

Comparative study between surgical lateral internal sphincterotomy and botulinum toxin injection in the treatment of chronic anal fissure

Ahmed M. Rashad^a, Hesham A. Nafady^a, Tamer M. El-Gaabary^b

^aDepartment of Surgery, Faculty of Medicine, Beni-Suef University, Beni-Suef, ^bDepartment of Surgery, Faculty of Medicine, El Fayoum University, Fayoum, Egypt

Correspondence to Ahmed M. Rashad, MD, Beni Suef Al-Zohor Area, Al-Yasmeen Building, 5th Floor. Postal code: 62521.
Tel: 01208514541, 01118004334;
e-mail: ahmedrashad101077@gmail.com

Received: 6 September 2020

Accepted: 19 September 2020

Published: 24 December 2020

The Egyptian Journal of Surgery 2020,
39:1242–1249

Introduction

Anal fissure is a longitudinal ulcer from below the dentate line to above the anocutaneous line. In 90% of cases, it is posterior. The second location is anterior commissure. In women, ~80% are posteriorly, whereas 20% occur anteriorly. Botulinum toxin (BTX) action is mediated by its action on the autonomic nervous system. The treatment goal for BTX is the interruption of the internal sphincter spasm. Indeed, sphincter manometry after BTX injection has demonstrated a lowering of resting internal pressure. The aim is to compare effectiveness of surgical lateral internal sphincterotomy (LIS) versus BTX injection.

Patients and methods

A total of 60 patients were randomly allocated into two equal groups of 30 patients each: group I (lateral internal sphincterotomy group) and group II (BTX injection group).

Results

Chronic anal fissure can be successfully treated with surgical LIS with a 90% healing rate after 2 months, with no recurrence rate recorded, in comparison with a 70% healing rate in BTX injection, with a 20% incidence of recurrence.

Conclusion

LIS is a satisfactory treatment for chronic anal fissure, being quick and easy to be performed with minimal complications. Recurrence is uncommon. BTX is safe and easy, with rapid relief of pain, with no risk of anesthetic or operative complications. It is relatively less invasive than surgical, with negligible complications, but it has a higher recurrence rate. The risk of anal incontinence is higher in the surgical group especially in elderly patients than BTX injection; therefore, BTX injection is preferred in middle aged and elderly patients, risk factor for anal incontinence, or those of recent complaint of anal fissure.

Keywords:

anal fissure, botulinum toxin injection, lateral internal sphincterotomy

Egyptian J Surgery 39:1242–1249
© 2020 The Egyptian Journal of Surgery
1110-1121

Introduction

An acute anal fissure will heal spontaneously or in response to medical management, whereas chronic fissure usually requires interference. Therefore, anal fissures are treated either conservatively or surgically [1]. Initial therapy includes a proper diet and good personal hygiene. A large amount of fiber intake with at least 2 L of fluid consumption daily is mandatory. Bulking agents can be added. High-fiber diet intake itself has been shown to heal 60–87% of acute fissures and decrease recurrences. Creams and ointments, consisting of anti-inflammatory agents or local anesthetics, have not been proven to promote healing but may alleviate some symptoms. Anal suppositories should be avoided as their insertion is generally painful and tends to migrate to the upper part. Relief of symptoms and healing will be seen in up to 60% of the patients who use these conservative measures [2]. Some clinicians still use an anal dilator as part of conservative treatment of anal fissure.

