient care interviewed the patients about current symptoms, medications, and satisfaction with the treatment. Bowel function was evaluated by using a questionnaire previously validated in healthy children and patients with anorectal disorders.^{26,27} Questions about physical, emotional, and social functioning as well as overall life quality were used to assess quality of life (QoL).^{28,29} The hospital ethical committee approved the study protocol. Data are given as medians (interquartile ranges) or frequencies.

3. Results

3.1. Patients

CD was diagnosed at median age of 13.9 (12.5, 14.4) years, with perianal fistulas being the first manifestation of the disease in five patients. Two had been initially misdiagnosed as ulcerative colitis (UC) according to endoscopic and pathologic findings. Both had undergone restorative proctocolectomy (RPC) because of a steroid-resistant disease, and later developed perianal disease requiring temporary diversion. One had suffered from perianal strictures; following successful dilations, his ileostomy had been closed before he developed a first perianal fistula. The other had had multiple perianal fistulas and abscesses, which had healed during diversion. A remaining chronic fistula was later treated with seton and IFX. Other patients had no previous history of perianal fistulas. The baseline characteristics at time of fistula diagnosis are presented in Table 1.

3.2. Treatment of fistulas

All fistulas were complex, i.e. involving the sphincter muscles, having an internal opening above the sphincter muscles, or having multiple openings (Table 1). One to three seton bands were placed to each patient under anesthesia. Accompanying perianal abscesses were incised and drained in eight cases. One required a temporary diversion with

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