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Treatment for Anal Fissure: Where do we stand in 2020?

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ABSTRACT

Anal fissure is arguably the most painful common anorectal disorder. The severity of pain is disproportionate to the size of the lesion (often 8–10 mm located in the posterior midline of the anal canal). Numerous surgical procedures have been advocated but Lateral Internal Sphincterotomy (LIS) has become the standard of care and the procedure of choice. Due to concerns regarding fecal incontinence (FI) following LIS various chemicals have been applied to the anal canal in hope of finding an alternative "chemical" or "pharmacological sphincterotomy". Large numbers of studies in the literature suffer from being non-randomized case series with short follow-ups and with variable outcome measures. In 2020, LIS is the most reliable treatment for chronic anal fissure associated with almost immediate pain relief, lasting results, a very low recurrence rate, and a very small rate of postoperative FI.

Introduction

At the outset, it is important to point out that virtually all of the operations and pharmacologicals used in the treatment of anal fissure are designed to treat chronic anal fissure (CAF). Acute anal fissure is a brief, self-limited problem, which often responds to dietary modification to combat constipation, warm sitz baths, and topical lubricants. Only a very small percentage (<10%) of acute anal fissures last over 6 months or heal and recur to become CAF.

CAF is readily diagnosed by the typical appearance of the fissure with fibrotic margins in posterior midline of the anus often associated with a sentinel tag (pile), a corresponding hypertrophied anal papilla, and a tight anal canal. The severe and disabling pain associated with bowel movements lasts from minutes to hours. Bleeding is minimal.

Historical evolution of treatment

Throughout the decades following the description of CAF by Recamier[1] and his recommended treatment by anal dilation, all efforts and surgical procedures were designed to deal with the anal ulcer, anal stenosis, or both. Lockhart-Mummery at St. Mark's Hospital credited the anal stenosis to the scarring of the external sphincter posteriorly, which he called the "pectin band" and recommended its division.[2] Eisenhammer[3] of South Africa correctly attributed the anal stenosis to the internal sphincter and recommended internal sphincterotomy, later confirmed by Duthie and Bennett.[4]

The advent of anal manometry helped resolve the issue of cause and effect in CAF. For decades surgeons thought the healing and breakdown of anal fissure led to recurring anal stenosis and advocated excision of the fissure. Nothman and Schuster[5] in their landmark paper pointed out the high baseline internal sphincter (IS) pressure in some patients. The IS does not relax at defecation and following a bowel movement rises rapidly to very high levels, causing severe post-defecation pain and gradually relaxes to baseline but never to the normal level seen in non-fissure patients. This "overshoot phenomenon" was confirmed by many subsequent studies such as the one by Abcarian et al.[6]

For decades the recommended sphincterotomy was done at the bed of the fissure, *i.e.* posterior midline. Once healed it often left a scar called "Keyhole Deformity." This was blamed for anal seepage and patient dissatisfaction and was not easily correctable with another operation.

Samson and Stuart[7] proposed a technique of V-Y plasty using skin graft of provide coverage, but covering the fissurectomy wound did not necessarily prevent keyhole deformity. Leong and Seow Choen randomized 40 patients with CAF to lateral internal sphincterotomy (LIS) or anal advancement flap. The LIS group all healed, but the latter group had 15% failure to heal despite the flap.[8]

Eisenhammer proposed LIS in 1959.[9] Bennett and Goligher touched on this technique in 1962.[10] But the real credit should be given to MJ Notaras who devised the subcutaneous LIS and published his excellent results in 1969[11] and 1971.[12]

It was not long before LIS crossed the Atlantic. Dr. Ray spoke of this technique during his 1974 Presidential address of the American Society of Colon and Rectal Surgeons (ASCRS) and published the results of LIS from the Oschner Clinic.[13] Abcarian published a large series of 300 CAF patients treated by midline (150) *vs.* lateral

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(150) internal sphincterotomy and demonstrated the superiority of LIS as to less postoperative pain, faster healing, shorter hospital stay, and time off work.[14] (Sphincterotomy was an inpatient operation in the early 1970s.)

