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Trzpis, M.; Klaase, J. M.; Koop, R. H.; Broens, P. M. A.

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M. Trzpis¹ · J. M. Klaase^{2,3} · R. H. Koop² · P. M. A. Broens^{1,4}

¹ Department of Surgery, Anorectal Physiology Laboratory, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

² Department of Surgery, Medisch Spectrum Twente, Enschede, The Netherlands

³ Department of Surgery, Division of Hepatobiliary Surgery and Liver Transplantation, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

⁴ Department of Surgery, Division of Pediatric Surgery, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

Fissurectomy combined with botulinum toxin A: a review of short- and long-term efficacy of this treatment strategy for chronic anal fissure; a consecutive proposal of a treatment algorithm for chronic anal fissure

Introduction

Fissurectomy combined with botulinum toxin A injection is regarded as an effective and safe treatment for chronic anal fissure. The idea behind combining the two treatments is that fissurectomy removes the ischemic tissue, which stimulates healing, while botulinum toxin A reduces elevated anal basal pressure. As a result, blood flow in the anal submucosa can increase, which in turn prevents the fissure from recurring. In some patients, however, a fissure recurs after a median of 22 months, indicating that the factor underlying the development of the fissure has not been eliminated. We aimed to evaluate the efficacy and safety of the combined treatment and discuss this strategy in the light of current knowledge on the aetiology of chronic anal fissure.

Chronic anal fissure

An anal fissure is a longitudinal tear in the anal mucosa. Most acute anal fissures heal spontaneously or, following conservative medical treatment, in up to 4 to 8 weeks. If patients do not respond to treatment, the fissures are classified as chronic. A chronic anal fissure is typically located in the posterior position [19]. The most characteristic symptom of an anal fissure is a severe, tearing pain during and after defecation, sometimes accompanied by bleeding.

Treatment strategies and safety

Treating a chronic anal fissure aims at creating conditions that enable the fissure to heal and at preventing recurrence. This can be achieved by treating constipation and by decreasing anal basal pressure. Occasionally, removal of fibrotic tissue surrounding the fissure is required to support healing. Consti-

pation is usually treated conservatively by adjusting the patient's diet and with laxatives [22]. Initially, lateral internal sphincterotomy (LIS) and partial lateral internal sphincterotomy (PLIS) were developed to decrease anal basal pressure [5, 24]. Regarding short-term efficacy, LIS and PLIS seemed promising tools because they yielded healing rates as high as 95%, with low rates of recurrence [5, 24]. The safety, however, of sphincterotomy assessed in terms of faecal incontinence, which was as high as 10%, diminished the value of LIS and PLIS—especially as faecal incontinence in these cases was not temporary, as was the case after botulinum toxin A injections [24]. Instead, less invasive, topical pharmacological ointments were introduced to reduce anal basal pressure. These ointments continue to be used as the first line of treatment. The most frequently used ointments are glycerine trinitrate (GTN), isosorbide dinitrate, nifedipine, and diltiazem. In many hos-

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Fissurectomy combined with botulinum toxin A: a review of short- and long-term efficacy of this treatment strategy for chronic anal fissure; a consecutive proposal of a treatment algorithm for chronic anal fissure

Abstract

Background. Several studies have investigated the short- and long-term efficacy of fissurectomy combined with botulinum toxin A injection for patients with chronic anal fissure.

Objective. To evaluate the short- and long-term efficacy of the combined treatment strategy of fissurectomy with botulinum toxin A for chronic anal fissure and to discuss recurrence rates in the light of current theory on the aetiology of anal fissure.

Materials and methods. This is a narrative review. We conducted an article search using PubMed and calculated the means of the reported efficacy ranges.

Results. Fissurectomy combined with botulinum toxin A injections freed at least 78% of the patients from symptoms and yielded a fissure healing rate of up to 86%. Within 12 months after treatment a 3% recurrence rate was reported. On average, the long-term recurrence rate was 22%. One study reported a 50% recurrence rate 22 months after treatment.

Conclusion. The efficacy of fissurectomy combined with botulinum toxin A injection for chronic anal fissure is high. The short-term recurrence rate is low, while long-term recurrence is relatively high. Extended follow-up indicates that recurrence of chronic

anal fissure is possibly caused by anal basal pressure building up steadily once again. If so, the cause of renewed increase of pressure should be addressed. Based on the literature and on our clinical experience, we assume that the underlying cause of increasing anal basal pressure is that patients use their pelvic floor muscles inadequately and this in turn leads to chronic anal fissure.

Keywords

Chronic anal fissure · Botulinum toxin A · Fissurectomy · Recurrence

Fissurektomie plus Botulinumtoxin-A-Injektion zur Behandlung der chronischen Analfissur: Übersicht der bisherigen Resultate im Kurz- und Langzeitverlauf; Vorschlag eines Algorithmus zur Therapie

Zusammenfassung

Hintergrund. Die Wirksamkeit einer Fissurektomie kombiniert mit der Injektion von Botulinumtoxin A zur Therapie der chronischen Analfissur wurde in mehreren Studien sowohl im Kurzzeit- als auch im Langzeitverlauf untersucht.

