



**BOTULINUM TOXIN TYPE A (BTA)
INJECTION FOR CHRONIC ANAL FISSURE**

**HEALTH TECHNOLOGY ASSESSMENT SECTION
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Please contact: htamalaysia@moh.gov.my, if you would like further information.

Health Technology Assessment Section (MaHTAS),
Medical Development Division
Ministry of Health Malaysia
Level 4, Block E1, Precinct 1
Government Office Complex
62590 Putrajaya

Tel: 603 88831246

Fax: 603 8883 1230

Available at the following website: <http://www.moh.gov.my>

Author

Maharita Binti Ab Rahman
Principal Assistant Director
Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia

Co-Author

Gan Yan Nee
Principal Assistant Director
Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia

Reviewed by

Dr Junainah Sabirin
Public Health Physician
Senior Principal Assistant Director
Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia

Externally Reviewed by

Dato' Dr. Fitzgerald Henry
Consultant & Colorectal Surgeon
Colorectal Surgery Department
Hospital Selayang

DISCLOSURE

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BOTULINUM TOXIN TYPE A (BTA) INJECTION FOR CHRONIC ANAL FISSURE

EXECUTIVE SUMMARY

Background

Anal fissure is an ulcer in the squamous epithelium of the anus located just distal to the muco-cutaneous junction and usually in the posterior midline. It will be considered as acute if the anal fissure present for less than six weeks, superficial and have well-demarcated edges. The anal fissure is considered chronic if they have been present for more than six weeks and have keratinous edges. This technology review (TR) report will highlight the chronic anal fissure (CAF) instead of acute anal fissure (AAF).

Chronic anal fissures typically occur in the midline, with visible sphincter fibres at the fissure base, anal papillae, sentinel piles and indurated margins. Typically, CAF have a cyclical history of intermittent healing and recurrence, but about 35% will eventually heal, at least temporarily, without intervention. The exact pathogenesis of primary fissures remains uncertain, but a core point is hypertonicity of the internal anal sphincter, which leads to local ischaemia. Furthermore, inflammation and pain induce ongoing hypertonicity, giving rise to a vicious circle. Therefore, the aim of treatment strategies is to reduce the sphincter tone with either medical agent such as glyceryl trinitrate (GTN), calcium channel blockers (CCB) and botulinum toxin A (BTA), or surgical interventions such as lateral internal sphincterotomy (LIS).

However, there are various approaches that combined either surgical with medical treatment inclusive of BTA or surgical alone as well as medical treatment alone. The efficacy and effectiveness of either surgical alone, medical alone or combination varied. Because of this, the Deputy Director of Legislation Act & Globalisation Section, Medical Services Division requested for a TR report looking at the efficacy / effectiveness, safety and cost-effectiveness of BTA in treatment of CAF.

Objective/aim

To assess the safety, efficacy or effectiveness and cost-effectiveness of botulinum toxin A (BTA) injection for CAF

Results & Conclusion

The included studies consisted of three SRs and meta-analysis, one SR and network meta-analysis, one SR, five pre- and post- intervention studies, one non-RCT and one cost analysis study.

Efficacy / Effectiveness

- Combination of BTA and fissurectomy for CAF showed an improvement in CAF
- LIS surgery was more effective in healing and preventing recurrence of anal fissure compared with BTA but incontinence was lesser with BTA compared with LIS
- There was no significant difference in healing, recurrence rate and incontinence rate among BTA injection and topical nitrates
- BTA injection was significantly more effective than lidocaine
- Different doses of BTA, different injection sites and different types of BTA formulation, did not significantly affect the efficacy and effectiveness of BTA injection for CAF treatment

Safety

- Common complication in the combination treatment was anal bleeding that resolved spontaneously few days after treatment
- Other reported complications that occurred after combination treatment were perianal sepsis, recurrence anal fissure, pruritus ani, delayed healing, and headache
- Comparing BTA injection with topical nitrates, there was more significant complications especially headache occurred in topical nitrates group compared to BTA injection
- The systematic reviews reported BTA injection had low frequencies of adverse events which were mostly local post-operative complications such as hematoma, perianal thrombosis, perianal abscess and temporary incontinence that consisted of liquid and faeces
- One case of fourniere gangrene was reported in patient with diabetes mellitus
- Contraindications included hypersensitivity case, pregnancy, neurological disease including myasthenia, Lambert Eaton Syndrome and Amyotrophic lateral sclerosis and co-administration with amino-glycosides may enhanced the action of BTA