However, many patients find self-dilatation is painful, and compliance is probably poor, and studies reported a high relapse rate [3]. In a study by Sajid *et al.* [4], factors that were found to be associated with a poor long-term outcome following conservative therapy were the presence of skin tag and fibrous polyp. Operation was required in 72% of patients with tag, compared with only 42% without. Similarly, operative treatment was necessary in 84% of patients with an anal polyp, compared with only 48% without. Various pharmacological agents have been shown to lower anal pressure and promote fissure healing. Chemical sphincterotomy is now the accepted first line of treatment in many centers [5]. Organic nitrates and nitrite were introduced into

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

medicine in the 19th century. Nitration in the smooth muscle cell releases nitric oxide, which is the main physiological vasodilator, normally produced by endothelial cells. There is now good evidence that nitric oxide is one of the most important inhibitory neurotransmitters in the internal anal sphincter [6]. Nitrosamines can be formed from nitrates (usually agricultural runoff) in drinking water upon ingestion, but it is considered by The National Academy of Sciences as lacking margin of safety for sensitive individuals. Most nitrosamines are carcinogenic and associated with gastric cancer risk and esophageal cancer [7]. Topical application of glyceride trinitrate (GTN) ointment for the treatment of patients with anal fissure has been tried in several recent studies with encouraging results. There are three possible reasons for the failure of topical GTN to produce healing of chronic anal fissure: (a) a raised threshold to the relaxant action of topical GTN on the internal anal sphincter in patients with fissure, (b) a shorter than expected duration of action, and (c) the development of tachyphylaxis (a decrease in response to a drug owing to prior exposure to the agent) [6]. Topical application (2%, four times daily) has a higher healing rate than oral dosage (60 mg, twice daily) (65 vs. 38%). Comparative studies of GTN and nifedipine have shown equivalent healing, but fewer adverse effects, with nifedipine. Overall, 50% of patients failing treatment on GTN may heal with nifedipine [8]. The aim of surgical treatment is to reduce the activity of the internal anal sphincter or to cover the anal ulcer by well-vascularized skin to allow healing of the ischemic fissure [9–12].

Internal anal sphincterotomy

Internal anal sphincterotomy includes posterior midline sphincterotomy, lateral sphincterotomy, multiple sphincterotomies around the circumference of the anal canal, and bilateral partial sphincterotomies [13]. Open technique lateral internal sphincterotomy (LIS): it is usually performed under general anesthesia as a day procedure. Closed technique subcutaneous LIS: no bowel preparation is required, and it is possible to perform the procedure under local anesthesia. Botulinum toxin (BTX) is produced by *Clostridium botulinum*; it is a lethal biological toxin but has numerous therapeutic values in the treatment of various ophthalmological and neurological disorders [14]. Therapeutic indications include upper motor neuron syndrome, focal hyperhidrosis, blepharospasm, strabismus, and chronic migraine as well as a widely used cosmetic treatments [15]. BTX can cause botulism, a serious and life-threatening illness in humans and animals [16]. Several different

products are currently available from BTX; the most commonly used agents are Botox and Dysport. Both of which are BTX type. The injected dose of Botox is 2.5–10 U for each injection (total of 5–20 U) and 10–20 U (total 20–40 U) for Dysport [17].

Forms of BTX types A and B are available commercially for research and various medical and cosmetic procedures. BTX type-A is used for cosmetic treatment, because the benefits of treatment with BTX type-A last 2–4 times longer than BTX type-B, and BTX type-A causes little discomfort during injection, compared with BTX type-B, which is quite painful for many patients. The safety margin with BTX type-A medications is very high. Therefore, BTX type-B product is less commonly used [16]. BTX treatment for anal fissures produces pain relief in most patients within the first 2 days. Cure rates evaluated 2–3 months after injection are ~80%. A second injection for treatment failure will produce a cure in 70% of cases that failed [18].

Patients and methods

This is a randomized (using research randomizer) study conducted on 60 patients with chronic anal fissure. The patients received informed consent after sufficient research information (research characteristics, benefits, and potential complications) were presented. The research protocol was accepted by the Institutional Human Ethical Committee. The study was done in Beni-Suef University Hospital and El Fayoum University Hospital during the period from March 2017 to March 2019.

The 60 patients included in this study were subjected to preoperative assessment including the following:

- (1) Complete history taking, focusing on the following points: pain, bleeding, constipation, pruritus, and discharge.

All patients were categorized according severity of pain into mild, moderate, and severe.

