Botulinum Toxin treatment for Anal Fissures – An overview & The first report on experience of BTX from India.

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***Abstract**: Anal fissure is one of the commonest pathologies of the anal canal with agony of symptoms out of proportion compared to the size of the wound. Though the etiology remails controversial, spasm of the internal anal sphincter (IAS) muscle plays a central role. Treatment is therefore aimed to relieve IAS spasm. Severe headache is the major drawback & deterrent of compliance in Chemical Sphincterolysis. **LIPS** (Lateral Internal Partial Sphincterotomy – a terminology used by us to precisely describe the surgical procedure) of the IAS muscle is the proven gold standard treatment for anal fissures but a permanent sphincter damage renders the patient to higher chances of incontinence especially in multiparous females. Botox relieves IAS spasm by its temporary chemical denervation action, produces symptomatic relief and induces healing of the anal fissure. The present article gives a brief description of patho-physiology, various modalities of treatment & an overview of Botulinum Toxin (BT) treatment with personal experience in Indian patients with anal fissures.*

***KEY WORDS**: Anal fissure, Botulinum Toxin (BT), India*

INTRODUCTION

Anatomical facts

An Anal fissure is a superficial elliptical ulcer in the anal mucosa exposing the internal anal sphincter muscle in its floor. It is caused due to injury by hard stool mass thereby exposing the nerves and the small blood vessels. The oval arrangement of muscles fibres of the External Anal Sphincter (EAS) leaves the IAS devoid of support in the anterior and posterior midline. Anal fissures classically occur at 12 &/or 6 o'clock positions. Anal fissures positioned at any other place are called 'atypical fissures' & are usually associated with inflammatory bowel disease, anal infection or cancer. The myenteric plexus with myenteric ganglia is located between the circular and longitudinal smooth muscle layers along the entire extent of the IAS[1, 2, 17].

Pathophysiology of anal fissure

Repeated trauma to the fissure by the stools cause pricking pain while defecating and burning pain after defecation which may last from a few minutes to few hours. There is reflex spasm of the IAS (involuntary smooth muscle) which further causes decreased perfusion to the fissure thereby creating relative hypovascularity or avascularity that jeopardizes the healing[4]. Due to pain at defecation, there is incomplete evacuation of feces leading to increased stasis of stools in rectum which over a period of time becomes hard. This further increases the trauma at the fissure site and delays the healing. Thus a cycle of trauma – spasm – constipation is created in the acute stage. A cycle of trauma – healing by fibrosis – scar contracture – constipation is created in the chronic stage. A scar tissue is vulnerable to repeated tear due to loss of elasticity thereby causing recurrence of the anal fissure. A hypertrophied anal papilla and a sentinel pile mass at the cranial and caudal ends of the fissure respectively are the hallmarks of a chronic anal fissure. There are various theories of their occurrence like heaping up of cells at the ends of the elliptical fissure, lymphatic blockage[5].

TREATMENT OF ANAL FISSURE

Conservative

Laxatives are given to form loose stools which would cause less trauma at the fissure site. Warm Sitz's baths are advised in view of the warmth causing increased perfusion at the fissure site which will bring in the mediators of healing and wash away the noxious chemicals of inflammation. Increased intake of fluids and fibres is advised to avoid constipation. Local anaesthetic creams are prescribed for symptomatic relief.

Chemical Sphincterolysis

Glycerine trinitrate(GTN), isosorbide dinitrate, diltiazem, nifedipine (Calcium channel blockers), hydrocortisone, lignocaine, minoxidil, indoramin (α-blocker) ointments and creams are advised for local application which will release the spasm and relax the IAS thus promoting healing. Shub showed 70% healing with silver nitrate, Antebi with 80% healing with sclerotherapy, Zaberi used NTG patches and found to be better tolerated and 60% fissures healed in Cundall's study who used hyperbaric oxygen therapy.

Though healing rates are better, severe headache remains the common side-effect leading to poor patient compliance apart from the other drug related specific side-effects.

