

## Inter sphincteric Botulinum Toxin A Injection for the Management of Chronic Anal Fissure

Nashwan Q. Mahgoob<sup>1</sup> FRCMS, Muhammed M. kamal<sup>2</sup> PhD, MRCS

<sup>1</sup>Dept. of Surgery, College of Medicine, Mosul University, <sup>2</sup>Dept. of Surgery, Hawler Medical University

### Abstract

- Background** Surgical sphincterotomy (SS) has been the most commonly used treatment for chronic anal fissure (CAF). Although effective, it is associated with gas and or fecal incontinence in (0-20%) inter-sphincteric Botulinum Toxin A (BTXA) injection is a non-surgical technique that may be used as an option under certain circumstances for treatment of such condition.
- Objective** To verify the effectiveness of the BTXA injection in relieving symptoms and healing of chronic anal fissures.
- Methods** Thirty patients with CAF were treated by BTXA 1 U/kg injected into the inter-sphincteric plane; as an outpatient procedure, patients were re-evaluated after 1 week, and then every 2 weeks until the fissure healed or surgery was required. The patients were followed up for one year by regular attachment through phone call or visit, to evaluate the effects of treatment. Results, complications and follow up were recorded.
- Results** In 25 patients (83%), the pain was disappeared after the first week; 20 patients (66%) presented with a complete healing of the fissure in a period ranging between 1 to 3 months. Gas incontinence was reported in 2 patients (6%) and solved spontaneously. No major complications were found, in 3 cases (10%) surgery was needed later on.
- Conclusion** Since it avoids the greater risk of incontinence associated with SS, and it can be done as outpatient procedure without admission or general anesthesia. We recommend the use of BTXA as the first therapeutic approach for patients with chronic anal fissure.
- Keywords** Botulinum Toxin A, anal fissure.
- Citation** Nashwan Q. Mahgoob, Muhammed M. kamal. Inter sphincteric botulinum toxin A injection for the management of chronic anal fissure. *Iraqi JMS*. 2017; Vol. 15(2): 181-187. doi: 10.22578/IJMS.15.2.11

**List of abbreviations:** BTXA = Botulinum toxin A, CAF = Chronic anal fissure, LIS = Lateral internal sphincterotomy, NIPC = National Initiative on Pain Control, SS = Surgical sphincterotomy

### Introduction

An anal fissure is a common problem that causes substantial morbidity in people who are otherwise healthy. It is one of the most common proctological diseases, which manifests as pain and rectal bleeding on defecation <sup>(1)</sup>. Chronic anal fissure (CAF) is associated with persistent hypertonia and

fibroses of the internal anal sphincter. Manometric evidence of sphincter spasm reflects elevated resting anal pressure <sup>(2,3)</sup>, which is responsible for its chronicity, thus, conservative therapy alone rarely suffices. Surgical sphincterotomy (SS) is highly effective in providing good symptomatic relief and healing. However, in up to 16% of cases, it can be associated with significant complications, such as fecal incontinence <sup>(4,5)</sup>, as well as, it is a relatively invasive procedure requiring hospital

admission and a general anesthesia. In order to reduce the risk of fecal incontinence, alternative non-surgical approaches have been described in the international literatures during the last three decades to decrease the spasm in the internal anal sphincter, thereby allowing the fissure to heal with less complications and morbidity <sup>(6)</sup>. Jost and Schimrigk reported for the first time the treatment of anal fissures with Botulinum Toxin A (BTXA) in 1993 <sup>(7)</sup>. Pharmacological treatments such as BTXA produce a reversible reduction in sphincter pressure and have become the first line of treatment for CAF due to their lack of permanent complications <sup>(8-10)</sup>.

The objective of this study is to evaluate the effectiveness using BTXA technique in healing rate and to describe its side effects in the management of CAF.

### **Methods**

The study included 30 patients who have presented to authors private clinic with CAF between August 2014 to September 2015; the diagnosis was on clinical bases. The procedure was discussed thoroughly with the patients regarding its effectiveness and side effects; a formal consent was signed by them.