Cost

- No local cost analysis was retrieved on the management of CAF with BTA injection
- One cost analysis from United State of America showed that combination of treatment (BTA injection and surgery for any fail BTA case) was cost saving compared to only surgery (LIS) approach

Methods

Electronic databases were searched through Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1948 to present, EBM Reviews-Cochrane Database of Systematic review, EBM Reviews-Cochrane

Methodology Register of Controlled Trials, EBM Reviews-Health Technology Assessment, EBM Reviews-NHS Economic Evaluation Database, and Embase 1996 to 17 8 Jun 2018. Searches were also run in PubMed, FDA website and INAHTA for any published reports.

No limit in the study year. Google and Google Scholar were also used to search for additional web-based materials and information about the technology. Besides, additional articles were also search by reviewing the references of retrieval articles.

BOTULINUM TOXIN TYPE A (BTA) FOR CHRONIC ANAL FISSURE

1. BACKGROUND

Anal fissure is an ulcer in the squamous epithelium of the anus located just distal to the muco-cutaneous junction and usually in the posterior midline.¹ Anal fissure is very painful; during defaecation the lesion is stretched with consequent painful symptomatology, which can persist for quite some time and accompanied with slight bleeding. It will be considered as acute if the anal fissure present for less than six weeks, with superficial and well-demarcated edges. The anal fissure is considered chronic if they have been present for more than six weeks and have keratinous edges.²

This technology review (TR) report will highlight the chronic anal fissure (CAF) instead of acute anal fissure (AAF). Chronic anal fissures typically occur in the midline, with visible sphincter fibres at the fissure base, anal papillae, sentinel piles and indurated margins. Typically CAF have a cyclical history of intermittent healing and recurrence, but about 35% will eventually heal, at least temporarily, without intervention.³

The cause of anal fissure can be divided into two; primary fissure and secondary fissure. The primary fissure is not caused by underlying chronic disease and most common among young adults of both sexes. Whereas secondary fissure is associated with other diseases, such as chronic inflammatory intestinal diseases, human immunodeficiency virus, tuberculosis, syphilis and some neoplasms.²

The exact pathogenesis of primary fissure remains uncertain, but a core point is hypertonicity of the internal anal sphincter, which leads to local ischaemia. Furthermore, inflammation and pain induce ongoing hypertonicity, giving rise to a vicious circle. Therefore, the aim of treatment strategies is to reduce the sphincter tone with either medical agent such as glyceryl trinitrate (GTN), calcium channel blockers (CCB) and botulinum toxin A (BTA) or surgical interventions such as lateral internal sphincterotomy (LIS).⁴

Surgical method specifically LIS is often claimed to be the gold standard therapy for CAF due to its efficiency compared with other therapies.^{4, 5} However, there are various approaches that combined either surgical with medical treatment inclusive of BTA or surgical alone as well as medical treatment alone. The efficacy and effectiveness of either surgical alone, medical alone or combination varied. Because of this, the Deputy Director of Legislation Act & Globalisation Section, Medical Services Division

requested for TR report looking at the efficacy / effectiveness, safety and cost-effectiveness of BTA in treatment of CAF.

2. OBJECTIVE/AIM

To assess the safety, efficacy / effectiveness and cost-effectiveness of botulinum toxin A (BTA) injection for CAF

3. TECHNICAL FEATURES

Botulinum toxin (BTX) is produced by *Clostridium botulinum* a gram-positive anaerobic bacterium. It is broken into seven neurotoxins (labeled as types A, B, C, D, E, F and G) which are antigenically and serologically distinct but structurally similar. The various BTX possess individual potencies, and care is required to assure proper use and avoid medication errors. Recent changes to the established drug names by the Food & Drug Administration (FDA) were intended to reinforce these differences and prevent medications errors. The products and their approved indications include the following:⁶

- i. *OnabotulinumtoxinA* (Botox[®], Botox Cosmetic[®])
 - a. Botox[®] - Cervical dystonia, severe primary axillary hyperhidrosis, strabismus, blepharospasm, neurogenic detrusor overactivity, chronic migraine, upper limb spasticity
 - b. Botox Cosmetic[®] - Moderate to severe glabellar lines, moderate to severe lateral canthal lines, known as crow's feet
- ii. *AbobotulinumtoxinA* (Dysport[®]) – Upper and lower limb spasticity, cervical dystonia, and moderate-to-severe glabellar lines in adults; it is also indicated for lower limb spasticity in children aged 2 years or older
- iii. *IncobotulinumtoxinA* (Xeomin[®]) – Upper limb spasticity, cervical dystonia, blepharospasm, moderate to severe glabellar lines
- iv. *RimabotulinumtoxinB* (Myobloc[®]) – Cervical dystonia

Different preparations of BTX have different potency. The most common BTX formulations in Malaysia are botulinum toxin type A (BTA) namely Botox and Dysport.