- (1) Clinical examination (general and local):

Anorectal examination, aiming to detect the site of the fissure ensuring its chronicity and presence of associated anal pathology.

- (1) Laboratory investigations: it included hemoglobin %, bleeding and clotting times, INR, serum creatinine, SGPT, and FBS.

Exclusion criteria

The exclusion criteria were age less than 16 years old and more than 60 years old, complicated anal fissure, associated complicated piles, atypical anal fissure, and recurrent surgically treated patients.

A total of 60 patients were randomly allocated into two equal groups of 30 patients each.

- (1) Group I (LIS group).
- (2) Group II (BTX injection group).
 - (a) Group I (LIS group):

The 30 patients of this group were subjected to surgical treatment of the chronic anal fissure in the form of open LIS; the operation was done under general anesthesia without muscle relaxant. The patient started liquid diet four hours after the operation and anal dressing was removed eight hours after the operation with application of local anesthetic cream before defecation. In this group, the patients were discharged on the next postoperative day with instructions concerning high residue diet, analgesics, and warm sitz baths.

Follow-up criteria: patients were followed up in outpatient clinic for relief of pain, fissure healing, posttreatment bleeding, infection, and incontinence, as well as recurrence and satisfaction. Follow-up was carried out at one week, then second week, then 1st month then, 2nd month, and then 3rd month after treatment. During every follow-up visit, treatment success and improvement of the previous symptoms were evaluated. Healing and recurrence rates were determined, with healing being defined as complete re-epithelialization of the fissure site as documented by the physician. Recurrence was defined as fissure identified after documentation of complete healing. Incontinence was categorized as soiling of underclothing or lack of flatus control.

Table 1 Age distribution in the two groups

Technique	Age			
	20–29	30–39	40–49	50–60
LIS	9	3	9	9
BTX	3	15	9	3
Total	12	18	18	12

BTX, botulinum toxin; LIS, lateral internal sphincterotomy. *P* value 0.198; $\chi^2=4.66$.

Table 2 Technique=lateral internal sphincterotomy

Sex	Valid <i>n</i> (%)
Male	12 (40.0)
Female	18 (60.0)

- (1) Group II (BTX group):

BTX was injected in the internal anal sphincter. The toxin was diluted in saline to 20 u/ml. Overall, 20 units of BTX were administered, and then internal anal sphincter was palpated between index finger and thumb of the left hand while patient in the left side position. An equal volume (10 U) of BTX was injected on each side of anterior midline. Local anesthesia was used during the procedure. The age distribution was almost similar in the two groups (mean age: 39–40 years) (Table 1).

The sex distribution was also similar in the two groups, and they were mainly females (60%) in BTX group (Tables 2–4).

Technique = Botox injection

Site of anal fissure

The posterior midline (posterior commissure) was the most common site for fissure followed by the anterior midline site (Table 5).

Clinical presentation

Pain was almost always present in 100% in all the patients of the two groups (Table 6).

Pain during defecation varied from mild, moderate to severe which was appreciated subjectively according to

Table 3 Sex distribution

Sex	Valid <i>n</i> (%)
Male	15 (50.0)
Female	15 (50.0)

Table 4 Sex distribution in the two groups

Sex	Valid <i>n</i> (%)
Male	27 (45)
Female	33 (55)

P value 0.65; $\chi^2=0.202$.

Table 5 Site of anal fissure

Site of anal fissure		Technique	
		LIS	BTX
Posterior	Count	27	24
	% within technique	90.0	80.0
Anterior	Count	3	6
	% within technique	10.0	20.0
Total	Count	30	30
	% within technique	100.0	100.0

BTX, botulinum toxin; LIS, lateral internal sphincterotomy. *P* value 0.531; $\chi^2=0.392$.