### **Patients selection**

The patients in whom the injection method was applied have to fulfill the following criteria:

- 1- Single posterior or anterior fissure.
- 2- No previous anal surgery.
- 3- No underlying pathology for the fissure.
- 4- No other anal condition.
- 5- Patient acceptance for the treatment.

### **Procedure**

The patients were injected with BTXA (Botox, Allergan100U). A 1ml insulin syringe with 26 G and 0.8 mm length needle was used for injection. The content of the vial was diluted in 1 ml isotonic saline and a dose of 1 U/kg (minimum of 50 U and maximum of 100 U, each 0.1 ml contain 10 U) was injected at 9 o'clock (lithotomy position) in the inter sphincteric plane while the patient laying on

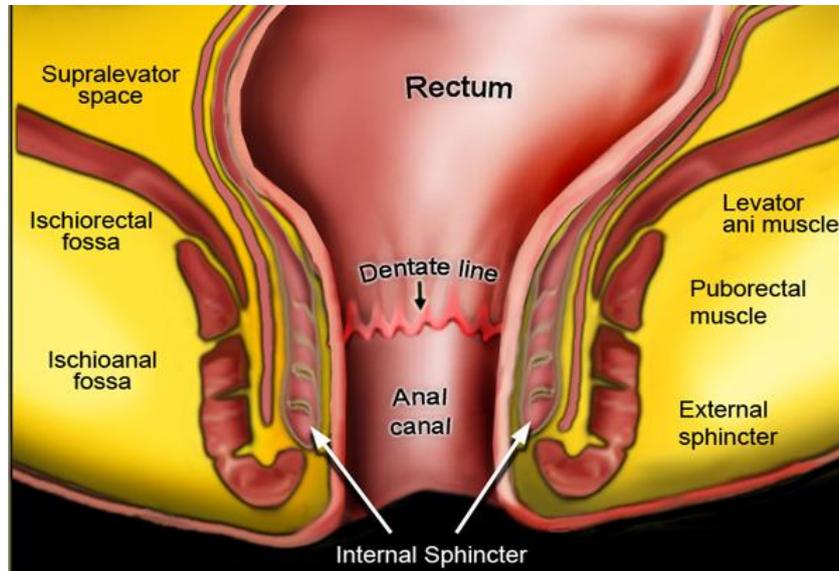
his/her left side (figure 1). The site of injection determined by putting the left index finger at the anus and the thumb at inter sphincteric plane, the needle introduced for its full length and the drug injected slowly by using the right hand. No sedation was used but local EMLA cream (lidocaine 2.5% and prilocaine 2.5%) was applied to the anal verge 10 minutes before the procedure. The patients were followed up after one week and then every 2 weeks until the fissure healed or surgery was required. The patients were followed up for one year by regular attachment through phone call or on need visit, to evaluate the effects of treatment. No special advices wear given to patients. The patients' records were reviewed for improvement, healing, occurrence of side effects, surgery, as well as recurrence of symptoms.

### **Results**

The study composed of 30 patients (20 males, 10 females; mean age (SD) of 33.3 (8.3) years), the pain threshold was assisted by using Numeric Pain Rating Scale by The National Initiative on Pain Control (NIPC). From total of 30 patients, 25 patients (83%) were pain free after the first week of injection; 4 patients (14%) experienced less pain in comparison to pre-injection time but still have pain especially after defecation, one patient (3%) showed no improvement regarding the pain. Bleeding was the next main presentation, which was found in 22 patients; it was disappeared from 17 patients (77%) after 1 week and from other 3 patients (13%) within two weeks, but continues in 2 patients (9%) after one month of injection. Twenty patients (66%) presented a complete healing of the fissure in a period ranging between 1 to 3 months; other 6 patients (20%) had healing within 6 months; 4 patients failed to show healing 6 months after injection (13%) and 3 of them (10%) underwent surgery, while one patient failed to be followed. Gas incontinence was reported in 2 patients (6%) and solved spontaneously within 2 weeks. No major complications were found. All patients remained continent for stool after 1 year. From 26 patients who underwent complete healing

in the first 6 months, 2 patients (7%) had recurrence of the fissure within 6 months post

BTXA injection the patients follow up is shown in table (1).



