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**SURGICAL CLOSURE, MAINLY WITH GLUE INJECTION AND ANTI TNF ALPHA,
IN FISTULIZING PERIANAL CROHN'S DISEASE: A MULTICENTER RANDOMISED
CONTROLLED TRIAL**

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ABSTRACT

Aim: In patients with fistulizing perianal Crohn's Disease (FPCD), the need for a secondary surgical step is not defined. The aim was to assess the efficacy of surgical closure compared to a single seton removal in patients with drained FPCD treated by adalimumab

Methods: This was a multicenter, randomized controlled trial, comparing seton removal + surgical closure [closure group] to seton removal alone [control group] with a stratification according to AGA classification. Primary end point was fistula closure at month 12 defined by the association of the following criteria: no seton, absence of a visible external opening, absence of discharge from the tract after finger compression, absence of an internal opening, absence of perianal pain/abscess and absence of fistula-related abnormalities.

Results: Among the 64 included patients (262 expected) (48 complex fistula, 75%), 33 were randomized to the closure group and 31 to the control group. In the closure group, 26 patients (78.8%) had glue. At month 12, overall fistula closure was achieved in 35 of the evaluable 58 patients (60%): 18/32 (56%) in the surgery group and 17/26 (65%) in the control group ($p=0.479$). In the closure group, fistula closure was observed in 13/25 (52%) and 5/7 (71%) patients with complex and simple fistula respectively ($p=0.426$), as compared with 12/18 (67%) and 5/8 (63%), respectively in control group ($p=1.000$).

Conclusions: Seton removal alone seems to be no more effective than secondary surgical (in particular glue injection) in patients having fistulizing perianal CD controlled by an initial drainage combined with adalimumab. The results should be interpreted with caution.

What does this paper add to literature?

Seton removal alone seems to be no more effective than secondary surgical closure (in particular glue injection) in patients with fistulizing perianal CD controlled by an initial drainage combined with adalimumab. At 12 months of follow-up, clinical closure rate is observed in 60% of patients. As the study is underpowered, these results should be interpreted with caution.

ClinicalTrials.gov Identifier : NCT01388257

Key words: Fistulizing perianal, Crohn's Disease, Surgical closure, Seton removal

INTRODUCTION

The disease burden from fistulizing perianal Crohn's disease (CD) is high in the first four decades of CD course with a 24% cumulative incidence after 30-40 years from CD diagnosis¹. Perianal CD dramatically impairs the patient's quality of life, especially social and sexual activities²⁻⁴. Perianal CD encompasses a wide range of entities⁵ including non-fistulizing and fistulizing lesions. The treatment of fistulizing perianal CD remains challenging despite the increasing number of biologic agents available within recent decades^{1,5}. In the most recent studies from the modern era, chronic fistulizing perianal CD is still a critical situation as proctectomy with definitive stoma was reported in up to 40% of patients⁶⁻⁸.

The initial management of fistulizing perianal CD requires the combination of perianal drainage with systemic treatments⁹. During the past two decades, tumour necrosis factor antagonists (anti-TNF α) have revolutionized the approach for treating fistulizing perineal CD refractory to conventional therapies^{10,11}. Although studies have demonstrated anti-TNF efficacy, the proportion

of patients with partial or no response at the end of the induction regimen remains high. Present and co-workers reported a closure rate of 45% at 18 weeks with infliximab¹¹. Moreover, less than half of patients experienced sustained remission after one year of follow-up on infliximab¹² or on adalimumab¹³. However, in these studies, surgical options were not detailed.

After primary drainage, the surgical management of fistulizing perianal CD remains controversial and with poor evidence for efficacy. Several trials focused on secondary surgical procedures evaluating fibrin glue, plugs or stem cell therapy and provided conflicting results¹⁴⁻¹⁶. Very often, in daily practice, surgical management of fistulizing perianal CD is based on a case by case decision.

The aim of the present randomized controlled trial was to determine if a secondary surgical procedure associated with seton removal was more effective than simply seton removal in fistulizing perianal CD treated initially with a combination of anti-TNF and primary drainage with insertion of a seton.

MATERIALS AND METHODS

The present study was a multicenter, open-label, randomized, controlled trial conducted by the GREP (Proctological Research Group of the French Society of Coloproctology (SNFCP) [N°ID RCB 2010-A01452-37]. Recruitment took place at 11 referral centers for surgical proctology from September 2011 to June 2017. The study design is presented in **Figure 1**.

Patients

Patients eligible for entry into the study were adults with CD diagnosed according to usual criteria¹⁷. Patients had at least one active ano-perineal fistula, present for at least 2 months, and drained with a seton for at least 1 month. Treatment with adalimumab had been commenced for more than 1 month. Alternative treatments with azathioprine, 6-mercaptopurine, methotrexate, were permitted over the previous 3 months. Patients with an anal abscess, a recto-vaginal fistula, needing corticosteroids > 20mg/day, pregnancy, or those with a contraindication to anesthesia or unable to consent for inclusion in the study, were excluded.