Ziel. Ziel der Arbeit ist es, die Wirksamkeit der Therapie der chronischen Analfissur mittels Fissurektomie plus Botulinumtoxin A zu untersuchen und die Rezidivraten in Anbetracht der aktuellen Theorie zur Ätiologie der Analfissur zu erörtern.

Methoden. Es handelt sich um eine wissenschaftliche Übersichtsarbeit. Dazu führten die Autoren eine Suche in der Datenbank PubMed durch und berechneten

die Durchschnittswerte aus den dortigen Angaben.

Ergebnisse. Eine Fissurektomie plus Injektion von Botulinumtoxin A führt bei mindestens 78 % der Patienten zur Symptombefreiheit und bei bis zu 86 % zur Fissurheilung. Bis 12 Monate nach der Therapie wurde eine Rezidivrate von 3 % angegeben. Im Langzeitverlauf fand sich im Durchschnitt eine Rezidivrate von 22 %, wobei in einer Studie von einer Rezidivrate von 50 % nach 22 Monaten berichtet wurde.

Schlussfolgerungen. Die Wirksamkeit der Fissurektomie plus Botulinumtoxin-A-Injektion zur Therapie der chronischen Analfissur ist hoch. Die Rezidivrate im Kurzzeitverlauf ist niedrig, im Langzeitverlauf dagegen

relativ hoch. Langzeitnachbeobachtungen zufolge könnten die Rezidive durch einen erneut kontinuierlich ansteigenden analen Ruhedruck bedingt sein. Stimmt das, so sollte dieser Anstieg des Ruhedrucks behandelt werden. Eine Hypothese gemäß Angaben aus der Literatur und den klinischen Erfahrungen der Autoren lautet, dass der ansteigende Ruhedruck durch eine Fehlsteuerung der Beckenbodenmuskulatur bei manchen Patienten bedingt ist und dies dann zum Rezidiv der chronischen Analfissur führt.

Schlüsselwörter

Chronische Analfissur · Botulinumtoxin A · Fissurektomie · Rezidiv

pitals, including our centres, treatment of anal fissures in adult patients is usually initiated with these pharmaceuticals in combination with conservative treatment of constipation and continued for approximately 16 weeks [24]. The efficacy of this non-invasive treatment varies around 50% and fissures recur in more than 50% of the patients who underwent treatment with glycerine trinitrate [24]. Additionally, these patients suffer site effects, the most common being severe

headaches [1, 8]. Such management, if unsuccessful, is usually followed by one or more botulinum toxin A injections. Botulinum toxin A results in an overall healing rate of 68%. The healing rates in different studies vary from 41 to 91% after 3 months and the recurrence rates range from 21 to 54% after 6 months [25]. The efficacy after treatment with only botulinum toxin A does not reach 100% and the injections need to be repeated in approximately half of the patients

because of recurring symptoms. The management pathway described above aims at decreasing anal basal pressure, but it does not eliminate fibrosis that results from the ischemic anal mucosa and the surrounding tissue of the fissure, which hampers the healing process. Fissurectomy was described for the first time in 1930 by Gabriel for adult patients and since then, it has been one of the main treatments for anal fissure in the German Coloproctologist community

Table 1 Short- and long-term efficacy and recurrence rates reported in studies involving patients treated with a combination of fissurectomy and botulin toxin for chronic anal fissure

Reference	Patients n	Medicine	Dose (in IU)	Time to follow-up	Symptomatic improvement (in %)	Healing rate (in %)	Safety (in %)	Recurrence (in %)
Andicochea Agorria et al. 2019	52	Botulinum toxin A, BTA (Botox®, Allergan, Inc.; Irvine, CA, USA)	33–50	– 27 months	n.a. Not reported	94.2 Not reported	Not reported Not reported	n.a. 34.7
Barnes et al. 2015	103	Botulinum toxin A, BTA (Botox®, Allergan, Marlow, Buckinghamshire, United Kingdom)	100	12 weeks 12 months ^a Median 33 months ^b	95 Symptom-free: 100 n.a.	Complete: 67 Incomplete: 28 No healing: 5 n.a.	Temporary light FI: 7 (liquid/flatus); absent after 12 weeks No FI n.a.	Not reported Not reported No recurrence
Karabulut et al. 2012	36	Botulinum toxin A (Botox®, Abdi İbrahim, Istanbul, Türkiye)	20	2 weeks 4 weeks ^c 8 weeks	Symptom-free: 61 Incomplete: 28 Persistent symptoms: 11 Symptom-free: 78 Incomplete: 11 Persistent symptoms: 11 Symptom-free: 78 Incomplete: 11 Persistent symptoms: 11	Not reported Complete: 78	Not reported Not reported	n.a. Not reported Not reported
Patti et al. 2010	10	Botulinum toxin A, BTA (Botox®, Allergan, Westport, Ireland)	30	30 days 12 months	Symptom-free: 100 Not reported	Complete: 100 Not reported	FI: 30 (3 patients) FI: 10 (1 patient)	n.a. No recurrence
Witte et al. 2009	21	Botulinum toxin A, BTA (Dysport®, Ipsen, Hoofddorp, The Netherlands)	80 (20)	12 weeks	Symptom-free: 76 Incomplete: 14	Complete: 90 No healing: 10	Temporary light FI: 14 (liquid/flatus)	n.a.
Arthur et al. 2008	28	Botulinum toxin A, BTA (Botox®)	40	12 weeks	Symptom-free: 90	No healing: 10	Temporary FI: 7 (soiling)	n.a.
Baraza et al. 2008	46	Botulinum toxin A, BTA (Botox®, Marlow, Buckinghamshire, United Kingdom)	25–100	11 months	Symptom-free: 78	Healing: 78 No healing: 22	Urge FI: 2 Chronic perianal sepsis: 2 (1 patient)	n.a.
Scholz et al. 2007	40	Botulinum toxin A, BTA (Botox®, Allergan, Lachen, Switzerland)	10	22 months 6 weeks ^d	Symptom-free: 28 Symptom-free: 65 Persistent symptoms: 10	Not reported After 1st treatment: Complete: 25 Incomplete: 65 No healing: 10 After 2nd treatment: Complete: 90	Chronic perianal sepsis: 3 FI: 4.5 (1 patient)	40–50 n.a.
Sileri et al. 2007	22	Botulinum toxin A, BTA (Botox®, Allergan, Milan, Italy)	25	12 months 19 months	For pain: 92 For Bleeding: 100 n.a.	Healing: 79 Complete: 82	Not reported Temporary FI and flatus: 6	10 14