**Figure 1. Site of Botulinum Toxin A injection. Picture by Henry Vandyke Carter [Public domain], via Wikimedia Commons**

**Table 1. Follow up of patients**

Follow up	Number and percentage
Persistent post-injection pain	1 (3%) from 30 patients
Persistent post-injection bleeding	2 (9%) from 22 patients
Gas incontinence	2 (6%) from 30 patients
Fecal incontinence	0% from 30 patients
Failure of healing	4 (13%) from 30 patients
Recurrence of fissure	2 (7%) from 26 patients
Surgery needed	3 (10%) from 30 patients

### Discussion

Anal fissure was first described by Recamier in 1829 who recommended stretching the anal sphincter to treat this condition <sup>(11)</sup>. Anal fissure affects all age groups, particularly young adults. Ninety percent of all fissures occur posteriorly and 10 percent anteriorly. Less than 1 percent of patients have both anterior and posterior fissures <sup>(12)</sup>. The etiopathogenesis of CAF is not well understood. There is increased intra-anal pressure at rest that might contribute to an ischemic state of the anal sphincter muscles. Indeed, the anodermal

blood flow of the posterior midline has been shown to be reduced <sup>(13)</sup> and once wound happened by trauma, which is mostly caused by passing of hard stool, a devil's circle of spasm, pain, constipation and re-wounding develops <sup>(14,15)</sup>. The conservative treatment involves using appropriate nutrition, fluid intake, laxative and pain killer. Such treatment is easy, cheap, safe and remains the basis for all other treatments as well, but rarely suffices alone in CAF. Surgical sphincterotomy is the standard surgical management of CAF. However, it can be associated with significant

complications, such as fecal incontinence<sup>(5,6)</sup>, which may occur many years after sphincter damage by anal surgery because sphincter tone decreases by age<sup>(16)</sup>. For that reason, incontinence after SS has probably been underestimated<sup>(17)</sup>.

A Cochrane review<sup>(18)</sup>, including three trials on 235 patients, showed that lateral internal sphincterotomy (LIS) compared to BTXA had superior healing rates (94% versus 67%). But BTXA caused no incontinence compared to LIS (0% versus 11%) in two trials including 191 patients<sup>(18)</sup>. Same results through a meta-analysis, Sajid *et al.* compared surgical vs chemical sphincterotomy using BTXA for the treatment of CAF found that SS had a significantly higher healing rate [P < 0.011] and a significantly lower recurrence rate [P < 0.0221] than BTXA. However, there was a higher complication rate [P < 0.0163] and a higher risk of transient fecal incontinence [P < 0.0001] in the sphincterotomy group than in the BTXA group<sup>(19)</sup>.

The mechanism of action of BTXA is probably by reduction in squeeze pressure and resting pressure of the internal sphincter, these effects should be related to the fibrosis of the internal anal sphincter that is more prominent in the site of the fissure than other sites in the smooth muscle, BTXA blocks sympathetic and parasympathetic nerve function and myogenic tone of the internal anal sphincter and the acetylcholine receptor at external sphincter (chemical sphincterotomy), (Acetylcholine is a neurotransmitter at somatic neuromuscular junctions, the parasympathetic nervous system and sympathetic preganglionic fibers (cholinergic fibers), eliminating the sphincter hypertonia resulting in increase in the local tissue perfusion and healing of the CAF<sup>(20,21)</sup>. Muscle paralysis occurs within hours and the effect remains for 3-4 months. This prolonged effect allows the fissure to heal. This effect is reversible because it is followed by axonal regeneration and formation of new nerve endings which avoids the risk of permanent injury to the sphincter<sup>(22,23)</sup>. Sphincter

manometry after BTXA injection has demonstrated a lowering of resting internal pressure<sup>(24)</sup>. On the other hand, BTXA has a direct analgesic effect causing relief of pain before the healing of the fissure<sup>(25-27)</sup>. BTXA has also a good safety profile and tolerability<sup>(28)</sup>.