Figure 1: Techniques of botulinum toxin injection

3.1 Botulinum toxin A Injection for Chronic Anal Fissure (CAF)

Currently, BTA for CAF has been used as a second line therapy if the pharmacological treatment failed before proceeds to LIS.⁷ Although this method of treatment has been used worldwide, a firm recommendation for the injection of BTA is still under debate. Moreover, there are limited established intervals between further injections and number of injections should be made per session. There is also limited information about how the dose of BTA influences the potential post-operative gas or stool incontinence.⁸

Mechanism of Action in Treatment of CAF

Injection of BTA leads to the blockade of acetylcholine release and causes short-term paralysis of internal sphincter muscle, resulting in a reduction of anal tone.⁸

4. METHODS

4.1. Searching

Electronic databases were searched through Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1948 to present, EBM Reviews-Cochrane Database of Systematic review, EBM Reviews-Cochrane Methodology Register of Controlled Trials, EBM Reviews-Health Technology Assessment, EBM Reviews-NHS Economic Evaluation Database, and Embase 1996 to 18 Jun 2018. Searches were also run in PubMed, FDA website and INAHTA for any published reports.

No limit in the study year. Google and Google Scholar were also used to search for additional web-based materials and information about the technology. Besides, additional articles were also search by reviewing the references of retrieval articles.

Appendix 1 showed detailed of the search strategies.

4.2. Selection

Two reviewers screened the titles and abstracts against the inclusion and exclusion criteria and then evaluated the selected full-text articles for final article selection.

The inclusion and exclusion criteria were:

Table 1: Inclusion Criteria

Inclusion criteria	
Population	Chronic anal fissure, CAF
Interventions	Botulinum toxin type A
Comparators	Conventional therapy (pharmacological and surgical)
Outcomes	Effectiveness, safety, economic implications
Study design	Systematic reviews, HTA, meta-analysis, pre- and post-intervention study and randomised controlled trial (RCT)
	English full text articles

Table 2: Exclusion Criteria

Exclusion criteria	
Study design	Animal studies, laboratory studies, case reports, case series
Intervention	Other than for anal fissure
Outcome	Non-medical condition e.g wellness, dermatology
	Non English full text article

Relevant articles were critically appraised using Critical Appraisal Skills Programme (CASP), Cochrane tools, and evidence graded according to the US / Canadian Preventive Services Task Force (Appendix 2). Data were extracted from included studies using a pre-designed data extraction form (evidence table as shown in Appendix 3) and presented in tabulated format with narrative summaries. No Meta-analysis was conducted for this review.

5. RESULTS AND DISCUSSION

A total of 261 titles were identified through the Ovid interface: MEDLINE (R) In-process and other Non-Indexed Citations and Ovid MEDLINE (R) 1948 to present, Embase 1988 to present and PubMed. After removal of 218 duplicates and irrelevant titles, abstracts of 43 titles were intensively screened. From the abstracts, nine were not related to the objective of the technology review and were excluded. Full text articles were retrieved for the remaining 34 abstracts. Of these, one full text could not be retrieved, and 33 articles were appraised. After critical appraisal only 12 studies were included in the technology review.

The included studies consisted of three SRs and meta-analysis, one SR and network meta-analysis, one SR, one non-RCT, and five pre- and post-

intervention studies, one cross-sectional study, and one cost analysis study. The characteristics of included studies were discussed in the next section. A simplified flow diagram showing the numbers of articles identified is shown in Figure 2.