SURGICAL TREATMENT OF ANAL FISSURE

Anal dilatation

Jean-Claude-Anthelme Recamier in 1838 first demonstrated M.A.D. (manual Anal Dilatation) ie: controlled stretch (? 4-finger) under G.A. 30 seconds. Anal stretching and dilatation causes the tear of muscle fibres (both IAS & EAS) at random places and results in higher chances of incontinence of 12-27% (upto 38%-esp. multiparous). At a later stage these torn muscle fibres are replaced by fibrous tissue. Scar contracture, which is the last stage of healing process, leads to anal stenosis causing further difficulty in passing stools, potentiates constipation and causes recurrence of fissure. Other side effects include bleeding, new anal mucosal tears, perineal bruising, perianal infection, fournier's gangrene, bacteremia & rectal prolapse/ procedentia

IAS sphincterotomy

1839, Brodie 1st to perform anal sphinterotomy. In (1818) Boyen, Dupuyren, Goodsall & Miles (1936) did posterior sphincterotomy without knowing the scientific physiological basis of what they were

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doing and still got good symptomatic relief to their patients[5]. Eisenhammer[6] 1st to advocated 'lateral' sphincterotomy of IAS by open technique in 1951. Notaras[7] in 1971 proposed subcutaneous sphincterotomy with a medial to lateral cut=outward cut. Bell[8] suggested incision in perianal skin outside anoderm. It was Lewis & Corman[9] who 1st evolved 'inward' direction sphincterotomy which is widely practiced today.

LIPS (Lateral Internal Partial Sphincterotomy – a terminology used by us to precisely describe the surgical procedure) of the IAS muscle is the proven gold standard treatment for anal fissures[10] due to exceptional healing and low recurrence rates. The distal fibres of IAS are divided equivalent to the length of the anal fissure or below the dentate line. This relieves the sphincter spasm instantly and breaks the spasm cycle thereby inducing healing of the fissure. Technical points in LIPS include incision site away from fissure, LIS site should have intact mucosa, divide all fibers of IAS distal to dentate leaving the proximal 1/3 IAS intact and avoid mucosal button hole. It can be done by Open or Closed methods with similar efficacy & side effects[11] Though a gold standard treatment, LIPS is not without side effects like hematoma, perianal abscess, sinus and fistula formation. A permanent[1-3] sphincter anatomical cut renders the patient to higher chances of dreaded side effects of fecal incontinence. Multiparous female patients are more prone for higher incidences of fecal incontinence after LIPS surgery owing to the already weakened pelvic musculature along with associated degree of stretch neuropraxia of the pudendal nerve which occurs during labour. Few incidences of incontinence in literature are by Goligher[12] showing incontinence to flatus in 34% & to stools in 15%. The incidence of incontinence was higher in early post-operative period but improves later (13% to flatus & 9% to stools). In 1988 Lewis et al demonstrated short term incontinence of 10% & reduced to a long term in 6%. 1989 Khubchandani et al had flatus incontinence in 35% & stools incontinence in 5.3%. Overall Anal Incontinence to flatus 0 – 30%, stools 0 – 27%

BOTULINUM TOXIN TREATMENT FOR ANAL FISSURE

Jost & Schimrigh were the 1st to use BT (botulinum neurotoxin-A) in sphincter in anal fissure. Since then, this has gained popularity as a treatment modality.

BT is an Exo-Neuro-Toxin derived from the anaerobic bacteria Clostridium botulinum. It binds to the pre-synaptic terminals at neuromuscular junction and cleaves synaptic protein SNAP -25 thereby blocking the release of neurotransmitter. This causes temporary paralysis of skeletal muscle and sympathetic blockade of smooth muscles (IAS). This relaxation of the anal sphincters causes a physiological discontinuity (compared to anatomical discontinuity as in LIPS) of the circular IAS muscle thereby relieving the spasm with enhancing microcirculation at the fissure site and promoting fissure healing. The effect of BT is reversible after 3-4 months by which time the fissure would have healed (50% - 88%). Of the non-healed or recurrent fissures, a repeat BT would heal the fissures upto 96% [13].

Site & Dose of Injection

Brisinde[14] injected on either sides of the fissure & concluded that 20U on either side of fissure gives good results. Mínguez M. etal. of Spain[15] concluded that 7U of BT on either sides of the fissure and in the fissure base gave better results than less doses & other sites. The optimal angle for injection was 60 degrees as shown by Bhardwaj R[20] (UK).