Table 6 The presenting symptoms in the two groups

		Technique		
		LIS	BTX	
Pain as presenting symptom	Count	30	30	<i>P</i> value 1
	% within pain	50.0	50.0	
	% within technique	100.0	100.0	
Pain during defecation	Technique			
	LIS	BTX		
	Count	21	21	
Sever (7–10)	% within technique	70.0	70.0	
Moderate (4–5)	Count	6	6	
	% within technique	20.0	20.0	
Mild (1–3)	Count	3	3	
	% within technique	10.0	10.0	
Constipation	Technique	Total		
	LIS	BTX		
Yes	Count	24	24	48
	% within technique	80.0	80.0	80.0
No	Count	6	6	12
	% within technique	20.0	20.0	20.0
Bleeding	Technique	Total		
	LIS	BTX		
Yes	Count	21	24	45
	% within bleeding	46.7	53.3	100.0
	% within technique	70.0	80.0	75.0
No	Count	9	6	15
	% within bleeding	60.0	40.0	100.0
	% within technique	30.0	20.0	25.0
Pruritus	Technique			
	LIS	BTX		<i>P</i> value 0.606
Yes	Count	9	6	$\chi^2=0.267$
	% within technique	30.0	20.0	
No	Count	21	24	
	% within technique	70.0	80.0	
Discharge	Technique			<i>P</i> value 1
	LIS	BTX		
Yes	Count	3	3	
	% within technique	10.0	10.0	
No	Count	27	27	
	% within technique	90.0	90.0	

BTX, botulinum toxin; LIS, lateral internal sphincterotomy.

patient's complaint, which was given a score (ranging from 1–3 for mild, 4–6 for moderate, and 7–10 for severe pain) experienced by the patient before entering the trial (Table 6).

Patients were complaining of constipation, bleeding, pruritus, and discharge (Table 6).

Results

Postoperative healing

Complete healing of the fissure was asymptotically higher after LIS 90% than 70% after BTX injection. In addition, in 10% of patients of LIS group and 20% of patients of BTX group, the fissure did not heal and the patients were asymptomatic, and in 10% of cases of

BTX group, the fissure did not heal with persistence of complaint (Table 7).

Operative pain relief

A relief of pain was maximum (80%) after the first month from LIS group, and 20% of patients from this group were relieved at the second month. The same report was recorded in BTX group, but with maximum incidence of pain relief at the end of first month (70%) (Table 8).

Complication

(1) Postoperative bleeding:

Postoperative bleeding was recorded in 10% of cases of LIS group (Table 9).

Table 7 Incidence of healing of the fissure in the two groups 2 months posttreatment

		Technique	
		LIS	BTX
Healing	Count	27	21
	% within healing	56.0	44.0
	% within technique	90.0	70.0
Nonhealing (asymptomatic)	Count	3	6
	% within healing	66.0	33.0
	% within technique	10.0	20.0
Nonhealing (symptomatic)	Count	0	3
	% within healing	0.0	100.0
	% within technique	0.0	10.0
Total	Count	30	30
	% within healing	50.0	50.0
	% within technique	100.0	100.0

BTX, botulinum toxin; LIS, lateral internal sphincterotomy. *P* value 0.45; variance 1.

Table 9 Incidence of bleeding as complication in the two groups

		Technique	
		LIS	BTX
Mild (complication)	Count	3	0
	% within bleeding (complication)	100.0	0.0
	% within technique	10.0	0.0
No	Count	27	30
	% within bleeding (complication)	47.4	52.6
	% within technique	90.0	100.0
Total	Count	30	30
	% within bleeding (complication)	50.0	50.0
	% within technique	100.0	100.0

BTX, botulinum toxin; LIS, lateral internal sphincterotomy. *P* value 0.305; $\chi^2=1.05$.

Postoperative infection: it occurred in 10% of patients with LIS group (Table 10).

Postoperative incontinence

Temporary uncontrolled flatus appeared in 10% of LIS group and 10% of BTX group.

Temporary soiling of under appeared only in 10% of LIS group (Table 11).

By the end of the first month, this symptom disappeared in all patients.

Incidence of recurrence: The incidence of recurrence was 20% of the BTX group (Table 12).