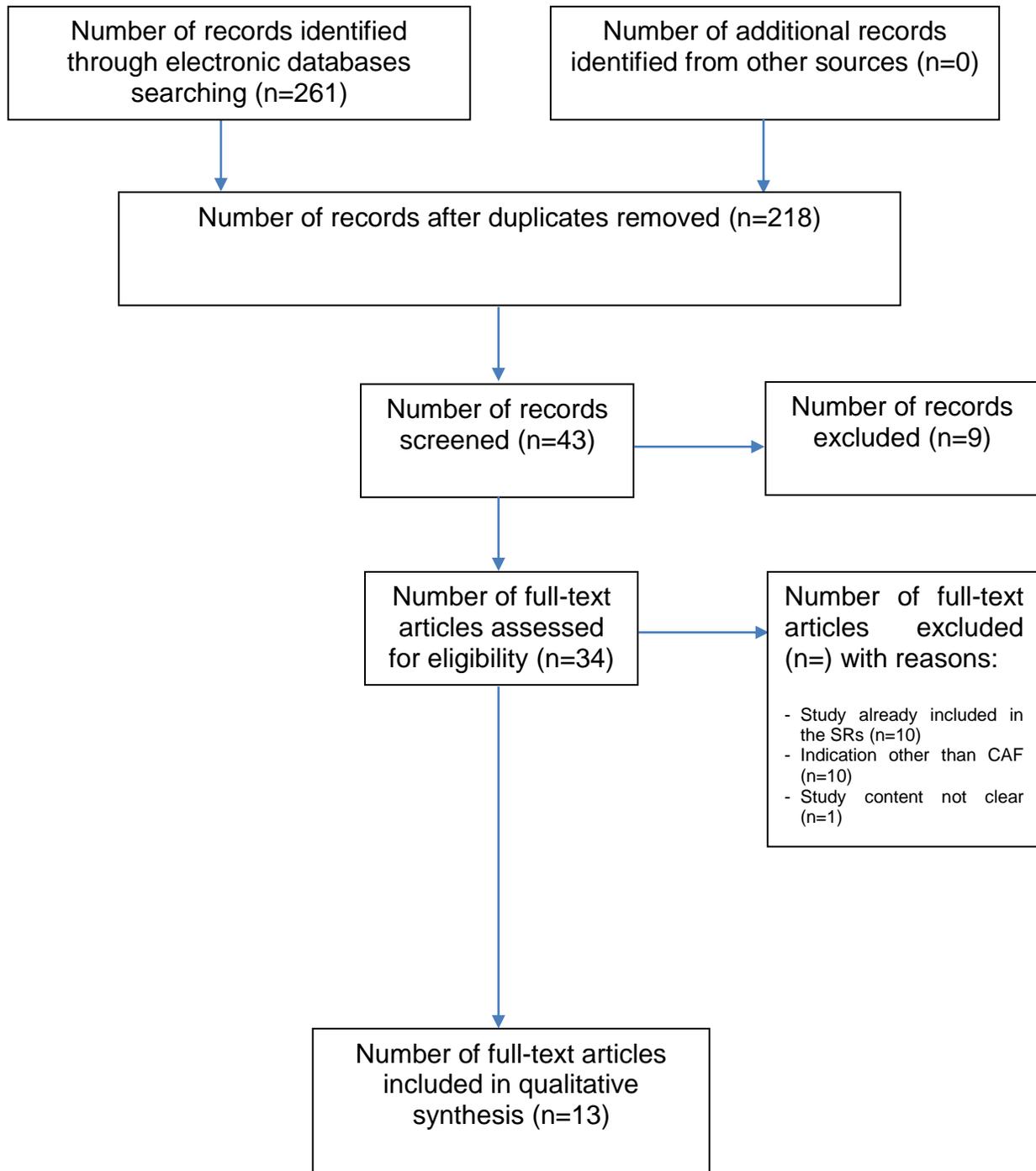


Figure 2: Study Selection

5.1 RISK OF BIAS

One of the tools that are being used by MaHTAS to assess the risk of bias is the CASP checklist which consists of eight critical appraisal tools designed for SR, RCT, cohort studies, case control studies, economic evaluations, diagnostic studies, qualitative studies, and clinical prediction rule. This is achieved by answering a pre-specified question of those criteria assessed and assigning a judgement relating to the risk of bias as either:

+	Indicates YES (low risk of bias)
?	indicates UNKNOWN risk of bias
-	Indicates NO (high risk of bias)

The assessment of risk of bias revealed that the SRs had low risk of bias; meanwhile, the non-RCT is moderate. On the other hand, the pre- and post-intervention studies were considered to have moderate of bias. Most of the included studies involved small sample size and no blinding.

The results of risk of bias of included studies are summarised in Table 3 to table 5.