Many years later, the success of LIS in the treatment of CAF was explained on the basis of improvement in anal blood circulation. Schouten and colleagues used doppler flow measurement of microvascular perfusion of the anoderm in 27 patients.[15] Blood flow at the site of the fissure was significantly lower than in controls. Reduction of internal anal sphincter pressure improved the blood flow and resulted in healing of fissures, and is thought to be the basis of the effectiveness of sphincterotomy in treatment of CAF. A similar circulation study in much larger groups of patients (178), demonstrated that anodermal blood flow was lower in posterior midline than other quadrants of the anal canal.[16]

LIS soon became the procedure of choice and standard of care for CAF. Early healing, shorter sick days, and excellent healing with very low recurrence, and lower complication rates all contributed to its popularity. A report of 306 patients followed for 1 year after LIS at the University of Minnesota showed 15 patients with minor FI (to flatus) and no patients had to wear a pad.[17]

However in 1989, Khubchandani and Reed published a large case series of LIS follow-ups showing FI to flatus in 36% and to solid stool 5%.[18] In 1996, the University of Minnesota Group, which had reported low incontinence rate in 1985,[17] published a retrospective case series of open *vs.* closed LIS. 30.3% of the patients had incontinence to flatus and 11.8% to solid stool.[19] Following these two reports there was a frenzy of publications reporting fecal incontinence after all sorts of sphincterotomy including LIS and this gave rise to a trend towards "chemical/pharmacological sphincterotomy" especially in the litigious environment of the United States of America. The following is a list of drugs used for medical therapies of anal fissure:

Nitroglycerine (NTG)
Calcium Chemical Blockers (CCB)
Botulinum Toxin
Hydrocortisone
Topical Anesthetic
Clove Oil
Smooth Muscle Relaxants
  Indoramine
  Monoxidil
  Sidenafil
Bulking Agents (Fiber)
Anal Dilatation (Back to the Future!!)

The problem with many of the published data is variability of outcome measures and the limitation of non-randomization, bias, short follow-up, persistence/recurrence, and of course fecal incontinence. Visual appearance of healing can be deceptive because appearance and symptoms may normally wax and wane, therefore length of follow-up and adequate sample size is critical. Specific outcomes such as headaches with NTG and tachyphylaxis with Botox must be recorded. Furthermore, when considering claims of success rate one must take into consideration that the rate of healing in all placebo controlled trials is 34%, a very important fact stressed by Nelson in his landmark systematic review of anal fissure treatments in 2012.[20] In the landmark systematic review by Nelson, 54 randomized controlled trials (RTC) consisting of 3904 patients included: NTG *vs.* Placebo, 15 RTC = 1190 patients. NTG at 0.2% or 0.4% ointments twice a day (bid) or three times a day (tid) for 6–8 weeks, NTG was significantly better than placebo 49% *vs.* 37%. Incidence of headaches with NTG was 24% *vs* 9% for placebo. Most trials had short follow-up.

Rational for use of topical NTG

- Nitric Oxide (NO) receptors are found in the internal anal sphincter (IAS)
- NO inhibits neurotransmitters causing relaxation of IAS
- NTG is NO donor resulting in IAS relaxation

There were there trials assessing dose of NTG for 0.05–0.4%. They showed no difference in healing. Dermal patch at distant location had the same results as topical NTG. Overall headache rate was 27%.[20]

A multicenter trial by Bailey et al. to define the strength and dosing interval of NTG, concluded that there was no difference in healing rate among the different groups. Those who received 0.4% NTG ointment had statistically significant decrease in pain intensity.[21]

Rational of use of calcium channel blockers (CCB)

Calcium (Ca^{++}) is important for smooth muscle contraction. CCBs can be useful in the treatment of CAF. Both Nifedipine and Diltiazem have been shown to be effective. Perotti et al. conducted a RCT comparing 0.3% Nifedipine with Lidocaine Hydrocortisone every twelve hours for six weeks. The healing rate was significantly better in the Nifedipine group 94.5% *vs.* 16.4%.[22] Diltiazem is another CCB which has been shown to heal CAF up to 75%.[23] Jones et al. used 2% Diltiazem gel bid in 39 patients with failed NTG ointment. Forty-nine percent healing was seen within 8 weeks. Side effects included drowsiness, headache, and mood swings.[24] Nelson reported 4 studies comparing NTG and CCB with no significantly different results.[20]

Rationale for use of botulinum toxin

Botulinum toxin, a powerful toxin which inhibits neurotransmission resulting in muscle relaxation or paralysis, first reported in 1994 by Jost and Schimrigk to heal anal fissure.[25] Maria and colleagues conducted a double blind controlled trial of 30 patients (Botox *vs.* Saline). After 2 months 11/15 patients in the Botox group had healed *vs.* 2/15 in the saline group ($p = 0.03$).[26]

There is no standardization of Botox injection as to the optimum dose (10–100 units), location (anterior, lateral, posterior) or into the IAS *vs.* intersphincteric groove. Side effects include allergic reactions, increased bladder residual volume, muscle weakness, postural hypotension, and injection site infection. Transient flatus incontinence is common. Whenever Botox is employed one has to consider its tachyphylaxis requiring repeat injection in 3–4 months (similar to achalasia). Comparison of Botox to NTG showed similar results in 4 trials,[20] 67% *vs.* 53% (p = ns). Recurrence of healed fissure after 1 year is more than 50%. In 3 trials Botox was found to be inferior to surgery in fissure healing 67% *vs*. 94%.[20]

Anal dilation has also been employed to avoid surgery. Manual dilation, use of various operative anoscopes, and balloon dilation have been reported. Interestingly this alternative is employed for fear that LIS might cause incontinence. However, all reported series show a significant post dilation flatus or fecal incontinence.[27] Despite advocating anal dilatation by Sohn et al.[28] the enthusiasm for anal stretch has been on the decline in the last few decades. High recurrence/persistence rates, high incidence of flatus incontinence documented by a fragmented IAS on anal ultrasonography caused this procedure to be abandoned.