Satisfaction

Overall, 90% of patients in LIS group had shown complete satisfaction of the results but only 40% in

Table 8 Pain relief in the two groups

		Technique	
		LIS	BTX
1st month	Count	24	21
	% within pain relief	53.0	47.0
	% within technique	80.0	70.0
2nd month	Count	6	6
	% within pain relief	50.0	50.0
	% within technique	20.0	20.0
3rd month	Count	0	3
	% within pain relief	0.0	100.0
	% within technique	0.0	10.0
Total	Count	30	30
	% within pain relief	50.0	50.0
	% within technique	100.0	100.0

BTX, botulinum toxin; LIS, lateral internal sphincterotomy. *P* value 0.587; $\chi^2=1.067$.

Table 10 Incidence of infection in the two groups

		Technique	
		LIS	BTX
Yes	Count	3	0
	% within infection	100.0	0.0
	% within technique	10.0	0.0
No	Count	27	30
	% within infection	47.4	52.6
	% within technique	90.0	100.0
Total	Count	30	30
	% within infection	50.0	50.0
	% within technique	100.0	100.0

BTX, botulinum toxin; LIS, lateral internal sphincterotomy. *P* value 0.305; $\chi^2=1.05$.

Table 11 Incidence of temporary incontinence in the two groups

		Technique	
		LIS	BTX
Temporary uncontrolled of flatus	Count	3	3
	% within incontinence	50.0	50.0
	% within technique	10.0	10.0
Temporary soiling of under	Count	3	0
	% within incontinence	100.0	0.0
	% within technique	10.0	0.0
No	Count	24	27
	% within incontinence	47.1	52.9
	% within technique	80.0	90.0
Total	Count	30	30
	% within incontinence	50.0	50.0
	% within technique	100.0	100.0

BTX, botulinum toxin; LIS, lateral internal sphincterotomy. *P* value 0.58; $\chi^2=1.056$.

Table 12 Incidence of recurrence in the two groups

Recurrence		Technique	
		LIS	BTX
Yes	Count	0	6
	% within recurrence	0.0	100.0
	% within technique	0.0	20.0
No	Count	30	24
	% within recurrence	55.5	44.5
	% within technique	100.0	80.0
Total	Count	30	30
	% within recurrence	50.0	50.0
	% within technique	100.0	100.0

BTX, botulinum toxin; LIS, lateral internal sphincterotomy. *P* value 0.136; $\chi^2=2.2$.

BTX group had shown complete satisfaction (Table 13). six (20%) patients of BTX group had recurrence, nine (30%) patients had nonhealing fissure, and three (10%) patient was not satisfied by the technique itself, so 60% from BTX group were not satisfied by BTX injection treatment.

Discussion

Anal fissure is a common, painful condition that causes significant morbidity, mostly in young adults. Acute anal fissures often heal spontaneously or with the help of medical treatment. Recurrence rates range from 30 to 70% if treatment is abandoned after the fissure is healed [19].

Chronic anal fissure is a nonhealing linear tear in the distal anal mucosa below the dentate line. An anal fissure is likely to be nonhealing if the fissure persists beyond 4 weeks. A chronic fissure can be identified by the presence of indurated edges, visible internal sphincter fibers at the base of the fissure, a sentinel polyp at the distal end of the fissure, or a fibro-epithelial polyp at the apex. A chronic fissure classically occurs at the posterior midline position (6 o'clock position), with the anterior midline position occurring in 10% of females and 1% of males [20].

The present study included 60 adult patients with chronic anal fissure. Their ages ranged between 16 and 60 years old. It was similar to the statement that most patients who develop anal fissures are young to middle aged adults. However, patents of all ages, including infants and the elderly, can develop an anal fissure, as reported by Costilla and Foxx-Orenstein [21].