Table 3: Assessment of risk of bias of Systematic Review (Cochrane)

Criteria assessed	Authors look for the right type of papers?	Selection of studies (all relevant studies included?)	Assessment of quality of included studies?	If the results of the review have been combined, is it reasonable to do so (heterogeneity)?
Sahebally SM et al 2018	+	+	+	+
Ebinger SM et al 2017	+	+	+	+
Bobkiewicz A et al 2016	+	+	+	+
Lin JX et al 2016	+	+	+	+
Yiannakopoulou E. et al 2012	+	+	+	+

Table 4: Assessment of risk of bias of quasi experimental studies non-RCT (JBI)

Criteria assessed	Arthur JD. et al 2008
Clear what is the cause and what is the effect?	+
Participants included in any comparisons similar?	+
Participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	+
Was there a control group?	+
Multiple measurements of outcome pre and post the intervention/ exposure?	+
Follow-up complete, and if not was follow-up adequately reported and strategies to deal with the loss to follow-up employed?	+
Outcomes of participants included in any comparisons measured in the same way?	+
Outcome measure in reliable way?	+
Appropriate statistical analysis used?	+

Table 5: Assessment of risk of bias of pre-post studies with no control (NIH)

Criteria assessed	Barnes TG et al 2015	Patti R et al 2010	Witte et al 2009	Scholz Th et al 2007	Lindsey lan et al 2004
Question or objective clearly stated?	+	+	+	+	+
Eligibility/selection criteria for study population clearly described?	+	+	+	+	+
Were participants representative for those who would be eligible for the test/ service/ Intervention in the population of interest?	+	+	+	+	+
Were all eligible participants that met the pre-specified entry criteria enrolled?	+	+	+	+	+
Sample size sufficiently large to provide confidence in findings?	+	-	-	-	-
Test/service/intervention clearly described and delivered consistently?	+	+	+	+	+
Outcome measures pre-specified, valid, reliable, and assessed consistently?	+	+	+	+	+
People assessing the outcome measures blinded to participants exposure/ interventions?	-	-	-	-	-
Loss to follow-up after baseline 20% or less? Loss to follow-up accounted for in the analysis?	+	+	+	+	+
Statistical methods examine changes in outcome measures from before to after intervention? p value?	+	+	-	+	+
Outcome measures taken multiple times before and after intervention? Use interrupted time-series design?	?	?	?	?	?
If intervention conducted at group level, did statistical analysis take into account of individual level data to determine effects at group level?	Not Applicable				

5.2. EFFICACY/ EFFECTIVENESS

The efficacy and effectiveness of BTA were subdivided according to the procedure involved; either combination of BTA injection with surgery (sphincterotomy and fissurectomy) or BTA injection alone compared with surgery and other non-invasive treatments.

5.2.1 Surgery with Botulinum Toxin Type A Injection (Combination)

Barnes et al. (2015) conducted pre- and post-intervention study to determine the efficacy/effectiveness, safety and durability of using a combination of fissurectomy and BTA in the management of CAF. The main concern was on patients that failed to respond to topical therapy, CAF with signs of chronicity and patients that had both conditions. The study involved 102 patients (62 women and 42 men) with age range of 41 years to 70 years old. The patients were treated with fissurectomy and total dose of 100 units of BTA which was diluted with 1 ml isotonic saline. The procedure was performed as a day case between September 2008 and March 2012. All patients were evaluated in the outpatient clinic approximately 12 weeks. All the patients were contacted at 12 months post-operatively, via telephone whether they had any recurrence of anal fissure symptoms (post-defecation pain and / or bleeding) or if they sought any medical advice relating to anal fissure post-discharge. The outcomes observed were resolution, improvement or persistence of symptoms; healing which was defined as complete epithelialization of the fissure area or persistence of fissure and continence status. The continence status was assessed using Clinical Faecal Incontinence Score (CCFIS). At the 12 weeks post-operative review via telephone, 95% of patients (97 out of 102) showed resolution or improvement of symptoms. Out of the 97 patients, 68 patients (70%) reported resolution of symptoms with complete fissure healing and were discharged. Meanwhile, in other 29 of 97 patients (30%), the symptoms improved but fissure healing was incomplete. Twenty-five of them were prescribed topical diltiazem (DTC) and Fybogel for eight weeks. Another four patients declined any topical therapy and opted repeated treatment with either BTA with fissurectomy or without fissurectomy if there was sign of chronicity. No recurrence of CAF signs of chronicity was observed. The 29 patients had subsequent fissure healing and discharged later. Remaining 5 out of 102 patients showed no improvement and they declined to repeat the same combination treatment. They underwent other alternative surgery and also healed at 12-weeks post-operative review. For incontinence, seven patients (6.9%) were reported having a degree of incontinence in the immediate post-operative period; 4 patients having liquid stool and flatus with CCFI score of 2, 3, and 4. Another three patients experienced flatus alone with CCFI score of 2 and 3. Fortunately all of them returned to normal continence at 12-weeks followed-up. Followed-up period between 12 months and 54