Table 1 (Continued)

Reference	Patients n	Medicine	Dose (in IU)	Time to follow-up	Symptomatic improvement (in %)	Healing rate (in %)	Safety (in %)	Recurrence (in %)
Lindsey et al. 2004	30	Botulinum toxin A, BTA (Botox TM , Allergan, High Wycombe, United Kingdom)	25	8 weeks	Not reported	Complete: 93 Unhealed: 7	Temporary flatus FI: 7	n.a.
<i>On average:</i> (a mean calculated on the outcomes reported in the studies)				16 weeks	Not reported	Complete: 93	None	n.a.
				<i>Short term:</i> <12 months	78	86	6	3
				<i>Long term:</i> ≥12 months	n.a.	n.a.	0	22

FI faecal incontinence, IU International Units; n.a. not applicable

^aTelephonic interview

^bClinical records were reviewed

^cAnoscopic examination; of the 36 patients, 18 underwent only botulin toxin injections and 18 received the combination of botulinum toxin A and fissurectomy

^dQuestionnaire, response rate 93%

[9]. Fissurectomy has also been used to remove the fibrotic tissue in paediatric patients [26]. A relatively recent suggestion was to combine a botulinum toxin A injection with fissurectomy in case treatment involving only botulinum toxin A injection failed [13]. If this strategy also fails to yield satisfactory results, sphincterotomy is recommended.

Fissurectomy combined with botulinum toxin A injection

Efficacy

In case of chronic anal fissure, the efficacy of the combined treatment is assessed primarily in terms of relief from symptoms, of which pain or bleeding or both are the most important. Wound healing is also taken into consideration when assessing treatment efficacy. In 2004, the first study describing outcomes of the combined treatment strategy was published by Lindsey and colleagues ([13]; **Table 1**). They showed that fissurectomy–botulinum toxin A management leads to healing more than 90% of fissures that were previously resistant to medical treatment. This result led them to conclude that combined treatment is highly effective and, more importantly, that it is associated with a minimal risk of faecal incontinence. Nevertheless, after 16 weeks of follow-up, 7% of the patients reported temporary incontinence for flatus, albeit not for stool. In addition, 7% of the fissures had not healed completely, while symptomatically, patients’ conditions had improved. Similarly, Scholz and colleagues [20] reported a high prevalence of symptomatic improvement, but the healing rate in their cohort (25% complete and 65% incomplete healing) was slightly lower than that reported by Lindsey and colleagues [13] (79%). Furthermore, Sileri and colleagues compared different methods of treating chronic anal fissure. They confirmed that the healing rate of fissurectomy combined with botulinum toxin A injection was significantly higher than that of topical pharmacological ointments, anal dilators and combinations thereof [21]. At the same time, Arthur and colleagues published a pilot study

in which they compared outcomes of fissurectomy combined with botulinum toxin A with fissurectomy combined with 2% diltiazem ointment (DTC) [3]. His idea was that a botulinum toxin A injection is less safe than DTC, because the former could cause temporal incontinence and perianal sepsis, while the effect on sphincter pressure following botulinum toxin A and 2% DTC seem to be comparable [3]. Moreover, DTC treatment is less expensive than botulinum toxin A. Arthur and colleagues suggested that fissurectomy, followed by topical DTC treatment for 8 weeks, might be just as efficient as fissurectomy combined with botulinum toxin A injection. However, no prospective study with a larger cohort and longer follow-up has been presented until now. Other researchers confirmed high healing rates after the combined treatment [4, 5, 15, 24]. Noteworthy is that Patti and colleagues included anal basal pressure in their outcomes alongside the symptoms reported by patients, the outcomes of physical examinations regarding symptomatic improvement and the healing rates of anal fissures, and they confirmed that pressure decreased significantly after botulinum toxin A injections [15]. Such an observation is most valuable because basal anal pressure is the key issue to be addressed in the treatment of chronic anal fissure.