Procedures and randomization

The study recruited patients between 2011 and 2017. Pelvic MRI was performed using MRI scanners of the centre. Where MRI imaging was performed the acquisition protocol used high-resolution, T2-weighted, fat-saturation, fast-spin echo pulse sequences and T1-weighted, fat-saturation, fast-spin echo or three-dimensional gradient echo sequences before and after intravenous injection of gadolinium. The MRI scans were assessed by experienced radiologists within each centre. Data collected from MRI scans included : Van Assche classification, inflammation of the fistula, T1 and T2 intensity, presence of any collection (>3mm) and presence of proctitis.

Patients whose fistula had been drained with seton for at least one month were randomized into two arms of treatment. In the surgical closure group, patients had seton removal and a surgical technique for closure of the fistula with general anesthesia. The choice of surgical technique was left to the choice of the individual surgeon (fistulotomy, glue, rectal flap advancement...). Surgery was done when the seton was removed and had to be performed a maximum one month after

randomization (**Figure 1**). In the control group, patients underwent a clinical examination without general anesthesia with seton removal.

Patients were randomly assigned to have either surgery with seton removal [closure group] or observation after seton removal [control group]. Randomization was centralized using permutations tables in a ratio 1:1, stratified for both centre and complexity of the fistula according to the AGA classification¹⁸. The numbers were allocated sequentially in the order of enrolment. After obtaining informed consent, investigators used a specific form which assigned the eligible patient to the next randomization number for the centre..

Follow-up

Follow-up commenced from the date of seton removal to month 24. The medical history, with past and current medications, Perianal Disease Activity Index [PDAI]¹⁹, Inflammatory Bowel Disease Questionnaire [IBDQ]²⁰, MRI data, anal continence, were recorded at baseline. Follow-up visits were planned at months 3, 6, 12 and 24. At each visit, patients underwent a clinical examination without general anesthesia. Fistula closure was assessed clinically¹¹. Perianal Disease Activity Index [PDAI]¹⁹ was assessed at each visit, and the Inflammatory Bowel Disease Questionnaire [IBDQ]²⁰ was recorded at months 12 and 24. MRI was performed at months 6, 12 and 24. Anal continence was assessed by the continence score²¹ at months 12 and 24. Tolerance was recorded between randomization and the end of follow-up.

Study endpoints

The primary end point was fistula closure at month 12, defined according to the Present's Criteria¹¹ as the association of the following criteria: no seton, absence of visible external opening, absence of discharge of the tract after gentle finger compression, absence of visible internal opening, absence of perianal pain or abscess and absence of fistula-related abnormalities.

Prespecified secondary end points were: PDAI at months 3, 6, 12 and 24, continence score and IBDQ at months 12 and 24, activity of the fistula tract at MRI²² and the need of surgery for drainage of perianal abscess during the study period at months 12 and 24.

Sample size and statistical analysis

The sample size calculation was based on the assumption that secondary surgery associated with seton removal would be superior to seton removal alone. With a risk alpha of 5% and a power of 80%, under the assumption that the success rate was 65% in group 1 and 55% in group 2, we would need 262 patients to detect a 25% difference. Categorical variables were described globally or per treatment group using frequencies and percentages, and continuous variables were expressed using the median and range. Chi-square or Fisher's exact tests were used for categorical variables, and Student or Wilcoxon's test were used for numerical variables. Results were considered significant when the p value was less than 0.05. Data were analysed with SAS 9.4 [SAS Inc., Cary, NC]. No procedures for dealing with missing data were carried out; all analysis was done on the available data.

Ethical considerations

All patients provided written informed consent before entering the trial. This study was conducted in accordance with the Declaration of Helsinki, in compliance with the consolidated Good Clinical Practice guideline of the International Conference on Harmonisation and with the applicable regulatory requirements [N°ID RCB 2010-A01452-37]

RESULTS

Among the 65 patients included, 64 were randomized: 33 patients were allocated to the closure group and 31 patients to the control group. The single, non-randomized patient, had an insufficient response to adalimumab to allow a local procedure to be performed and therefore was excluded.

The flowchart diagram of the study is shown in **Figure 2**.

Characteristics of the patients are depicted in **Table 1**. Three sites included 43/58 patients (74.0%). All characteristics of the patients were comparable except for duration of the fistula ($p=0.026$) and past-treatment with infliximab ($p=0.021$): patients randomized to the closure group had longer fistula duration and received more treatments with infliximab. When looking at complexity of the fistulas 75% were complex and with no difference between the two groups (**Table 2**). Of note, 3 patients had anal ulceration (2 in the closure group and 1 in the control group; $p=1.00$) and 7 had an anorectal stricture (3 in the closure group and 4 in the control group; $p=0.592$).

With regard to adalimumab treatment, the median duration of adalimumab was comparable between the 2 groups (14.5 [0-158] months in the closure group vs 12.1[1-74] months in control group; $p=0.281$). Most (70.0%) received 40 mg every 2 weeks and 59.4% received only adalimumab alone without any immunosuppressive agent. No patients had any perianal or abdominal surgery from inclusion to randomization.

