New frontiers in Crohn's perianal fistulae disease

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1. Introduction
2. Seton
3. The OVESCO Proctology Clip
4. Collagen fistula plugs
5. Sealents
6. Mucosal advancement Flaps
7. VAAFT/LIFT/Other
8. Stem Cells
9. Conclusion
10. References

1: Introduction

The American Surgical colorectal society recommendations are a good review of what should be done in this population group. In 2011 they published their practice parameters.

Practice Parameters for the management of perianal abscess and fistula-in-ano(1)

1. Asymptomatic fistulas in patients with Crohn's disease do not require surgical treatment. Grade of Recommendation: Strong recommendation based on low quality evidence 1C
2. Symptomatic simple low Crohn's fistulas may be treated by fistulotomy. Grade of Recommendation: Strong recommendation based on low-quality evidence 1C
3. Complex Crohn's fistulas may be well palliated with long-term draining Setons. Grade of Recommendation: Strong recommendation based on low-quality evidence 1C
4. Complex Crohn's fistulas may be treated with advancement flap closure if the rectal mucosa is grossly normal. Grade of Recommendation: Weak recommendation based on low-quality evidence 2C
5. Complex Crohn's fistulas may require permanent diversion or proctectomy for uncontrollable symptoms. Grade of Recommendation: Strong recommendation based on low-quality evidence 1C

There was quite a substantial change in the guideline in 2016 after newer procedures were brought to fore.

Clinical Practice Guideline for the Management of Anorectal Abscess, Fistula-in-Ano, and Rectovaginal Fistula (2)

1. Asymptomatic fistulas in patients with Crohn's disease do not require surgical treatment. Grade of Recommendation: Strong recommendation based upon low-quality evidence, 1C.

2. Symptomatic, simple, low anal fistulas in patients with Crohn's disease may be treated by fistulotomy. Grade of Recommendation: Strong recommendation based on low-quality evidence, 1C
3. Loose Setons are useful in the multimodality therapy of fistulizing perianal Crohn's disease and may also be used for long-term disease control. Grade of Recommendation: Strong recommendation based upon low-quality evidence, 1C.
4. Endoanal advancement flap, anal fistula plug, and the LIFT procedure may be used to treat fistula-in-ano associated with Crohn's disease. Grade of Recommendation: Weak recommendation based on moderate-quality evidence, 2B.
5. Complex Crohn's fistulas may require permanent diversion or proctectomy for uncontrollable symptoms. Grade of Recommendation: Strong recommendation based on low-quality evidence, 1C.

All in all, not strong evidence with a lot of expert opinion.

2: Seton

Setons are a non-invasive method to manage fistula-in-ano. By keeping the internal and external openings of the fistula open, the Seton prevents buildup of pus/blood within the fistula tract. It's this buildup of material that results in pressure within the tract, and the pressure is what causes the pain.

By draining the tract persistently with a Seton there is a decrease in local inflammation and as such improves the quality of the local tissue. It is these factors that improve the likelihood of success when procedures are undertaken to close the fistula. In short the crucial steps to optimize the success of fistula surgery are:

a. No sepsis
b. Well drained fistula
c. Healthy pliable local tissue

Draining Setons as the definitive management for patients with fistula-in-ano have been reported as a feasible option however, no patients with crohns disease were included in this study(3).

A systematic review comparing Seton drainage and anti-TNF treatment for perianal fistulas in Crohn's disease (4) concluded that there was no definitive conclusion as to the better option. Their primary end-point was fistula closure rate and the secondary end-point was partial closure and recurrence rates. A

total of ten studies were included (n = 305) and the complete closure rate varied from 13.6% to 100% and recurrence rates from 0% to 83.3%.

3: The OVESCO Proctology Clip

The OVESCO proctology clip performs a dynamic closure of the internal opening of the fistula rather than a static closure. A static closure is potentially an inadequate closure, as is seen with sutures. There is minimal injury to the internal opening with this technique and as such, should the closure fail, the associated scaring at the internal opening is minimal thereby having less impact on the success of future procedures.

To date there is no evidence published using this product in patients with Crohns disease. However, we have used it with success in patients with crohns disease at the WDGMC.