The value of fissurectomy regarding healing rate was investigated by Karabulut and colleagues [12]. They performed a randomized study in which half of the patients were treated with fissurectomy combined with botulinum toxin A injections, while the other half received only botulinum toxin A. Although the difference in the outcomes was not statistically significant, the healing rates of the patients who had received the combined treatment were approximately 10% higher than in the patients who had been treated with only botulinum toxin A.

Side effects

Transient incontinence as a side effect has been described previously in patients treated with only botulinum toxin A. It is therefore not surprising that after the

combined treatment of fissurectomy with botulinum toxin A, approximately 3% of the patients reported soiling or involuntary loss of flatus and liquid stool (Table 1). Only one study reported a case of faecal urge incontinence that persisted for more than 18 months [4]. The low prevalence of the lightest form of incontinence and especially the fact that it was a temporary problem, indicates that fissurectomy combined with botulinum toxin A injections is a safe strategy for treating chronic anal fissure (Table 1).

Recurrence of anal fissure

Recurrence is one of the factors that determine the long-term efficacy of treatment. This issue seems ambiguous in studies describing outcomes of fissurectomy combined with botulinum toxin A injection. We found no recurrence, or a low rate of approximately 3%, in studies with a follow-up of 12 months at most (Table 1). We found four studies that reported recurrence in patients followed for longer than 12 months. What struck us, however, is that the long-term studies showed an average recurrence rate of 22%, which indicates that almost every fourth patient needed to undergo the treatment again. The highest recurrence rate reported was 50%, which was observed after 22 months of follow-up. In fact, this result resembles the recurrence rate reported after treatment with only botulin toxin A [4].

The short- and medium-term outcomes show low recurrence rates and indicate that combining fissurectomy and botulin toxin A is a promising treatment strategy. The long-term outcomes, however, contest this statement.

Botulin toxin A dosage

Studies on the efficacy of different doses of botulinum toxin A and its side effects report ambiguous, even contradictory, conclusions. In the studies we reviewed, the doses varied from 10 and 100 units of botulinum toxin A (Table 1). Currently, Botox® and Dysport® (manufacturers and location specified in Table 1) are the two preparations of botulinum

toxin serotype A are available for clinical use. Although their efficacy and tolerability are comparable, Botox® is used more frequently [6]. The dosage of Dysport® is four times the dosage of Botox®, which allows the injection volumes of Dysport® to be reduced and to prevent local pressure effects [23]. There seems to be no significant difference in therapeutic efficacy between Botox® and Dysport® [11].

Aetiology of chronic anal fissure

To date, the aetiology of chronic anal fissure is unclear, which hampers treatment optimization. Originally, constipation and specifically its symptoms, such as a hard stool and abnormal straining during defecation, were considered to be the main causal factors underlying the development of anal fissure. Currently, we know that elevated basal anal pressure is strongly associated with the occurrence of anal fissure. Elevated basal anal pressure compromises blood flow, which leads to local ischemia in the anal mucosa. Ischemia weakens tissue, making it more prone to damage and thus prevents the healing process. Until recently, constant contraction of the internal anal sphincter (IAS), known as IAS spasm, was seen as the cause of the elevated anal basal pressure because researchers were unaware that the external anal sphincter can contract involuntarily [7]. Following from this awareness, it seemed logical to assume that continuously elevated contraction of the external part of the anal sphincter could be associated with elevated anal basal pressure [14]. This hypothesis was supported by the fact that the receptors of the anal external continence reflex, which mediate the involuntary contraction of the external anal sphincter, are located in the anal mucosa. Damage to the anal mucosa caused by, for instance, hard stool and/or straining, can trigger receptors of the anal external sphincter continence reflex continuously, causing overreaction. Overreaction, in turn, would result in chronic contraction of the external anal sphincter and elevated basal pressure in the anal canal, which results in reduced blood flow, which in turn prevents the fissure from healing.