Surgery to the perianal fistulas for patients in the surgery group were as follows: 26 patients (78.8%) had glue, 3 (9.1%) had rectal flap advancement, 1 (3.0%) had fistulotomy, 1 (3.0%) had plug and 2 (6.1%) had OVESCO clip.

Primary end points

At 12-month follow-up, 58 of the 64 patients (90.6%) were available for evaluation. Overall, clinical closure rate was observed in 35/58 patients (60.3%). Clinical closure rates were comparable between the 2 groups: 18/32 (56.3 %) in the surgery group and 17/26 (65.4%) in the control group ($p=0.479$).—No interaction in treatment effect with complexity of the fistula was found, with fistula closure in 13/25 (52.0%) patients with complex fistula and in 5/7 (71.4%) patients with simple fistula in the surgery group ($p=0.426$), as compared with 12/18 (66.7%) and 5/8 (62.5%), respectively in control group ($p=1.000$). Regarding adalimumab treatment, 6 patients in the surgery group and 3 in control group had modification of their treatment ($p=0.715$) during the 12 months of follow-up.

Secondary end points

The evolution of clinical closure at months 3, 6 and 24 is shown in **Table 3**. There was no evidence that clinical closure differed between the two groups during the follow-up. In the simple fistula group clinical closure at months 3, 6, and 24 was observed in 6/7 patients (85.7%), 5/6 (83.3%) and 7/7 (100.0%) in the surgery group respectively compared with 4/9 (44.4%), 5/8 (62.5%) and 6/8 (75.0%) in the control group respectively ($p=0.321$; $p=0.580$; $p=0.467$). In those with a complex fistula, clinical closure at months 3, 6, and 24 was observed in 14/26 patients (53.8%), 13/26 (50.0%) and 9/20 (45.0%) in the surgery group respectively compared with 11/21 (52.4%), 12/21 (57.1%) and 9/15 (60.0%) in the control group respectively ($p=0.920$; $p=0.626$; $p=0.380$). The clinical closure rate of simple fistula was higher compared with complex fistula at 24 months of follow-up (13/15 (86.7%) vs 18/35 (51.4%), $p=0.019$).

During the median follow-up of 22 months (6.5), 16/64 patients (25.0%) underwent surgical drainage and 7/64 (10.9%) underwent perineal surgery. The rates of surgical drainage during the follow-up are shown in **Table 3** and were comparable between the two groups. In looking at adalimumab treatment, 6 patients in the closure surgery group and 7 in the control group had optimization of their treatment ($p=0.599$) during the follow-up.

The time course of PDAI scores, according to the group, is shown in **Table 3**. There was no significant difference between groups. Overall, the PDAI score was significantly decreased at 3 months of follow-up ($p>0.0001$). Magnetic Resonance Imaging (MRI) was performed at 6, 12 and 24 months in 62, 58 and 57 patients respectively. At 6 months, fistula tract healing on MRI was observed in 15/32 (46.9%) in the surgical closure group and in 14/30 (46.7%) in the control group ($p=0.371$). At 12 months, fistula tract healing at MRI was observed in 27/58 (46.6%), 14/31 (46.7%) in the closure group and 13/28 (46.4%) in the control group ($p=0.308$). At 24 months, fistula tract healing at MRI was observed in 35/57 (61.4%) (15/29 (51.7%) in the closure surgery group and 20/28 (71.4%) in the control group ($p=0.308$)). There was no significant difference between groups regarding Van Assche scores, hyperintensity of the fistula tract, Vaisey or IBDQ scores.

Safety

During the whole follow-up, 18 patients (9 in the closure group and 9 in the control group) experienced 64 adverse events. Twenty-three adverse events occurred in the closure group and 41 in the control group ($p=0.282$). Among the 64 adverse events, 7 were classified as severe without

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difference between the 2 treatment groups ($p=1.000$). Main adverse events were: anal abscesses, hospitalization and CD flare. Anal abscess occurred, respectively, in 4/9 (44.0%) and 4/9 (44.0%) patients in the closure and control groups ($p=1.000$)

DISCUSSION

This national multicenter randomized controlled trial failed to demonstrate that secondary surgical closure was more effective than simple seton removal in patients with fistulizing perianal CD controlled by an initial drainage, insertion of a seton and treatment with adalimumab. At 12 months of follow-up, clinical closure rate was observed in broadly 60% of patients.