Regarding the healing rate in the present study, there was high success with complete healing after treatment with lateral internal anal sphincterotomy (90% for LIS

Table 13 Incidence of satisfaction in the two groups

Satisfaction		Technique	
		LIS	BTX
Yes	Count	27	12
	% within satisfaction	69.2	30.8
	% within technique	90.0	40.0
No	Count	3	18
	% within satisfaction	14.3	85.7
	% within technique	10.0	60.0
Total	Count	30	30
	% within satisfaction	50.0	50.0
	% within technique	100.0	100.0

BTX, botulinum toxin; LIS, lateral internal sphincterotomy. *P* value 0.019; $\chi^2=5.4$.

and 70% for BTX). The time to complete healing was earlier with LIS than with BTX.

In patients treated by surgical LIS, healing occurred in 90% of cases within 2 months. These findings go hand in hand with Romano *et al.* [22] and Arroyo *et al.* [23], who found the healing rates approaching 90–100% in some clinical trials.

Floyd *et al.* [24] found the healing rate after lateral sphincterotomy in 62% patients within 2 months, which goes hand in hand with the present study.

In patients treated by BTX injection, healing occurred in 70% of cases. These findings go hand in hand with Menten *et al.*, [25], whose study was carried on 61 patients for 2-year follow-up.

Maria *et al.* [14], reported a small randomized trial in 30 patients of 20 U BTX-A versus saline injected into the internal anal sphincter in outpatients with neither sedation nor anesthesia. Within 2 months, 73% of treated patients had healed compared with 13% of controls (group received placebo).

In a study by Godevenos *et al.* [26], 78% of patients treated with BTX presented with completely healed anal fissure, whereas 10% needed LIS.

The study by Giral *et al.* [27] showed that LIS and BTX injection treatment modalities had similar fissure healing rates (82 vs. 70%).

In the present study, incontinence was reported in 10% of cases with LIS, which was temporary uncontrolled flatus and improved within 3 weeks, and 5% of cases with BTX, which represented with fecal incontinence. This result goes hand in hand with Romano *et al.* [22], which were 15 and 9%, respectively.

Continence disturbance in the present study occurred in 5% of patients in BTX group, which was insignificantly different from that of 10% of patients in the LIS group. These findings go hand in hand with Hyman [28] and Nelson [29], in which continence disturbance was seen in less than 10% and primarily involved incontinence to flatus, which often improved with time.

A study by Hieda *et al.* [30] carried out on 89 patients showed success rate of 100% after LIS and recurrence rate of 5.6%.

In a study by Arroyo *et al.* [23] carried out on 40 patients, after LIS, the recurrence rate was 7.5% after 3-year follow-up.

Long-term follow-up and number of patients were responsible for differences between results in the studies. However, in the present study, we found a recurrence rate in the BTX injection group of ~20% among the cases, which is similar to the results carried out by Mentas *et al.*, [25] whose study was carried out on 61 patients for 2-year follow-up, with recurrence rate of 11.4%.

Regarding complication after treatment in the present study, the complications included bleeding, infection, and incontinence, with insignificant differences between surgical sphincterotomy and BTX injection. This goes hand in hand with Arroyo *et al.* [23] who found no significant differences between the two methods of treatment in the immediate complication rates following treatment.

In the present study, pain after defecation was the presenting symptom in all patients, constipation in 80% and bleeding in 75%. This goes hand in hand with Ammari *et al.* [31], who found pain and bleeding after defecation were the presenting symptom in all patients.

Giral *et al.* [27] injected the VTX on each side of the fissure, mainly to the posterior of the anal sphincter. However, it was suggested that anterior injection of BTX could better reduce the resting pressure of the anal sphincter (88 vs. 60% respectively), which could be due to the fibrotic base of the fissure or ischemic degeneration of the myenteric plexus of the posterior sphincter.

On the contrary, LIS causes irreversible effects on internal anal sphincter, and low doses of BTX (20 IU) were used in the present study, which might be one

of the causes attributing to the increase in recurrence rate after treatment with it. This explanation might be supported by the published data confirming that higher dose of BTX are associated with improved rates of healing [32].