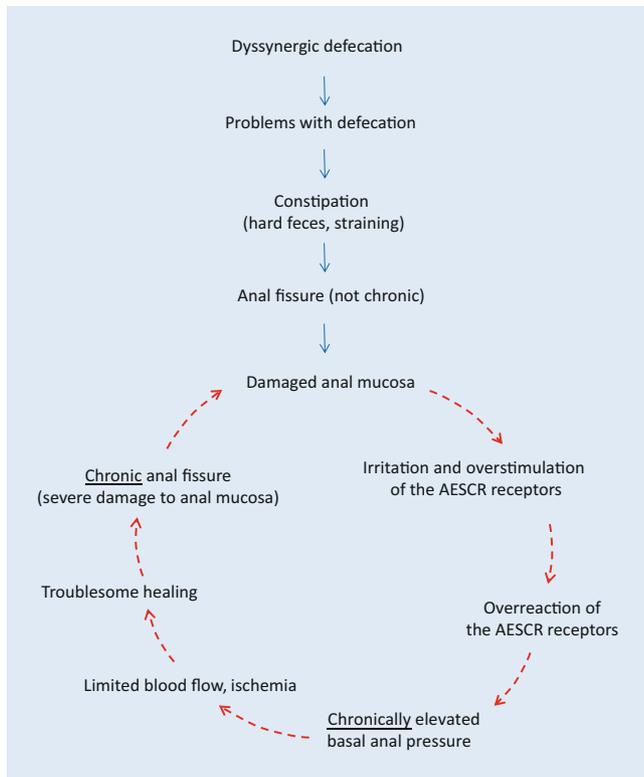


Fig. 1 ▲ The vicious circle underlying chronic anal fissure. Dyssynergic defecation, the condition whereby patients do not use the muscles of their pelvic floor adequately, leads to problematic defecation and results in constipation. Constipation, and especially hard stool and straining during defecation, results in damage to the anal mucosa, which contains the receptors of the anal external sphincter continence reflex (AESCR) [7]. This reflex is known to regulate involuntary contraction of the anal external sphincter. Damage to the anal mucosa triggers continuous activation of these receptors, thus causing chronic involuntary contractions of the anal external sphincter, which in turn contributes to chronically elevated basal anal pressure. Subsequently, local ischemia prevents healing of the anal fissure, which leads to the chronic nature of this problem. As a consequence, the mucosa cannot heal, the severity of the fissure increases, and the patient is unable to escape from the vicious circle. The key issue to curing chronic anal fissure is therefore to find the treatment that will enable the patient to escape from this vicious circle

Treatment efficacy versus aetiology

The efficacy of symptomatic improvement and safety of fissurectomy combined with botulinum toxin A injection is as high as 90%. The main limitation of the combined treatment is long-term recurrence, which can be as high as approximately 22%. It would seem that the underlying causal factor of chronic anal fissure is not addressed correctly by the treatments discussed in this review. Seeing that elevated anal basal pressure is considered to be the direct cause of chronic anal fissure, the question is what causes the recurrence of elevated anal basal pressure. Previously, it was assumed that increased pressure occurred

as a result of an acute fissure. This assumption, however, can be rejected in patients in whom chronic anal fissures healed following botulinum toxin A injections. Once the fissure had healed, pressure should not increase again.

It is known that dyssynergic defecation, i.e., inadequate use of the pelvic floor muscles, is strongly associated with increased anal basal pressure [16]. Dyssynergic defecation affects up to half of patients with chronic constipation [17]. One could hypothesize, therefore, that between 35 and 50% of patients in whom anal fissures recur suffer from dyssynergic defecation, as reported by both Andicoechea Agorria and colleagues and by Baraza and colleagues [2, 4]. Studies involving manometry, which

not only measure anal basal pressure but the synchronization of the pelvic floor muscles as well, would be useful in an attempt to confirm this hypothesis. None of the current treatment strategies for chronic anal fissure pay attention to dyssynergic defecation. Nevertheless, treatment of this dysfunction is relatively easy with pelvic physical therapy or biofeedback therapy. Such a therapy could be started in patients who are free of pain, shortly after the fissure has healed.

Treatment objectives

The main point concerning the treatment of chronic anal fissure is to simultaneously eliminate the factors that lead to the development of the fissure and the factors that prevent it from healing. A therapy was therefore developed that combines the treatment of constipation, the reduction of basal anal pressure and the removal of ischemic mucosa located in the anal fissure. Nevertheless, it appears that fissurectomy combined with botulinum toxin A injection does not treat the underlying cause that leads to elevated anal basal pressure, and that a relatively high rate of recurrence persists in the long term.

Discussion and practical conclusion

Even though topical ointments are currently routinely prescribed as the first line of treatment, we propose to alter clinical practice by introducing botulinum toxin A injections as the first line of treatment. At present, Botox® and Dysport® are typically given as second-line treatment on account of the relatively high cost and the more invasive nature of these treatment options [24]. Nevertheless, botulinum toxin A injections are more effective compared to topical ointments and patients might already benefit from a single injection. In fact, administering botulinum toxin A may even be more economical, particularly if one takes into account the amount of time patients spend on multiple repeat consultations with medical specialists in case of unsuccessful treatment. More-