The originality of this work is that the type of surgery was left to the choice of the surgeon. Some might argue that it is a weakness because it introduces heterogeneity into the surgical treatments. To our knowledge, no study^{14,15,23} has shown the superiority of one surgical technique over another in the longer term when dealing with fistulizing perianal CD. Furthermore, the surgical management of a controlled fistulizing perianal CD depends on its complexity, its location (anterior/posterior), the past surgical history and the technical feasibility²⁴. Published controlled trials and cohort studies have usually focused on one main strategy (glue, plug, stem cells or infliximab)^{14–16} but combined approaches are usually necessary to control both Crohn's disease and fistulizing perianal CD. In our study most of the patients in the surgical closure group had glue (79%), which probably reflects individual choice and the ease and non-invasive nature of the procedure, as well as surgeons' habits and experience. Yet the efficacy of glue to close fistulizing perianal CD is unsatisfactory in the published randomized study¹⁵ although patients in this study had no anti-TNF, as compared with this present study. There is recent evidence in the literature²⁵ that glue still has a place in the therapeutic management of Crohn's anal fistulas, especially as this treatment is simple, low-risk and low-cost. It should be noted that, to date, surgical closure is not recommended as initial treatment of the fistula. Thus, selected surgical techniques reflect real-life daily practice.

In this work, the clinical closure rate at 12 months was around 60%. In the literature, closure rates after seton drainage and anti-TNF widely vary and relates to the differences in design, the variability in the classifications of the fistula or in documented periods of anti-TNF treatments, and the definition of clinical response differ between studies. Systematic reviews^{26,27} report closure rates of between 50 and 80% in patients treated with anti-TNF and surgery or removal of seton. This is in accordance with our results particularly when considering the high proportion of complex fistulas in our study (75%).

The important main finding in this study is that results of secondary surgical closure and of seton removal alone, in patients with controlled fistulizing perianal CD, previously treated with drainage, seton insertion and treatment with adalimumab, are comparable at 12 months of follow-up. These results should be treated with caution because some features were not comparable between the 2 groups. Indeed, patients in the closure group had a longer disease duration and had been treated with infliximab more often in the past which might suggest a more aggressive disease. Similarly, patients in the control group more often had signs of active fistula inflammation on MRI. These differences raise several questions. First, seton removal alone is very simple, does not require general anaesthesia, hospitalization or medical leave, and does not expose the patient to any specific complication., and the cost is practically zero compared to surgery. The lack of difference in our study does not mean that all surgical procedures are ineffective. Some surgeries such as stem cells injection or Video-assisted-anal-fistula-treatment (VAAFT)²⁸ were not performed in this study because they were not in common practice at the time of this study albeit that they may be promising. Regarding stem cells injection, combined remission was observed in 51.5% of patients who received treatment vs 35.6% of controls ¹⁶ at 24 weeks. Longer-term evaluations are needed. Finally, we can assume that we do not yet know the ideal surgical technique and that further research is necessary ²⁹.

Importantly, MRI assessment was performed at referral and at months 6, 12 and 24 which allowed assessment of the evolution of the fistula tract activity. It has been shown that MRI assessment of the fistula tract was necessary to optimize therapeutic management³⁰. According to MRI, fistula tract healing was observed in 46.6% at 12 months and in 61.4% at 24 months. Published controlled trials ¹⁴ did not evaluate the MRI data with such a long follow-up. MRI allows an objective assessment of evolution, even if the MRI score is not sensitive enough as it may not change significantly over time¹⁶. Therefore, it would appear that MRI healing is slower than clinical healing³¹ and we can assume that some differences will appear later on. In addition, the rate of unhealed fistulas at 2 years remains high. There are several explanations for these observations. Crohn's disease is a chronic disease with flare-ups, which may explain the lack of healing. On the other hand, the fistulas were often complex, which makes healing more difficult to achieve. Finally, the fistula may be dry (good clinical result) but not cured (still present on MRI).

The main strengths of this work are the duration of follow-up, and the MRI assessment at referral, and at 12 and 24 months. The definition of the primary end point used validated criteria ¹¹ and was

at month 12 while evaluation is often earlier in published studies ^{14–16}. This is the third randomized controlled trial evaluating the efficacy of surgical closure in fistulizing perianal CD and the first performed with patients treated with adalimumab. However, this study has several limitations. The underlying fistulae were complex in 75% of cases and this is reflected in the fact that the centres involved were specialist units and might explain the bias in recruitment. This is why we performed a stratum analysis according to the complexity of the fistula. The investigator who evaluated the primary end point was not blinded for the assigned treatment. It was not possible to get rid of this bias as the surgery is identifiable (glue, plug ...). As described, the number of included patients was smaller than expected and the study is underpowered, with only 58 patients available for evaluation: as a consequence, no definitive conclusions can be drawn here. The outcomes of this study should be interpreted with caution, since the number of included patients was smaller than the minimum sample size required to achieve sufficient power. Yet, it is uncertain as to what extent over- or underestimation of treatment effects may have occurred. The original hypothesis was based on retrospective studies with different inclusion criteria and with a rather short duration of follow-up, especially for seton treatment. Based on the actual difference observed between the 2 arms and after recalculation, it should have been necessary to include 615 patients per group, i.e. 1230 patients in total. Moreover, adalimumab was the preferred anti TNF biologic in this trial whereas scientific evidence was supported with infliximab at the time of the inclusion period. Thus, numerous patients received infliximab and they were not eligible for the study.

