Reviewer's report

Title: Botulinum Toxin Injection versus Lateral Internal Sphincterotomy in the treatment of Chronic Anal Fissure: a non-randomized controlled trial.

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Reviewer: Giuseppe Brisinda

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General
I read with great interest this paper. The paper is scientifically accurate. Furthermore, it is complete and more comprehensive. This paper confirms that the management of chronic anal fissure has undergone extensive reevaluation with renewed emphasis during the past few years. This rejuvenation of interest is attributable to the application of neurochemical treatment, which has contributed to the tendency to treat the disease on an outpatient procedure basis.

A chronic fissure shows great reluctance to heal without intervention. Spasm of the internal anal sphincter (IAS) has been noted in association with chronic fissure and for many years treatment has focused on alleviating IAS hypertonia. The cause of chronic fissures and the reasons for their failure to heal remain unclear. Also unexplained are the main characteristics of this painful condition, including the predilection for posterior midline and the lack of granulation tissue at the fissure site. Several theories have been advanced to unravel the underlying cause of anal fissure. Most of them are conflicting and none gives a satisfactory explanation for the characteristic features of chronic fissure. Recognized features common to most chronic fissure are a high resting anal pressure due to hypertonicity of the IAS, reduced vascular perfusion index at the site of the anal fissure, and the presence of ultraslow pressure wave activity in the IAS. It is generally believed that small traumatic tears in the lining of the anal canal fail to heal due to a reduced blood supply, and produce anal fissure.

It has been postulated that the IAS of patients with anal fissure is fibrotic, compared with that of controls. It was then postulated that a myositis might occur early in the course of a fissure and that this is the underlying cause of both spasm and fibrosis. Furthermore, in patients healed by a conservative treatment, resting pressure tends to increase to pretreatment level while the patient remains symptom free. This probably means that sphincter hypertonus does not necessarily cause pain.

It has been postulated that the increased incidence of fissure in the anterior and posterior midline positions is related to the distribution of vessels supplying blood to the anal canal. Relief of symptoms and healing induced by treatment could be attributed to a decrease in anal pressure, that would increase the mucosal blood flow and relieve ischemia. The inferior rectal arteries branching from the internal pudendal artery provide blood supply to the distal anal canal. These vessels cross the ischiorectal fossa; their divisions pass through the anal sphincters to reach the mucosa. Postmortem angiography of the inferior rectal artery has revealed a paucity of inferior rectal artery branches at the posterior commissure in 85% of 41 subjects. A morphologic study of the capillaries revealed a reduced density in the subanodermal space and within the IAS in the posterior midline in the majority of subjects. The predilection of anal fissures for the posterior midline and the lack of granulation tissue seen in the base of a chronic fissure may be explained by ischemia.

Decreased anodermal blood flow may be promoted by endothelial cells dysfunction associated with reduced synthesis of nitric oxide (NO), which is known to be involved in the regulation of local blood flow. Interruption of the endothelial continuity does not only remove the anticoagulant and vasodilator functions of the endothelium, but also exposes the subendothelium that has several pro-coagulant functions. In addition, even in the absence of detectable microscopic changes, endothelial function can change from vasodilator to vasoconstrictor and from anticoagulant to procoagulant. These
changes may be induced by inflammatory or immune cytokines. Activation of the endothelium may express antigens as the endothelial cells can act as antigen-presenting cells. Anti-endothelial cell antibodies have been found in many patients with anal fissure, but not in healthy controls. In antibody-positive patients, higher resting anal tone, with no change of maximum voluntary contraction, has been observed. The finding of circulating anti-endothelial cell antibodies induces the authors to maintain that the lesion is primarily endothelial rather than at the level of the sphincter: a modification of rectoanal inhibitory reflex was not observed in any of the positive patients. This supports a role of the endothelium in the pathogenesis of anal ischemia. Circulating antibodies may activate the endothelium to produce vasoactive autacoids, which could contribute to the increased basal tone and aggravate the ischemia at the level of the posterior anal commissure. The observation that the topical application of glyceryl trinitrate (GTN) may induce healing of anal fissure in up to 60% of cases supports a pathogenic role of endothelial NO synthesis.

A primary IAS disturbance may be a contributing etiologic factor. This may be induced by a prolonged absence of the neurotransmitter, by abnormalities at neurotransmitter or metabolic level, or by a modification of cholinergic and adrenergic receptors. BoNT efficacy in inducing fissure healing and reduction of resting tone suggests that increased IAS adrenergic or cholinergic activity is likely to occur in patients with chronic fissure.

LIS has been the most commonly used treatment for chronic fissure since the 1950s. It may be performed under local or general anesthesia, through a radial or circumferential incision, or using a subcutaneous approach. Open or subcutaneous methods produce adequate and equivalent falls in anal pressure. The IAS may be divided from medial to lateral or vice versa. LIS results have been reported from many centers. Surgery is associated with several complications, most of which can be prevented by the use of a judicious technique and, of course, by familiarity with anorectal anatomy. Although LIS heals and relieves symptoms of chronic fissure in nearly all patients (96%), the incidence of incontinence varies. The largest studies report impairment of continence in up to 30% of patients. Although most episodes of incontinence are minor and transient, in a subset of patients incontinence is permanent.