BTXA is either injected directly into the internal anal sphincter muscle to promote anal sphincter relaxation and subsequent healing or into both the internal as well as the external sphincter muscles<sup>(29)</sup> since both sphincters play a role in the pathogenesis of CAF. Maria *et al.* demonstrated that a peri fissural injection in the posterior-median localization is less effective than an injection along the anterior midline. They observed an increased relaxation effect by the latter technique<sup>(30)</sup>. Huang *et al.*<sup>(31)</sup> by using three-dimensional trans-perineal sonographic evaluation of the anal sphincter complex and Starck *et al.* by using endosonography<sup>(32)</sup> showed that, the internal anal sphincter started about 6 mm from the anal verge, at the junction between subcutaneous and the superficial part of the external anal sphincter and ended at the anorectal junction and it possess the same thickness throughout its length ( $0.19 \pm 0.09$  to  $0.21 \pm 0.075$  cm), while the external sphincter is thicker at its superficial part and more thicker at 3 and 9 o'clock ( $0.40 \pm 0.10$  cm and  $0.39 \pm 0.11$  cm respectively). Tacking in consideration that BTXA shows a three-dimensional diffusion of about 2 cm, which is considered adequate to reach both the internal and external anal sphincter<sup>(33)</sup>, we choose the inter sphincter plane for injection to cover both external and internal sphincter, and to have the injection at the thickest part of the sphincter complex.

Different dosage schedules have been used for BTXA injection in the treatment of CAF. Most investors use higher dosages as the response rate is higher and the relapse rate is lower. Up to 100 U BTXA have been used without any severe adverse effects<sup>(33)</sup>. The median lethal dose (LD50) of BTXA is estimated to be 3000 U for a 70-kg male<sup>(23)</sup>. We think that a dose of 1

U per/kg is safe and effective and reflect the slandered dose through all other references. The current recommendation of the American Society of Colon and Rectal Surgeons states that BTXA injection may be used for CAF that fail to respond to conservative measures <sup>(34)</sup> (evidence level II, recommendation B). However, there was no consensus on dosage, precise site of administration (internal anal sphincter, external anal sphincter, or intersphincteric space) and number of injections. There were large variations between studies in reported fissure healing and recurrence rates with BTXA) injection. This may be partly because of differences in the specific toxin brand used, injection site, unit dose, volume of solution injected, and most importantly, length of follow-up used to assess fissure outcomes.

Radwan *et al.* study showed that treatment with BTXA was effective in 89% of patients (from 38 patients) with chronic uncomplicated anal fissure. Two patients' experienced minor incontinence in the form of a fecal soiling which disappeared later <sup>(35)</sup>. Others reported transient incontinence for air between 6 to 10% and for stool in up to 5% of patients <sup>(36-39)</sup>. Recurrence rates vary between 10 and 55% <sup>(40)</sup>. In this study, gas incontinence was reported in 2 patients (6%) and solved spontaneously within 2 weeks. No major complications were found. All our patients remained continent for stool after 1 year.