There are several messages to remember to avoid making the same mistakes in the future. Firstly a long recruitment period indicates inclusion difficulties and probability that the study design is no longer appropriate or that the inclusion criteria are too strict. The second message is that feasibility work is essential before carrying out a randomized study in order to avoid recruitment difficulties and the bias induced by the high glue rate. Finally, as suggested in a recent study ²³ that also had recruitment difficulties, optimal design for trials which compare medical vs surgical treatment might not be randomized control trial. Randomized design of study was in fact originally set up to compare medical versus placebo therapy ³². If the authors had the opportunity to do this work again, a feasibility study would be carried out and another design would be considered.

Conclusions: Our study does not support surgical closure, in particular glue, for fistulizing perianal CD controlled after initial drainage, insertion of a draining seton and treated with adalimumab as it seems no more effective than seton removal alone. Newer techniques should be assessed by adequate studies. As the study is underpowered, these results should be interpreted with caution.

BIBLIOGRAPHY

1. Park SH, Aniwan S, Scott Harmsen W, Tremaine WJ, Lightner AL, Faubion WA, et al. Update on the Natural Course of Fistulizing Perianal Crohn's Disease in a Population-Based Cohort. *Inflamm Bowel Dis*. 2019;25:1054-60. DOI: 10.1093/ibd/izy329
2. Kasperek MS, Glatzle J, Temeltcheva T, Mueller MH, Koenigsrainer A, Kreis ME. Long-term quality of life in patients with Crohn's disease and perianal fistulas: influence of fecal diversion. *Dis Colon Rectum*. 2007;50:2067-74. DOI: 10.1007/s10350-007-9006-5
3. Mahadev S, Young JM, Selby W, Solomon MJ. Self-reported depressive symptoms and suicidal feelings in perianal Crohn's disease. *Colorectal Dis Off J Assoc Coloproctology G B Irel*. 2012;14:331-5. DOI: 10.1111/j.1463-1318.2011.02613.x
4. Mahadev S, Young JM, Selby W, Solomon MJ. Quality of life in perianal Crohn's disease: what do patients consider important? *Dis Colon Rectum*. 2011;54:579-85. DOI: 10.1007/DCR.0b013e3182099d9e
5. Ingle SB, Loftus EV. The natural history of perianal Crohn's disease. *Dig Liver Dis Off J Ital Soc Gastroenterol Ital Assoc Study Liver*. 2007;39:963-9. DOI: 10.1016/j.dld.2007.07.154
6. Linares L, Moreira LF, Andrews H, Allan RN, Alexander-Williams J, Keighley MR. Natural history and treatment of anorectal strictures complicating Crohn's disease. *Br J Surg*. 1988;75:653-5. DOI: 10.1002/bjs.1800750711

7. Brochart C, Siproudhis L, Wallenhorst T, Cuen D, d'Halluin PN, Garros A, et al. Anorectal stricture in 102 patients with Crohn's disease: natural history in the era of biologics. *Aliment Pharmacol Ther.* 2014;40:796-803. DOI: 10.1111/apt.12894
8. Schwartz DA, Ghazi LJ, Regueiro M, Fichera A, Zoccali M, Ong EMW, et al. Guidelines for the multidisciplinary management of Crohn's perianal fistulas: summary statement. *Inflamm Bowel Dis.* 2015;21:723-30. DOI: 10.1097/MIB.0000000000000315
9. Panes J, Bouhnik Y, Reinisch W, Stoker J, Taylor SA, Baumgart DC, et al. Imaging techniques for assessment of inflammatory bowel disease: joint ECCO and ESGAR evidence-based consensus guidelines. *J Crohns Colitis.* 2013;7:556-85. DOI: 10.1016/j.crohns.2013.02.020
10. Bouguen G, Siproudhis L, Gizard E, Wallenhorst T, Billioud V, Bretagne J-F, et al. Long-term outcome of perianal fistulizing Crohn's disease treated with infliximab. *Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterol Assoc.* 2013;11:975-981.e1-4. DOI: 10.1016/j.cgh.2012.12.042
11. Present DH, Rutgeerts P, Targan S, Hanauer SB, Mayer L, van Hogezaand RA, et al. Infliximab for the treatment of fistulas in patients with Crohn's disease. *N Engl J Med.* 1999;340:1398-405. DOI: 10.1056/NEJM199905063401804
12. Sands BE, Anderson FH, Bernstein CN, Chey WY, Feagan BG, Fedorak RN, et al. Infliximab maintenance therapy for fistulizing Crohn's disease. *N Engl J Med.* 2004;350:876-85. DOI: 10.1056/NEJMoA030815
13. Colombel J-F, Sandborn WJ, Rutgeerts P, Enns R, Hanauer SB, Panaccione R, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology.* 2007;132:52-65. DOI: 10.1053/j.gastro.2006.11.041
14. Senéjoux A, Siproudhis L, Abramowitz L, Munoz-Bongrand N, Desseaux K, Bouguen G, et al. Fistula Plug in Fistulising Ano-Perineal Crohn's Disease: a Randomised Controlled Trial. *J Crohns Colitis.* 2016;10:141-8. DOI: 10.1093/ecco-jcc/jjv162