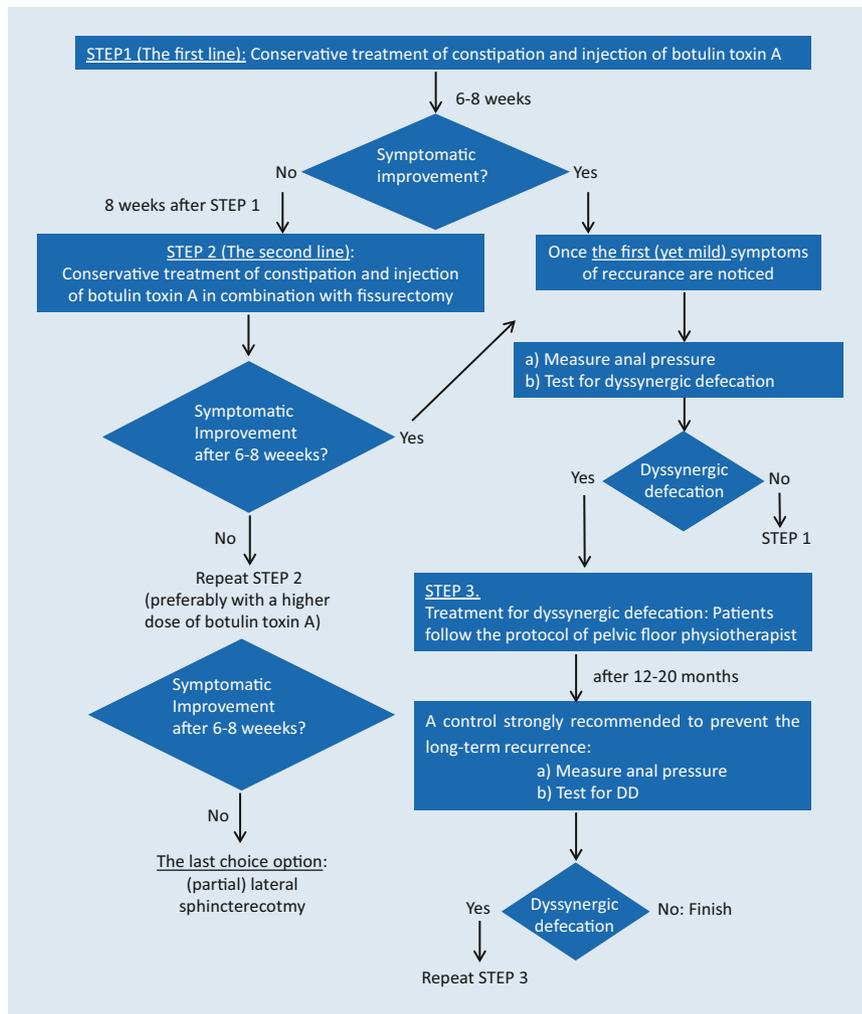


Fig. 2 ▲ Treatment algorithm proposed for treating chronic anal fissure and preventing it from recurring in the long term. DD Dyssynergic defecation

over, botulinum toxin A injections have fewer side effects than, e.g., instance GTN, which causes severe headaches in approximately 30% of patients [18]. From the reports on the efficacy of anal fissure treatments, it appears that the clinical outcomes of fissurectomy combined with botulinum toxin A injection into the anal sphincter might be superior to the efficacy of the therapies used separately. The combined treatment strategy, however, is more invasive than botulinum toxin injections alone. Therefore, we recommend fissurectomy combined with botulinum toxin A as the second line of treatment.

The strategy for treating chronic anal fissure should not be limited to botulinum toxin A injections that aim solely at decreasing basal anal pressure. Treatment

should also aim at helping the patient to escape from the vicious circle (Fig. 1). This could be achieved if overstimulation of the receptors of the anal external continence reflex can be silenced, as previously explained by Meegdenburg and colleagues [14]. This will be the case when the anal mucosa has healed and measures have been taken to prevent new damage to the mucosa. Therefore, besides treatment with botulin toxin A, laxatives should be given to soften the stool in order to ease healing of the anal mucosa. Based on our clinical experience, we recommend administering laxatives for at least 2–6 months after the combined treatment of fissurectomy with botulinum toxin A. There is, however, a study indicating that that maintenance therapy with unprocessed bran or a high-fibre residue diet

should be continued for at least 6 months or even for the whole life to prevent recurrence of anal fissure [10]. The decision how long a patient should use laxatives or other agents supporting easy defecation should possibly be personalized and adjusted to the particular case. In our opinion, in case of confirmed dyssynergic defecation, this period should be extended to as long as 6 months after finishing pelvic floor physical therapy. Once patients are free of dyssynergic defecation, also constipation-related symptoms should resolve, the risk of recurrence of chronic anal fissure decrease and usage of agents supporting defecation for the whole life might then be unnecessary.

The fact that the development of chronic anal fissure results from elevated anal basal pressure, and that this condition could in turn result from dyssynergic defecation, indicates the need of anorectal manometry in at least those patients suffering from recurring fissures. In such cases, it is important to first provide treatment that will free patients from anal pain before performing manometry. If dyssynergic defecation is confirmed and the fissure has healed, albeit perhaps temporarily, patients should receive pelvic physical therapy to learn how to properly relax their pelvic floor muscles and anal sphincters and to use them efficiently during defecation.

In summary, the treatment of chronic anal fissure should not only focus on healing of the fissure and on decreasing basal anal pressure, because these are merely two elements of the vicious circle. The circle consists of more elements that should be taken into consideration during treatment (Fig. 1). Escaping from the vicious circle will not only allow healing of the mucosa and fissure, but will also prevent the patients from re-entering the circle and, therefore, prevent recurrence of a fissure in the long term.

Concrete proposed treatment algorithm

Following from the above considerations, current literature and our clinical experience, we propose that the treatment of chronic anal fissure should be approached stepwise (Fig. 2). As the first line of

treatment, we recommend the combination of conservative treatment of constipation and botulinum toxin A injections without fissurectomy, thus reducing the invasiveness of the treatment as much as possible. Symptomatic improvement should be assessed after approximately 6–8 weeks, which is normally a sufficient time for healing. In case of no improvement, fissurectomy combined with botulinum toxin A should be performed as second-line treatment approximately 8 weeks after the first injection, to increase the chances of a beneficial outcome. Additionally, we recommend assessing basal anal pressure in these patients who have shown symptomatic improvement after the fissurectomy combined with botulinum toxin A, as well as in patients who have noticed the first, mild symptoms of recurrence of anal fissure. Increased anal basal pressure namely indicates that the original cause of the anal fissure has returned. In this case, examining whether the patients use their pelvic floor muscles adequately, that is determining dyssynergic defecation, would be of added value. Once dyssynergic defecation is confirmed, adequate treatment should be started to eliminate the cause of increased anal basal pressure, thus avoiding recurrence of chronic anal fissure. Ideally, patients should return after approximately 12 to 20 months for re-assessment of the outcomes of pelvic floor physical therapy and to ascertain whether or not anal basal pressure is increasing once again. If there are no signs of symptomatic recurrence and the anal basal pressure is comparable to the pressure recorded following fissurectomy combined with botulinum toxin A injection, then treatment was successful.