Comparison of medical treatment *vs*. surgical treatment

11 RCT examined the outcome of 741 patients. Healing rate with surgery 90% *vs*. 49% with medical treatment. Incontinence rate with surgery was similar to NTG and Botox. CCB was slightly better.

Late recurrence after surgery was uncommon. Three RCT with > 1 year follow-up showed healing rate of 97% with surgery *vs.* and 59% with medical treatment.[20]

One of the best published studies is that of comparison of LIS with t.i.d NTG in the treatment of CAF. A randomized controlled trial was conducted by the Canadian CRS Trial Group.[29] Ninety patients were accrued, 8 were excluded and 82 were randomized (38 LIS, 44 NTG). In 6 weeks 34 (89.5%) of the LIS group healed with no relapse *vs.* 13 (29.5%) in the NTG group with 5/23 relapse. At 6 months 25 (92.1%) of the LIS group were healed *vs.* 12 (27.2%) of the NTG with a relapse rate of 45.4%.[29] The LIS group had a 87.9% satisfaction rate and 100% would opt for surgery again. The NTG group had a satisfaction rate of 32.3%, 9 had stopped treatment due to headaches and only 41% would have the treatment again. The same group followed 51 (62%) of the patients with surveys after 6 years. Symptoms in the LIS group occurred in 0 *vs*. NTG 41%, subsequent surgery in LIS was 0 *vs* GTN 59%. Choosing the same treatment again LIS 92% *vs*. NTG 63%. Fecal incontinence score was similar between the two groups. They concluded that LIS was durable over time, had high patient satisfaction, and caused no compromise in fecal incontinence.[29]

Nelson[20] concluded the following: a) medical therapy for anal fissure was statistically significant, but only marginally better than placebo, b) the risks were not great, primarily headaches, c) healing rates were clearly inferior to surgery, d) late recurrences were common, and e) best reserved for individuals wishing to avoid surgery or those with preexisting incontinence.

So where do we stand in 2020?

I am a firm believer in the meta-analysis of the randomized controlled trials and I believe that the most recent extensive work by Nelson and colleagues is a wonderful compass showing us where we are and where we should aim to go.[30] This is the most up to date and reliable reference for those interested in the subject (Tables 1 and 2).

The outcome measures were the following:

- Fissure non-healing
- Fissure recurrence
- Anal incontinence incidence (assessed mostly in surgical studies)
- Headaches mostly in NTG and ISMN (Isosorbide Mononitrate Studies).

Table 1
Effectiveness of treatment (Adapted from Nelson[30]).

- LIS is superior to manual stretch
- Open and closed LIS are equally effective
- Length of LIS is important but the quality of evidence does not allow any conclusion
- Posterior internal sphincterotomy seems no worse than LIS in healing
- NTG is superior to controls with very poor quality of evidence
- NTG is superior to lidocaine
- NTG is roughly equivalent to Botox
- CCBs are superior to NTG
- LIS is far superior to medical therapies

Table 2
Adverse events (Adapted from Nelson et al[30]).

Studies	Headache rate		Incontinence	
NTG all studies	504/1801	28%	7/634	1.1%
LIS all studies	3/253	1.2%	138/3093	4.4%
LIS after year 2000			31/803	3.9%
Botox	7/138	5.1%	8/354	2.3%
Topical CCB	20/169	16%	4/287	1.4%
Manual dilation			32/264	12.1%
Placebo	36/428	8.4%		

Conclusion

If I see a patient with CAF, I would prescribe Nifedipine 0.3% ointment bid for 8 weeks – if effective I will follow the patient as needed. If ineffective, I would switch to NTG 0.2% ointment bid for 8 weeks. If the patient cannot tolerate the headaches (which is significantly reduced if the patient applies NTG in the recumbent position rather than sitting or standing), I would offer Diltiazem 2% ointment bid. I have never been a Botox fan but I can offer that to the patient if all of the above fails (a colleague of mine would gladly administer Botox). I will continue to offer LIS with a very low 3.9–4.4% rate of incontinence if the patient continues to be miserable or has frequent relapses. In the meantime, the search for the perfect chemical for pharmacologic sphincterotomy will continue.

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