Conclusion

We believe that LIS is a satisfactory treatment for chronic anal fissure, being quick and easy to be performed with minimal complications. Recurrence after this mode of therapy is uncommon.

Injection of BTX is an accepted method of treatment. It is safe and easy to use, with rapid relief of pain and no risk of anesthetic or operative complications; however, it is an effective alternative modality in the treatment of chronic anal fissure. It is relatively less invasive than surgical approach, and the complications are negligible, but it has a higher recurrence rate than LIS. The risk of anal incontinence is higher in the surgical group especially in elderly patients.

On the contrary, BTX injection is a preferred option in the middle aged and elderly patients or those with the risk factor for anal incontinence or those of recent complain of anal fissure.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

- Alexander S. Dermatological aspects of anorectal disease. *Clin Gastroenterol* 2000; 29:651–657.
- Bohl JL, Herline AJ. 20 surgery and nonoperative therapy of anal fissure. Improved outcomes in colon and rectal surgery. Winston Salem North Carolina/Hollywood, Florida: CRC Press; 2016. 199.
- Coskun H, Duran Y, Dilege E, Mihmanli M, Seymen H, Demirkol MO. Effect on gastric emptying and weight reduction of botulinum toxin-A injection into the gastric antral layer: an experimental study in the obese rat model. *Obes Surg* 2005; 15:1137–1143.
- Sajid MS, Whitehouse PA, Sains P, Baig MK. Systematic review of the use of topical diltiazem compared with glyceryltrinitrate for the nonoperative management of chronic anal fissure. *Colorectal Dis* 2013; 15:19–26.
- Wagenlehner FME, Del Amo E, Santoro GA, Petros P. Live anatomy of the perineal body in patients with third-degree rectocele. *Colorectal Dis* 2013; 15:1416–1422.
- Bansal AR, Yadav PK, Godara R, Pal N, Tripura R. Comparative evaluation of 0.2% glyceryl trinitrate vs. 2% diltiazem ointment in treatment of chronic anal fissure. *Hellenic J Surg* 2016; 88:25–30.
- Jakszyn P, Gonzalez CA. Nitrosamine and related food intake and gastric and oesophageal cancer risk: a systematic review of the epidemiological evidence. *World J Gastroenterol* 2006; 12:4296–4303.
- Felt-Bersma RJF, Bartelsman JF. Haemorrhoids, rectal prolapse, anal fissure, peri-anal fistulae and sexually transmitted diseases. *Clin Gastroenterol* 2009; 23:575–592.