15. Grimaud J-C, Munoz-Bongrand N, Siproudhis L, Abramowitz L, S  n  joux A, Vitton V, et al. Fibrin glue is effective healing perianal fistulas in patients with Crohn's disease. *Gastroenterology*. 2010;138:2275-81, 2281.e1. DOI: 10.1053/j.gastro.2010.02.013
16. Pan  s J, Garc  a-Olmo D, Van Assche G, Colombel JF, Reinisch W, Baumgart DC, et al. Long-term Efficacy and Safety of Stem Cell Therapy (Cx601) for Complex Perianal Fistulas in Patients With Crohn's Disease. *Gastroenterology*. 2018;154:1334-1342.e4. DOI: 10.1053/j.gastro.2017.12.020
17. Gomoll  n F, Dignass A, Annese V, Tilg H, Van Assche G, Lindsay JO, et al. 3rd European Evidence-based Consensus on the Diagnosis and Management of Crohn's Disease 2016: Part 1: Diagnosis and Medical Management. *J Crohns Colitis*. 2017;11:3-25. DOI: 10.1093/ecco-jcc/jjw168
18. Gece KB, Bemelman W, Kamm MA, Stoker J, Khanna R, Ng SC, et al. A global consensus on the classification, diagnosis and multidisciplinary treatment of perianal fistulising Crohn's disease. *Gut*. 2014;63:1381-92. DOI: 10.1136/gutjnl-2013-306709
19. Irvine EJ. Usual therapy improves perianal Crohn's disease as measured by a new disease activity index. McMaster IBD Study Group. *J Clin Gastroenterol*. 1995;20:27-32.
20. Guyatt G, Mitchell A, Irvine EJ, Singer J, Williams N, Goodacre R, et al. A new measure of health status for clinical trials in inflammatory bowel disease. *Gastroenterology*. 1989;96:804-10.
21. Vaizey CJ, Carapeti E, Cahill JA, Kamm MA. Prospective comparison of faecal incontinence grading systems. *Gut*. 1999;44:77-80. DOI: 10.1136/gut.44.1.77
22. Van Assche G, Vanbeckevoort D, Bielen D, Coremans G, Aerden I, Noman M, et al. Magnetic resonance imaging of the effects of infliximab on perianal fistulizing Crohn's disease. *Am J Gastroenterol*. 2003;98:332-9. DOI: 10.1111/j.1572-0241.2003.07241.x
23. Wasmann KA, de Groof EJ, Stellingwerf ME, D'Haens GR, Ponsioen CY, Gece KB, et al. Treatment of Perianal Fistulas in Crohn's Disease, Seton Versus Anti-TNF Versus Surgical

Closure Following Anti-TNF [PISA]: A Randomised Controlled Trial. *J Crohns Colitis*. 2020;14:1049-56. DOI: 10.1093/ecco-jcc/jjaa004

24. Bouchard D, Abramowitz L, Bouguen G, Brochard C, Dabadie A, de Parades V, et al. Anoperineal lesions in Crohn's disease: French recommendations for clinical practice. *Tech Coloproctology*. 2017;21:683-91. DOI: 10.1007/s10151-017-1684-y

25. Vidon M, Munoz-Bongrand N, Lambert J, Maggiori L, Zeitoun JD, Corte H, Panis Y, Seksik P, Treton X, Abramowitz L, Allez M, Gornet JM. Long-term efficacy of fibrin **glue** injection for perianal fistulas in patients with Crohn's disease. *Colorectal Dis*. 2021 Apr;23:894-900. doi: 10.1111/codi.15477.

26. Yassin NA, Askari A, Warusavitarne J, Faiz OD, Athanasiou T, Phillips RKS, et al. Systematic review: the combined surgical and medical treatment of fistulising perianal Crohn's disease. *Aliment Pharmacol Ther*. 2014;40:741-9. DOI: 10.1111/apt.12906

27. de Groof EJ, Sahami S, Lucas C, Ponsioen CY, Bemelman WA, Buskens CJ. Treatment of perianal fistula in Crohn's disease: a systematic review and meta-analysis comparing seton drainage and anti-tumour necrosis factor treatment. *Colorectal Dis Off J Assoc Coloproctology G B Irel*. 2016;18:667-75. DOI: 10.1111/codi.13311

28. Adegbola SO, Sahnun K, Tozer PJ, and al. Symptom Amelioration in Crohn's Perianal Fistulas Using Video-Assisted Anal Fistula Treatment (VAAFT). *J Crohns Colitis*. 2018; 29;12:1067-1072. doi: 10.1093/ecco-jcc/jjy071.