In patients who do not respond to the entire line of treatment or return on account of recurrent anal fissure, the most invasive form of treatment, namely (partial) lateral sphincterotomy, might be performed. Patients should, however, be forewarned about the possible negative consequences, of which, unfortunately, permanent faecal incontinence is the most frequent.

Conclusion

The efficacy of fissurectomy combined with botulinum toxin A injection for chronic anal fissure is high in the short term but still suboptimal in the long term. To prevent long-term recurrences, we have developed a new algorithm based on the literature and clinical experience. We propose that for chronic anal fissure, botulinum toxin A treatment should be introduced as the first line of treatment, and combined botulinum toxin A treatment and fissurectomy as the second line. At the same time, we encourage testing patients with recurring anal fissure for dyssynergic defecation, which is known to contribute to constipation, and increased anal basal pressure. Presumably, treatment of dyssynergic defecation would prevent constipation and recurrence of chronic anal fissure. This hypothesis requires evidence-based conformation provided by a randomised clinical study.

Corresponding address

M. Trzpis, PhD

Department of Surgery, Anorectal Physiology Laboratory, University of Groningen, University Medical Center Groningen
PO Box 30 001, Hanzeplein 1, 9700 RB Groningen, The Netherlands
m.trzpis-bremer@umcg.nl

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Compliance with ethical guidelines

Conflict of interest. M. Trzpis, J.M. Klaase, R.H. Koop and P.M.A. Broens state that there are no conflicts of interest and that no funding was received.

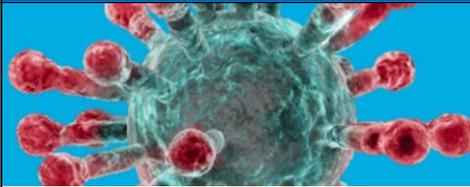
For this article, no studies with human participants or animals were performed by any of the authors. All studies performed were in accordance with the ethical standards indicated in each case.

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References

1. Altomare DF, Rinaldi M, Milito G et al (2000) Glyceryl trinitrate for chronic anal fissure—Healing or headache? *Dis Colon Rectum* 43:174–179. <https://doi.org/10.1007/bf02236977>
2. Andicoechea Agorria A, Del Casar Lizcano JM, Barbón Remis E et al (2019) Treatment of a chronic anal fissure with a botulin toxin A injection and fissurectomy. *Rev Esp Enferm Dig* 111:672–676. <https://doi.org/10.17235/reed.2019.6202/2019>
3. Arthur JD, Makin CA, El-Sayed TY, Walsh CJ (2008) A pilot comparative study of fissurectomy/diltiazem and fissurectomy/botulinum toxin in the treatment of chronic anal fissure. *Tech Coloproctol* 12:331–336. <https://doi.org/10.1007/s10151-008-0444-4>
4. Baraza W, Boereboom C, Shorthouse A, Brown S (2008) The long-term efficacy of fissurectomy and botulinum toxin injection for chronic anal fissure in females. *Dis Colon Rectum* 51:239–243. <https://doi.org/10.1007/s10350-007-9161-8>
5. Barnes TG, Zafrani Z, Abdelrazeq AS (2015) Fissurectomy combined with high-dose botulinum toxin is a safe and effective treatment for chronic anal fissure and a promising alternative to surgical sphincterotomy. *Dis Colon Rectum* 58:967–973. <https://doi.org/10.1097/DCR.0000000000000434>
6. Brisinda G, Albanese A, Cadeddu F et al (2004) Botulinum neurotoxin to treat chronic anal fissure: results of a randomized “Botox vs. Dysport” controlled trial. *Aliment Pharmacol Ther.* <https://doi.org/10.1111/j.1365-2036.2004.01895.x>
7. Broens PMA, Penninckx FM, Ochoa JB (2013) Fecal continence revisited: the anal external sphincter continence reflex. *Dis Colon Rectum* 56:1273–1281. <https://doi.org/10.1097/DCR.0b013e3182a42d16>
8. Bulus H, Varol N, Tas A, Coskun A (2013) Comparison of topical isosorbide mononitrate, topical diltiazem, and their combination in the treatment of chronic anal fissure. *Asian J Surg* 36:165–169. <https://doi.org/10.1016/j.asjsur.2013.01.010>
9. Gabriel WB (1930) The treatment of pruritus ani and anal fissure. *Br Med J.* <https://doi.org/10.1136/bmj.2.3634.311>
10. Jensen SL (1987) Maintenance therapy with unprocessed bran in the prevention of acute anal fissure recurrence. *J R Soc Med* 80:296–298. <https://doi.org/10.1177/014107688708000513>
11. Jost WH, Schrank B (1999) Chronic anal fissures treated with botulinum toxin injections: a dose-finding study with Dysport®. *Colorectal Dis* 1:26–28. <https://doi.org/10.1046/j.1463-1318.1999.00006.x>
12. Karabulut K, Aygen E, Kirkil C et al (2012) The impact of fissurectomy combined with botulinum toxin injection in the treatment of chronic anal fissure. *Firat Tip Derg* 17:135–138
13. Lindsey I, Cunningham C, Jones OM et al (2004) Fissurectomy-botulinum toxin: a novel sphincter-sparing procedure for medically resistant chronic anal fissure. *Dis Colon Rectum* 47:1947–1952. <https://doi.org/10.1007/s10350-004-0693-x>