Comparative outcomes of Botulinum Toxin

Brisinda[17] compared BT to 0.2% Nitroglycerine and after 2 months, the fissures were healed in 46 (92 %) of 50 patients in the botulinum toxin group and in 35 (70%) of 50 in the nitroglycerin group ($p=0.009$). Three patients in the botulinum toxin group and 17 in the nitroglycerin group reported adverse effects ($p<0.001$)

In comparison with LIPS Shao WJ[18]etal. from China proved that LIPS has high healing rates as well as high complication rates for incontinence with low recurrences, while BT showed high recurrence rates but low complications & less but good results.

In chronic anal fissures, fissurectomy was performed, with excision of the fibrotic fissure edges, curetting of the fissure base, and excision of the sentinel pile if present. 25U (BT) were injected into the internal sphincter. Fissurectomy-botulinum toxin heals over 90% of fissures resistant to medical therapy while avoiding the risk of incontinence associated with lateral internal sphincterotomy-Lindsey[19].

Side effects of Botulinum Toxin

The patients with chronic anal fissure complained of incontinence of flatus(9%), incontinence of faeces (5%), anal haematoma (5%), flu-like syndrome (3%), an acute inflammation of external anal varices (2%), epididymitis (1%) and haemorrhoid prolapse (1%). Patients with anismus suffered from intertrigo (1%); Most of the side effects were only transient symptoms. No life-threatening side effects after 181 injections of BT-A were observed[20].

CONCLUSION

Botulinum Toxin is shown to give promising results in healing of anal fissures sans the side effects of GTN (severe headache) and LIPS (Incontinence). Further studies are needed to arrive on a consences for the dose & the site of injection. BT thus is the 1st choice of treatment in fissures with resistance or recurrence after chemical sphincterotomy and before surgery.

FIRST REPORT ON USE OF BOTULINUM TOXIN FOR ANAL FISSURES - FROM INDIA

Introduction

Colorectal Surgery & Proctology is yet to gain its due recognition as a full-fledged speciality in India. As a results in very few centers are keeping abreast and making use of the newer treatment modalities in colorectal and anal diseases.

Case study

We review a small case study of five cases of anal fissure treated with BT injection. Four females and one male patient (4F:1M) with a median age of 34yrs (22 to 56yrs) were studied. 3 female patients had acute recurrent anal fissure which failed to heal with 3 weeks of conservative management (2 had severe headache with diltiazem and one failed to heal inspite of no side-effects). One female and the only male patient had chronic anal fissures with sentinel tags who also did not respond to 3 weeks of conservative treatment. 20 units of BT injection were injected at 2 sites each in the IAS under anaesthesia.

One female patient with chronic fissure had 20U BT injected at 3 & 9 o'clock position while the remaining 4 patients had injection on either sides of the fissure. All patients were observed over a period of 4 months for symptomatic relief and healing of fissure.

Observation

Of the 4 patients who were injected with BT on either side of the fissure, (3F & 1M) the male patient and 2 female patients showed good symptomatic relief from day-3 onwards and their fissure healed on examining after 6 weeks. One female patient had no effect at all and had to be taken for LIPS. While the female patient who received BT at 3 & 9 o'clock had partial relief of symptoms upto 4 weeks but recurred. She was treated with LIPS.

Thus 3 of 5 patients (60%) showed good symptomatic relief and healed fissuresat the end of 4 months. One patient (20%) failed on BT while one patient (20%) had partial relief of symptoms at 4wks and both had to be offered LIPS surgery (40%).

The patients who received BT injection on either sides of fissure did well compared to the one with 3 & 9 o'clock injection. One patient with chronic fissures needed LIPS while the acute fissures resistant to medical treatment healed with BT treatment. One patient had relapse of fissure after BT and one patient did not have any benefit at all.

This was a very mixed bag of results in a short follow-up of 16weeks (4-months).

Conclusion

In our case study there was good result in 60% cases. Chronic fissures had least benefit from Botulinum Toxin treatment and had to be treated with LIPS. A dose of 20 units of BT injected on either side of the fissure gave good results. BT is a good modality of treatment which should be offered to patients with anal fissures resistant to conservative treatment and before considering surgery. Further studies are required with larger group of patients with respect to site and dose of injection with a longer follow-up in order to come to a scientifically justifiable conclusion for the use and efficacy of BT injection in the treatment of anal fissures.

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