Abscess formation is very rare, whereas this adverse effect is seen in about 13% of SS patients <sup>(41)</sup>; we did not face this complication in our series. In Cutan study, the healing rates ( $\leq 6$  months) are 60-90% and partial responses are seen in many patients. However, non-responders are rare ( $< 5\%$ ) resulting mostly due to incorrect technique and/or diagnosis <sup>(29)</sup>. Menteş *et al.* <sup>(5)</sup> showed complete healing after single injection in 45 of the 61 patients (73.8 %) at the second month. After therapy with BTXA, higher recurrence rates are expected, because the sphincter tone is only temporarily reduced. However, we and others have shown that

relapse rates after BTXA injection was very low <sup>(36-42)</sup>. However, in March 2013, the Medicines and Healthcare Products Regulatory Agency advised that all patients receiving any product containing BTXA should be warned of the signs and symptoms of toxin spread, such as muscle weakness and breathing difficulties. They should be advised to seek medical attention immediately if they experience breathing difficulties, choking, or any new or worsening swallowing difficulties, as such side effects may be life-threatening. We included this warning in our consent form.

Regarding the cost, its worthy to said that 100 U of BTX A (Botox, Allergan) in the pharmacy is about 200 \$ only in our markets, the whole procedure cost about 400 \$, in comparison with SS which cost about 800 \$ as an average.

In conclusion BTXA injection for the management of CAF is a simple procedure, can be done in the outpatient clinic, avoids surgery and general anesthesia, cost effective and leads to healing of the fissure in an acceptable percentage, with its very low potential risk of incontinence. It can be regarded as the first-line treatment of choice for CAF. Surgery should be offered to patients who do not improve with BTXA. Patients presenting with CAF should be informed about the available treatment options as well as their risks.

The inter-sphincteric plane is preferable site for injection; more studies are needed to compare various sites of injections with each other. We think that a dose of 1 U per/kg is safe and effective and reflect the slandered dose through all other references.

### Acknowledgments

Authors thank all patients that participated and cooperated with us in the study.

### Authors' contribution

Both authors cooperate in the research and sampling, in addition to preparation of manuscript for publication.

### Conflict of interest

Authors declare no conflict of interest.

## Funding

There was no funding source for this research.