- 9 Rajaratnam S, Lindsey I, Wijffels N, Collinson R, Cuningham C. Chronic anal fissure. Dallas, Texas: In *Anus*; 2014. 211–220.
- 10 Bing L, Peet NP, Butler MM, Burnett JC, Moir DT, Bowlin TL. Small molecule inhibitors as countermeasures for botulinum neurotoxin intoxication. *Molecules* 2011; 16:202–220.
- 11 Mangera A, Andersson KE, Apostolidis A, Chapple C, Dasgupta P, Giannantoni A, *et al.* Contemporary management of lower urinary tract disease with botulinum toxin A: a systematic review of botox (onabotulinumtoxinA) and dysport (abobotulinumtoxin A). *Soc Gastroenterol* 2005; 8:190–193.
- 12 Mapel DW, Schum M, Von Worley A. The epidemiology and treatment of anal fissures in a population-based cohort. *BMC Gastroenterol* 2014; 14:1–8.
- 13 D'Ugo S, Franceschilli L, Cadeddu F, Leccesi L, Blanco GDV, Calabrese E, *et al.* Medical and surgical treatment of haemorrhoids and anal fissure in crohns disease. *BMC Gastroenterol* 2013; 13:1.
- 14 Maria G, Brisinda G, Bentivoglio AR, Cassetta A, Gui D, Albanese A. Botulinum toxin injection in the internal anal sphincter for the treatment of chronic anal fissure. *Ann Surg* 1998; 228:664–669.
- 15 Valizadeh N, Jalaly NY, Hassanzadeh M, Kamani F, Dadvar Z, Azizi S, Salehmarzjijarani B. Botulinum toxin injection versus lateral internal sphincterotomy for the treatment of chronic anal fissure. *Langenbeck's Arch Surg* 2012; 397:1093–1098.
- 16 Samim M, Twigt B, Stoker L, Pronk A. Topical diltiazem cream versus botulinum toxin a for the treatment of chronic anal fissure. *Ann Surg* 2012; 255:18–22.
- 17 Eisenach JH, Atkinson JL, Fealey RD. Hyperhidrosis: evolving therapies for a well-established phenomenon. *Mayo Clin Proc* 2005; 80:657–666.
- 18 Naumann M, So Y, Argoff CE, Childers MK, Dykstra DD, Gronseth GS, *et al.* Assessment: Botulinum neurotoxin in the treatment of autonomic disorders and pain (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 2008; 70:1707–1714.
- 19 Ibrahim OI. Bilateral versus posterior injection of botulinum toxin in the internal anal sphincter for the treatment of acute anal fissure. *S Afr J Surg* 2010; 48:20–22.
- 20 van Meegdenburg MM, Trzpis M, Heineman E, Broens PMA. Increased anal basal pressure in chronic anal fissures may be caused by overreaction of the anal-external sphincter continence reflex. *Medical Hypotheses* 2016; 94:25–29.
- 21 Costilla VC, Foxx-Orenstein AE. Constipation in adults: diagnosis and management. *Curr Treat Options Gastroenterol* 2014; 12:310–321.
- 22 Romano A, Mandato A, Cavaliere N, Pizza N, Russo A, Cappabianca S, *et al.* Three-dimensional anal endosonography in depicting anal-canal anatomy. *Radiol Med (Torino)* 2012; 117:759–771.
- 23 Arroyo A, Perez F, Serrano P, Candela F, Lavueva J, Calpena R. Surgical versus chemical (botulinum toxin) sphincterotomy for chronic anal fissure. *Am J Surg* 2005; 189:429–434.
- 24 Floyd ND, Kondylis L, Kondylis PD, *et al.* Chronic anal fissure: 1994 and a decade later: are we doing better?. *Am J Surg* 2006; 191:344–348.
- 25 Mentés B, Irkorucu 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; 46:232–237.
- 26 Godevenos D, Pikoulis E, Pavlakis E, *et al.* The treatment of chronic anal fissure with botulinum toxin. *Acta Chir Belg* 2004; 104:577–580.
- 27 Giral A, Memisoglu K, Gultekin Y, Imeryuz N, Kalayc C, Ulusoy NB, *et al.* Botulinum toxin injection versus lateral internal sphincterotomy in the treatment of chronic anal fissure. *BMC Gastroenterol* 2004; 22:4–7.
- 28 Hyman N. Incontinence after lateral internal sphincterotomy a prospective study and quality of life assessment. *Dis Colon Rectum* 2004; 47:35–38.
- 29 Nelson RL. Operative procedures for fissure in ano. *Cochrane Database Syst Rev* 2005; 2:CD002199.
- 30 Hieda K, Cho KH, Arakawa T, Fujimiya M, Murakami G, Matsubara A. Nerves in the intersphincteric space of the human anal canal with special reference to their continuation to the enteric nerve plexus of the rectum. *Clin Anat* 2013; 26:843–854.
- 31 Ammari FF, Bani-Hani KE. Faecal incontinence in patients with anal fissure: A consequence of internal sphincterotomy or a feature of the condition?. *Surg J R Coll Surg* 2004; 5:225–229.
- 32 Brisinda G, Bentivoglio AR, Albanese A. Comparison of botulinum toxin injection and lateral internal sphincterotomy for the treatment of chronic anal fissure. *Dis Colon Rectum* 2003; 46:232–237.