14. van Meeegdenburg MM, Trzpis M, Heineman E, Broens PMA (2016) Increased anal basal pressure in chronic anal fissures may be caused by overreaction of the anal-external sphincter continence reflex. *Med Hypotheses* 94:25–29. <https://doi.org/10.1016/j.mehy.2016.06.005>
15. Patti R, Famà F, Tornambè A et al (2010) Fissurectomy combined with anoplasty and injection of botulinum toxin in treatment of anterior chronic anal fissure with hypertonia of internal anal sphincter: a pilot study. *Tech Coloproctol* 14:31–36. <https://doi.org/10.1007/s10151-009-0562-7>
16. Rao SSC (2008) Dyssynergic defecation and biofeedback therapy. *Gastroenterol Clin North Am* 37:569–586. <https://doi.org/10.1016/j.gtc.2008.06.011>
17. Rao SSC, Patchararakul T (2016) Diagnosis and treatment of dyssynergic defecation. *J Neurogastroenterol Motil* 22:423–435. <https://doi.org/10.5056/jnm16060>
18. Ratnasingham K, Uzzaman M, Andreani SM et al (2010) Meta-analysis of the use of glyceryl trinitrate ointment after haemorrhoidectomy as an analgesic and in promoting wound healing. *Int J Surg* 8:606–611. <https://doi.org/10.1016/j.jisu.2010.04.012>
19. Schlichtemeier S, Engel A (2016) Anal fissure. *Aust Prescr.* <https://doi.org/10.18773/austprescr.2016.007>
20. Scholz T, Hetzer FH, Dindo D et al (2007) Long-term follow-up after combined fissurectomy and Botox injection for chronic anal fissures. *Int J Colorectal Dis* 22:1077–1081. <https://doi.org/10.1007/s00384-006-0261-z>
21. Sileri P, Mele A, Stolfi VM et al (2007) Medical and surgical treatment of chronic anal fissure: a prospective study. *J Gastrointest Surg* 11:1541–1548. <https://doi.org/10.1007/s11605-007-0255-3>
22. Villalba H (2007) Anal fissure: a common cause of anal pain. *Perm J* 11:62–65. <https://doi.org/10.7812/tpp/07-072>
23. Witte ME, Klaase JM (2007) Botulinum toxin A injection in ISDN ointment-resistant chronic anal fissures. *Dig Surg* 24:197–201. <https://doi.org/10.1159/000102899>
24. Witte ME, Klaase JM, Koop R (2009) Fissurectomy combined with botulinum toxin A injection for medically resistant chronic anal fissures. *Colorectal Dis.* <https://doi.org/10.1111/j.1463-1318.2009.02063.x>
25. Yiannakopoulou E (2012) Botulinum toxin and anal fissure: efficacy and safety systematic review. *Int J Colorectal Dis.* <https://doi.org/10.1007/s00384-011-1286-5>
26. Zeitoun JD, Blanchard P, Fathallah N et al (2018) Long-term outcome of a fissurectomy: a prospective single-arm study of 50 operations out of 349 initial patients. *Ann Coloproctol* 34:83–87. <https://doi.org/10.3393/ac.2017.06.12>

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Springer Medizin hat seit April die Initiative Corona-Webinar über sein Ärzteportal (www.springermedizin.de) gestartet. Ärzte, die auf diesem Portal registriert sind, gelangen über Videoseminare an kostenloses Wissen rund um das Corona-Virus. In jedem Webinar oder Videointerview kommt ein Experte zu einem bestimmten Thema zu Wort und gibt fachlich gesichertes Wissen an Kollegen weiter, die sich mit Symptomatik, Diagnostik und Therapie in Klinik und Praxis beschäftigen. Wöchentlich kommen neue Themen hinzu!

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- "Live" aus dem Sektionssaal – Pathologische Befunde bei COVID-19
- COVID-19 überstanden – der mühsame Weg zurück ins Leben
- Zurück zur Routine? Wie meistern wir zukünftige Pandemien?
- Wie kann sich medizinisches Personal vor einer Ansteckung schützen?
- Der Corona-Patient zwischen Hausarztpraxis und Corona-Ambulanz
- Geriatrie und COVID-19: Wo wir stehen und welche Herausforderungen es gibt
- Versorgung psychisch Erkrankter während und nach der Coronapandemie
- Neurologische Manifestationen bei COVID-19: Was bisher bekannt ist

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