## References

1. Lund NJ, Scholfield JH. Aetiology and treatment of anal fissure. *Br J Surg.* 1996; 83(10): 1335-44. <http://dx.doi.org/10.1002/bjs.1800831006>.
2. Gibbons CP, Read NW. Anal hypertonia in fissures: causes or effect? *Br J Surg.* 1986; 73(6): 443-5.
3. Oh C, Divino CM, Steinhagen RM. Anal fissure. 20-year experience. *Dis Colon Rectum.* 1995; 38(4): 378-82. <http://dx.doi.org/10.1007/BF02054225>.
4. Nyam DC, Pemberton JH. Long term results of lateral internal sphincterotomy for chronic anal fissure with particular reference to incidence of faecal incontinence. *Dis Colon Rectum.* 1999; 42(10): 1306-10.
5. Menteş BB, İrkörücü O, Akin M, *et al.* Comparison of botulinum toxin injection and lateral internal sphincterotomy for the treatment of chronic anal fissure. *Dis Colon Rectum.* 2003; 46(2): 232-7.
6. Steele SR, Madoff RD. Systematic review: the treatment of anal fissure. *Aliment Pharmacol Ther.* 2006; 24(2): 247-57. doi: 10.1111/j.1365-2036.2006.02990.x.
7. Jost WH, Schimrigk K. Use of botulinum toxin in anal fissure. *Dis Colon Rectum.* 1993; 36(10): 974.
8. Jost WH. Ten years' experience with botulinum toxin in anal fissure. *Int J Colorectal Dis.* 2002; 17(5): 287-97.
9. Brisinda G, Maria G, Bentivoglio AR, *et al.* A Comparison of Injections of Botulinum Toxin and Topical Nitroglycerin Ointment for the Treatment of Chronic Anal Fissure. *N Engl J Med.* 1999; 341(8): 65-9. doi: 10.1056/NEJM199908193410823.
10. Evans JE, Luck A, Hewett P. Glyceryl trinitrate vs. lateral sphincterotomy for chronic anal fissure: prospective, randomized trial. *Dis Colon Rectum.* 2001; 44(1): 93-7.
11. Kodner IJ, Fry RD, Fleshman JW, *et al.* Colon, rectum and anus. In: Schwartz SI, Fischer JE, Daly JM, *et al.*, (eds). *Principles of surgery.* 7th ed. USA: Mac Grow-Hill; 1999. p. 1265-82.
12. Gui D, Rossi S, Runfola M, *et al.* Botulinum toxin in the therapy of gastrointestinal motility disorders. A review. *Aliment Pharmacol Ther.* 2003; 18(1): 1-16.
13. Utzig MJ, Kroesen AJ, Buhr HJ. Concepts in pathogenesis and treatment of chronic anal fissure: A review of the literature. *Am J Gastroenterol.* 2003; 98(5): 968-74. [https://doi.org/10.1016/S0002-9270\(03\)00141-2](https://doi.org/10.1016/S0002-9270(03)00141-2).
14. Hörsch D, Kirsch JJ, Weihe E. Elevated density and plasticity of nerve fibers in anal fissures. *Int J Colorectal Dis.* 1998; 13(3): 134-40.
15. Wollina U, Konrad H. Botulinum toxin A in anal fissures: A modified technique. *J Eur Acad Dermatol Venereol.* 2002; 16(5): 469-71.
16. Lunniss PJ, Gladman MA, Hetzer FH, *et al.* Risk factors in acquired faecal incontinence. *J R Soc Med* 2004; 97(3): 111-6.
17. Casillas S, Hull TL, Zutshi M, *et al.* Incontinence after a lateral internal sphincterotomy: are we underestimating it? *Dis Colon Rectum* 2005; 48(6): 1193-9. doi: 10.1007/s10350-004-0914-3.
18. Nelson R. Non-surgical therapy for anal fissure *Cochrane Database Syst Rev.* 2012; (2):CD003431. doi: 10.1002/14651858.
19. Sajid MS, Vijaynagar B, Desai M, *et al.* Comparison of surgical vs chemical sphincterotomy using botulinum toxin for the treatment of chronic anal fissure: a meta-analysis. *Colorect Dis.* 2007; 10(6): 547-52. <http://dx.doi.org/10.1111/j.1463-1318.2007.01388.x>
20. Cook TA, Brading AF, Mortensen NJ. The pharmacology of the internal anal sphincter and new treatments of anorectal disorders. *Aliment Pharmacol Ther.* 2001; 15(7): 887-98. <http://dx.doi.org/10.1046/j.1365-2036.2001.00995.x>.
21. Jones OM, Moore JA, Brading AF, *et al.* Botulinum toxin injection inhibits myogenic tone and sympathetic nerve function in the porcine internal anal sphincter. *Colorectal Dis.* 2003; 5(6): 552-7. <http://dx.doi.org/10.1046/j.1463-1318.2003.00484.x>.
22. Jankovic J, Brin MF. Botulinum toxin: Historical perspective and potential new indications. *Muscle Nerve Suppl.* 1997; 6: S129-45.
23. Brin MF. Botulinum toxin: chemistry, pharmacology, toxicity, and immunology. *Muscle Nerve Suppl.* 1997; 6: S146-68.
24. Wollina U. Botulinum toxin: Non-cosmetic indications and possible mechanisms of action. *J Cutan Aesthet Surg.* 2008; 1(1): 3-6. <http://dx.doi.org/10.4103/0974-2077.41148>.
25. Radwan MM, Ramdan K, Abu-Azab I, *et al.* Botulinum toxin treatment for anal fissure. *Afr Health Sci.* 2007; 7(1): 14-7. doi: 10.5555/afhs.2007.7.1.14.
26. Kharkar S, Ambady P, Venkatesh Y, *et al.* intramuscular botulinum toxin in complex regional pain syndrome: case series and literature review. *Pain Physician.* 2011; 14(5): 419-24.
27. Runfola M, Di Mugno M, Balletta A, Magalini SC, Gui D. Antinociceptive effect of botulinum toxin: an added value to chemical sphincterotomy in anal fissure? *Dis Colon Rectum.* 2006; 49(7): 1078-9.
28. Naumann M, Jankovic J. Safety of botulinum toxin type A: a systematic review and meta-analysis. *Curr Med Res Opin.* 2004; 20(7): 981-90. DOI: 10.1185/030079904125003962.
29. Cutan J. Pharmacological Sphincterotomy for Chronic Anal Fissures by Botulinum Toxin A. *Aesthet Surg.* 2008; 1(2): 58-63. <http://dx.doi.org/10.4103/0974-2077.44160>.
30. Maria G, Brisidina G, Bentivoglio AR, *et al.* Influence of botulinum toxin site of injections on healing rate in patients with chronic anal fissure. *Am J Surg.* 2000; 179(1): 46-50. [http://dx.doi.org/10.1016/S0002-9610\(99\)00255-X](http://dx.doi.org/10.1016/S0002-9610(99)00255-X).