29. Siegmund B, Feakins RM, Barmias G, Ludvig JC, Teixeira FV, Rogler G, et al. Results of the Fifth Scientific Workshop of the ECCO (II): Pathophysiology of Perianal Fistulizing Disease. *J Crohns Colitis*. 2016;10:377-86. DOI: 10.1093/ecco-jcc/jjv228

30. Brochard C, Landemaine A, L'Heritier AM, Dewitte MP, Tchoundjeu B, Rohou T, et al. Anal Fistulas in Severe Perineal Crohn's Disease: Mri Assessment in the Determination of Long-Term Healing Rates. *Inflamm Bowel Dis*. 2018;24:1612-8. DOI: 10.1093/ibd/izy055

31. Tozer P, Ng SC, Siddiqui MR, Plamondon S, Burling D, Gupta A, Swatton A, et al. Long-term MRI-guided combined anti-TNF-alpha and thiopurine therapy for Crohn's perianal fistulas. *Inflamm Bowel Dis*. 2012 Oct;18(10):1825-34. doi: 10.1002/ibd.21940.

32. Bothwell LE, Greene JA, Podolsky SH, Jones DS. Assessing the Gold Standard--Lessons from the History of RCTs. *N Engl J Med*. 2016;374:2175-81. DOI: 10.1056/NEJMms1604593

Tables

Table 1: Characteristics of the 64 patients with fistulizing perianal Crohn's disease at presentation

Variables (<i>n patients</i>)	All patients n (%) or median [IQR 25-75]	Closure n (%) or median [IQR 25-75]	Control n (%) or median [IQR 25-75]	p-value
Patients number	64 (100)	33 (52)	31 (48)	
Age (years)	34 [19-63]	34 [19-55]	35.0 [19-63]	0.543
Female gender	41 (64)	21 (64)	20 (65)	0.942
Disease duration (years)	6 [0-27]	6 [1-27]	5 [0-24]	0.908
Weight (kg)	67 [35-128]	67 [41-128]	67 [35-97]	0.342
Current smoker	26 (1)	14 (42)	12 (39)	0.762
Disease location				
- Ileum	46 (72)	23 (70)	23 (74)	0.689
- Colon	34 (53)	19 (58)	15 (48)	0.462
- Rectum	29 (45)	16 (49)	13 (42)	0.599
Previous abdominal surgery	20 (32)	8 (24)	12 (40)	0.180
Previous fistula obstruction surgery	22 (36)	13 (41)	9 (31)	0.436
Number of previous fistula surgery	1 [1-6]	1 [1-6]	1 [1-1]	0.304
Fistula duration (months)	9 [0-158]	15 [0-158]	8 [0-83]	0.026
Previous treatment by Infliximab	19 (30)	14 (42)	5 (16)	0.021
PDAI	6 [2-15]	6 [2-11]	5 [1-13]	0.161
CDAI	54 [49-149]	59 [49-149]	52 [50-131]	0.911
CDEIS	4 [0-47]	16 [0-47]	4 [0-28]	0.098
IBDQ	177 [79-214]	177 [96-211]	176 [79-214]	0.412

Abbreviations:

IQR: Interquartile Range; MRI: Magnetic resonance Imaging; PDAI: Perianal Disease Activity Index; CDAI: Crohn Disease Activity Index; IBDQ: Inflammatory Bowel Disease Questionnaire

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Table 2. Fistulae characteristics for the 64 patients with fistulizing perianal Crohn's disease at baseline

Variables (<i>n patients</i>)	Closure group n (%) or median [IQR 25-75]	Control group n (%) or median [IQR 25-75]	p-value
Patients number	33 (52)	31 (48)	
Type of fistula			0.470
- Simple	7 (21)	9 (29)	
- Complex	26 (79)	22 (71)	
Description of fistula			0.262
- Multiple tract or Y or horseshoe	7 (21)	8 (26)	
- Transsphincteric/intersphincteric low	5 (15)	8 (26)	
- Transsphincteric high	18 (55)	17 (55)	
More than 1 fistula/patient	2 (8)	2 (9)	0.230
MRI data			
- Van Assche MRI-based score (48)	10 [3-18]	8 [3-19]	0.422
- Supralelevator extension (52)	4 (15)	2 (8)	0.670
- Absence of inflammation of the fistula (56)	17 (52)	25 (81)	0.014
- Hyperintensity T2 (54)			0.238
o No	6 (22)	8 (30)	
o Moderate	13(48)	16 (59)	
o Intense	8 (30)	3 (11)	
- Hyperintensity T1 (43)			0.206
o No	4 (19)	8 (36)	
o Yes	17 (81)	14 (64)	
- Abscess (MRI) (collection >3mm) (56)	5 (17)	4 (15)	
- Proctitis (54)	5 (19)	5 (19)	1.000
			1.000
Associated lesions			
- Ulceration/Fissure	2 (6)	1 (3)	1.00
- Stricture	3 (9)	4 (13)	0.592

Table 3: Primary and secondary endpoints for the 64 patients with fistulizing perianal Crohn's disease