The FICLOSE study compared OVESCO with rectal mucosal advancement flaps for complex anal fistulas(5). It was a prospective, randomised, controlled, single-blind, bicentre and interventional study. The primary outcome was the proportion of pts with a healed fistula at 3/12 and the secondary outcomes were:

- Anal fistula healing (6 and 12 months)
- Proctological pain (visual analogue scale)
- Fecal incontinence score (Jorge and Wexner questionnaire)
- Digestive disorders
- QoL

No outcomes published to date, and these should have been published by now. My concern is was there an issue with recruitment or were the results not statistically useful?

4: Collagen fistula plugs

The PISA Trial (6) is a multicenter RCT in the Netherlands which started recruiting in August 2013 however had to terminate their study due to poor accrual.

Their design would have answered questions regarding the optimal surgical option for patients with crohns disease fistula in ano (in the biologic naive):

- Chronic Seton Drainage, removal at 1 year
- Anti TNF and seton, removal after 6 weeks
- Seton, and then mucosal advancement plasty at 8 weeks with 4 months of anti-TNF

A randomised controlled trial in 2016 looked at the use of the fistula plug in fistulising perianal Crohn's Disease(7). It compared Seton removal with Seton removal and plug.

- 52 vs 54 pts
- Fistula closure at 12 weeks: 23% vs 31.5%

At week 12, 17 of the patients developed at least one adverse event in the fistula plug group vs 8 in the control are. The conclusion was that the fistula plug is not more effective than a seton removal alone to achieve closure in patients with crohns disease.

A systematic review published in 2016 looked at the anal fistula plug in Crohn's disease patients with fistula (8). 16 studies were extracted: 12 were included. A total of 84 patients with a median follow-up time of 9 (3–24) months. They published a closure rate of 49/84 (58.3%) and concluded that the fistula plug was a safe procedure with reasonable success, little morbidity and a low risk of incontinence.

However, we must remember that the current literature is limited by:

- small study cohorts
- grouping of fistulae in Crohn's disease with other pathology
- short and highly variable follow-up times
- multiple confounding factors such as:
    - number of fistula tracts
    - use of preoperative steroids or immunosuppressants
    - previous use of Setons
    - variation in surgical technique

This makes it extremely challenging to accurately interpret the benefits of different surgical procedures in this population group.

5: Sealants:

Let's not go there! A waste of time.

6: Mucosal advancement Flaps

A good operation however, when this procedure fails there is a significant amount of scarring over the internal opening; which impacts the success of future surgeries. As such I try to leave this surgical option as the last attempt after other attempts have failed.

There is no evidence comparing this technique to others.

7: VAAFT/LIFT/Other

Technically challenging and not for day to day practice. No evidence showing superiority, all state it is safe but not comment on longevity of the repair. (9, 10)

VAAFT require specialized equipment which is costly.

8: Stem cells

Where did the concept originate?

- Crohns disease fistulas likely result from a long-term effect of an autoimmune condition
- Idea for use in crohns disease resulted from observations in patients undergoing haempoeitic stem cell transplantation for malignancy
- The concept lies in resetting the exaggerated immune response

In 2018 a Systematic Review and Meta-Analysis of Mesenchymal Stem Cell Injections for the Treatment of Perianal Crohn's Disease was published (9). Their objective was to determine safety and efficacy of mesenchymal stem cells for the treatment of refractory perianal Crohn's disease. Three trials with control arms were included in this study. They concluded that the procedure was safe but did not comment on it's effectiveness.

From this study we were able to establish some important unanswered question:

1. What is the definition of fistula healing?
    a. MRI vs persistent drainage
2. It is safe option but is it effective?

The latest trial: Long-term Efficacy and Safety of Stem Cell Therapy (Cx601) for Complex Perianal Fistulas in Patients with Crohn's Disease(10) is a phase 3, randomized, double-blind, parallel-group, placebo-controlled study. 49 hospitals contributed from July 2012 to December 2015. They used allogeneic expanded adipose derived stem cells.

The primary end point at week 52 included:

- combined remission
    - closure of all treated external openings draining
    - absence of collections >2 cm confirmed by MRI
- clinical remission
    - absence of draining fistulas

At week 52, a significantly greater proportion of patients given Cx601 achieved:

- combined remission 56.3% vs 38.6% of controls
- clinical remission 59.2% vs 41.6% of controls

9: Conclusion

After all that; we still do not have good evidence on which procedure is better. So what does it come down to?

- Expert opinion
- Surgeon experience
- What the patient is willing to try

10: References

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