31. Huang WC, Yang SH, Yang JM. Three-dimensional transperineal sonographic characteristics of the anal sphincter complex in nulliparous women. *Ultrasound Obstet Gynecol.* 2007; 30(2): 210-20. doi: 10.1002/uog.4083.
32. Starck M, Bohe M, Fortling B, *et al.* Endosonography of the anal sphincter in women of different age and parity. *Ultrasound Obstet Gynecol.* 2005; 25(2): 169-76. doi: 10.1002/uog.1818.
33. Wollina U. Treatment of anal fissures with botulinum toxin. *Zentralbl Chir.* 2008 Apr;133(2):123-8. doi: 10.1055/s-2008-1004733.
34. Orsay C, Rakinic J, Perry WB, *et al.* Practice parameters for the management of anal fissures (revised). *Dis Colon Rectum.* 2004; 47(12): 2003-7. doi: 10.1007/s10350-004-0785-7.
35. Radwan MM, Ramdan K, Abu-Azab I, *et al.* Botulinum toxin treatment for anal fissure. *Afr Health Sci.* 2007; 7(1): 14-7. doi: 10.5555/afhs.2007.7.1.14.
36. Maria G, Cassetta E, Gui D, *et al.* A comparison of botulinum toxin and saline for the treatment of chronic anal fissure. *N Engl J Med.* 1998; 338(4): 217-20. doi: 10.1056/NEJM199801223380402.
37. Brisinda G, Maria G, Sganga G, *et al.* Effectiveness of higher doses of botulinum toxin to induce healing in patients with chronic anal fissures. *Surgery.* 2002; 131: 179-84. doi: 10.1067/msy.2002.119314.
38. Jost WH, Schrank B. Repeat botulin toxin injections in anal fissure in patients with relapse and after insufficient effect of first treatment. *Dig Dis Sci.* 1999; 44(8): 1588-9.
39. Arroyo A, Pérez F, Serrano P, *et al.* Long-term results of botulinum toxin for the treatment of chronic anal fissure: Prospective clinical and manometric study. *Int J Colorectal Dis.* 2005; 20(3): 267-71. doi:10.1007/s00384-004-0644-y.
40. Jost WH. One hundred cases of anal fissure treated with botulin toxin: early and long-term results. *Dis Colon Rectum.* 1997; 40(9): 1029-32.
41. Floyd ND, Kondylis L, Kondylis PD, *et al.* Chronic anal fissure: 1994 and a decade later - are we doing better? *Am J Surg.* 2006; 191(3): 344-8. doi: 10.1016/j.amjsurg.2005.10.035.
42. Gui D, Cassetta E, Asastasio G, *et al.* Botulinum toxin for chronic anal fissure. *Lancet.* 1994, 344: 1127-8.

---

**Correspondence to Dr. Nashwan Q. Mahgoob**

**E-mail: nashwanmahgoob@yahoo.com**

**Received Aug. 11<sup>th</sup> 2016**

**Accepted Jan. 18<sup>th</sup> 2017**