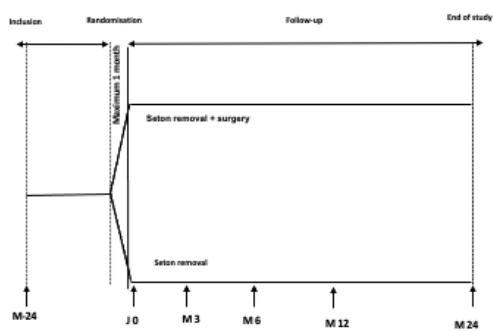
Variables (<i>N patients</i>)	Closure n (%) or median [IQR 25-75]	Control n (%) or median [IQR 25-75]	p-value
Clinical closure rate			
M3 (63)	20 (61)	15 (50)	0.397
M6 (61)	18 (56)	17 (59)	0.852
M12 (58)	18 (56)	17 (65)	0.479
M24 (50)	16 (59)	15 (65)	0.019
PDAI score			
- M0 (55)	6 [2-11]	5 [1-13]	0.161
- M3 (60)	3 [0-12]	2 [0-12]	0.621
- M6 (54)	1 [0-11]	1 [0-12]	0.973
- M12 (47)	2 [0-10]	0 [0-12]	0.407
- M24 (40)	1 [0-13]	1.0 [0-13]	0.709
MRI data			
Van Assche score			
- M0 (48)	10 [3-18]	8 [3-19]	0.422
- M6 (26)	8 [4-16]	9 [4-21]	0.485
- M12 (22)	9 [3-21]	5 [3-17]	0.221
- M24 (19)	4 [3-17]	5 [3-17]	0.847
Hyper T2 (moderate/intense)			
- M0 (54)	13(48)/8(30)	16(59)/3(11)	0.238
- M6 (39)	8 (38)/3 (14)	7 (39) /3 (17)	1.000
- M12 (36)	5 (26)/5 (26)	5 (29) /2 (12)	0.605
- M24 (27)	4 (25)/1 (6)	2 (18)/2 (18)	0.703
Vaizey score			
- M0 (55)	5 [0-15]	6 [0-19]	0.498
- M12 (46)	4 [0-14]	5 [0-18]	0.151
- M24 (31)	5 [0-16]	4 [0-17]	0.664
IBDQ			
- M0 (54)	177 [96-211]	176 [79-214]	0.412
- M12 (47)	185 [110 -215]	171 [112-224]	0.381
- M24 (31)	175 [99-216]	176 [99-223]	0.587

Surgical drainage required			
- M3	2 (6)	1 (3)	1.0
- M6	4 (14)	4 (14)	1.0
- M12	3 (10)	3 (13)	1.0
- M 24	9 (27)	7 (23)	0.665

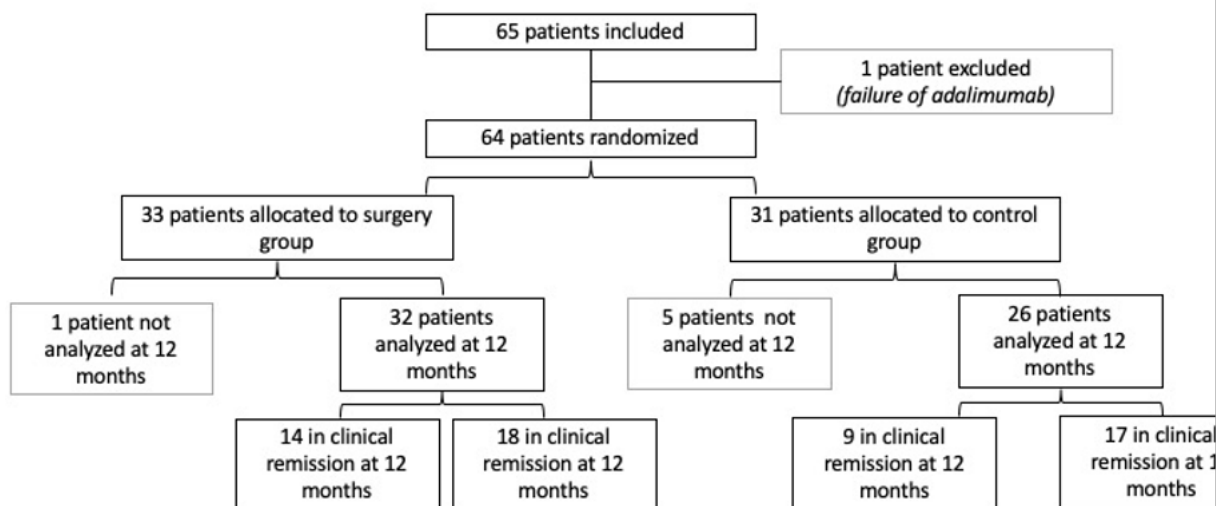
Figure Legends

Figure 1: Study design.

Figure 2. Flowchart of patients.



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