An incision of the IAS throughout its whole length is inadvisable, but it is uncertain how much of the sphincter should be divided. A common practice is to divide the sphincter for the length of the fissure. It has been suggested that the length of LIS does not affect the incidence of recurrence and the alterations of continence, but some disagreement has occurred on this point. A prospective study with endoanal sonography has revealed that more of the IAS than intended was divided by LIS, particularly in multiparous women, who were thought to have an unrecognized obstetric-related sphincter injury.

In a recent paper, a randomized, prospective trial to compare BoNT with LIS as definitive management for chronic anal fissure has been conducted. It has been showed in botulinum group a complete healing, after a single injection, in 45 of the 61 patients (73.8 percent) at the second month. Of the 16 failures, 6 patients refused further treatment, and 10 were treated with a second injection, which resulted in an overall healing rate of 86.9 percent (53/61) at 6 months. In the sphincterotomy group, the success rate was 82 percent (41/50) at one month and 98 percent (49/50) at two months. At six months, 2 patients who undergone LIS developed recurrences, and the healing rate was similar to that of BoNT group. At 12 months, the success rate of the Botox group fell to 75.4 percent (46/61) with 7 recurrences, whereas it remained stable in the sphincterotomy group (94 percent). Furthermore, the authors have been also documented that sphincterotomy was associated with a significantly higher complication rate (8 cases of anal incontinence), and they suggested that BoNT injection is inferior to LIS in the treatment of anal fissure, regarding healing rates within the time limit of their study. However, I have noted that at 12-months evaluation in LIS group healing rate (78 percent – 39 patients) was similar to that of BoNT group (75 percent); I believe that anal incontinence after LIS should be considered as a failure of the surgical treatment. Furthermore, no manometric study of both the IAS and external anal sphincter (EAS) were performed to demonstrate hypertonia; virtually every article in the literature impugning BoNT as a treatment of chronic anal fissure has manometric data demonstrating the efficacy of toxin in inducing reduction of resting tone and fissure healing. It has been noted that reduction of anal pressures is a dose-dependent phenomenon; in previous studies, I have shown that after 20 units posterior infiltration the mean
resting pressure, respect to baseline value, was 23-27% lower at one month evaluation and 22-28% lower at two months evaluation, while the maximum voluntary squeeze pressure was significantly unchanged. Furthermore, in recent studies, I have shown that choosing a different injection site (anterior aspect of the internal anal sphincter) and using higher doses (30 Botox units) of botulinum neurotoxin could induce a greater decrease in both resting anal pressure (from 26 to 32% lower than the baseline values in anterior injection, and from 32 to 35% lower after 30 Botox units infiltration) and maximum voluntary contraction (15% lower than the baseline after 30 units).

In my experience, patients with a posterior chronic fissure have better results, represented by a lowering of resting anal tone and early development of an healing scar, when BoNT is injected anteriorly into the IAS. Anteriorly placed injections induce a higher fall in resting pressure and improve clinical outcome. Fibrosis of the IAS, that is more prominent in the site of the fissure than elsewhere in the smooth muscle, may reduce IAS compliance and limit BoNT diffusion. It is known that the myenteric plexus with myenteric ganglia is located between the circular and longitudinal smooth muscle layers along the entire extent of the IAS. A chronic reduction of perfusion in the posterior part of the anus may affect the myenteric nervous fibers at this location and make them less sensitive to the action of BoNT.

In a recent study, the influence of different dosage regimens injected anteriorly in the internal anal sphincter on the clinical outcome of patients with a posterior chronic anal fissure has been investigated. Fissure healing and symptomatic improvement were achieved in both groups of patients. At one month after injection, complete healing was present in 73% of patients treated with 20 units (Group I) and 87% of patients treated with 30 units (Group II). A symptomatic fissure persisted in only 5 patients in Group I. At two months after injection, 89% of patients in Group I had a healing scar, while 96% in Group II had a healing scar; 3 patients in Group II had a persistent fissure in the absence of symptoms. These results confirm that higher doses lead to higher success rate. Resting anal pressures were significantly lower than pretreatment values in both groups; although maximum voluntary pressure was unchanged in patients treated with 20 units, it was significantly lower than pre-treatment value in patients treated with 30 units, probably related to a diffusion of BoNT to EAS. Five of these patients reported mild incontinence of flatus that lasted two weeks after treatment and disappeared spontaneously. BoNT diffusion in the tissues is a dose-dependent phenomenon: histochemical staining of acetylcholinesterase suggested that higher doses produced a biological effect throughout the entire muscle, whereas smaller doses produced a gradient down the length of the muscle studied.

In conclusion, I believe that BoNT injection is a safe treatment for patients with anal fissure. In the patients with a posterior chronic fissure better results are achieved when BoNT is injected anteriorly into the IAS. We believe that BoNT treatment should be considered the first-line therapy in patients with chronic anal fissure.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

The reference section is not adequate, and the references should be up-to-date.
I believe that the paper need a statistical inter-groups comparison.

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

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Discretionary Revisions (which the author can choose to ignore)
What next?: Accept after minor essential revisions

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No

Declaration of competing interests: None