months also reported that no patients had anal fissure related treatment since discharge. The authors also reported that there was no significant difference in fissure healing between posterior and anterior anal fissures (95% and 85% respectively; $p = 0.38$).^{7, level II-2}

Patti R et al. (2010) also conducted pre-and post-intervention study in order to evaluate the efficacy of fissurectomy combined with advancement flap and internal anal sphincter (IAS) injection of BTA in healing the chronic anterior anal fissure (CAAF) with hypertonia of IAS resistant to medical therapy. Only ten patients were involved (patients with hypertonia of IAS unresponsive to medical therapy and refused further medical treatment). They were enrolled from 2002 to January 2008. The treatment procedure consisted of fissurectomy and anoplasty followed with total dose of 30 units BTA that were equally divided on either side of posterior or midline of IAS. The primary outcome for this study was complete healing and maximum resting pressure (MRP) changes of anal sphincter. The secondary outcome was symptoms relief and complications. After the procedures, patients were examined after one month, six months and 12 months. After one month, all patients healed completely. Symptoms such as intensity and duration of pain post-defaecation were reduced significantly compared to the pre-operative values starting from the first defaecation ($p < 0.0001$ and $p < 0.0001$, respectively). None of patients complained other symptoms such as pain, bleeding or pruritis 30 days after surgery. The used of analgesic also decreased significantly after the first defaecation. Pre-operatively, the average of MRP value was 99 mmHg with range of 88 mmHg to 120 mmHg. Then, at six months post-operation, the median MRP value was 79.5 mmHg with range of 68 mmHg to 98 mmHg; $p < 0.001$. The overall reduction of the MRP value was 20.5%. The authors also observed the anal incontinence before and after procedure and they used Pescatori grading system. Pre-operatively, two patients reported anal incontinence, and both of them were classified as Grade A2. Grade A2 means incontinence of flatus and mucus occurred weekly. Then, after one month of the procedure, post-operative anal incontinence was reported in three patients (two patients were those who had the complaint before the procedure). Those patients were classified as grade A1 (incontinence of flatus and mucus occasionally) in one patient and grade A2 in another two patients.^{9, level II-2}

Witte ME et al. (2010) conducted pre- and post-intervention study in order to evaluate the effect of the combination of fissurectomy and BTA in CAF treatment. The study involved 21 patients which consisted of 10 male and 11 females with median age of 48 years old. All patients received fissurectomy and BTA injection 80 units under regional anaesthesia in day care. All of them were standardised with plan visit at six and 12 weeks post-operatively and longer when necessary. The assessment involved changes in continence, fissure healing and symptom improvement. At

follow-up, 16 patients (76.2%) healed with complete resolution of symptoms. Three other patients (14.3%) healed at physical examinations and symptoms partially resolved. Whereby two of them were referred to dermatologist because of perianal dermatitis and one patient became symptoms free after co-existing haemorrhoids treated with rubber band ligation. Meanwhile another two patients (9.5%) did not improve in symptoms and the fissure had not healed at physical examination. Those patients were treated with GTN, DTC and one BTA injection and LIS. Assessment in continence showed that, three patients (14.3%) experienced incontinence: one male patient complained fluid incontinence after defecation a few times a week for 3-4 weeks and then became normal, one female patient experience gas incontinence more than once a week but less than once a day and another female patient experience fluid incontinence more than once a week but less than once a day. Remaining 18 patients (85.7%) had no changes in continence. Within median followed-up of 16 months, none of the healed fissures recurred.^{10, level II-2}

Arthur JD et al. (2008) conducted a non-RCT to compare fissurectomy with BTA injection and fissurectomy followed by topical diltiazem (DTC) for the treatment of CAF. The study involved 51 patients who failed previous treatment for at least six weeks with either topical GTN or 2% DTC. Those patients were divided into two groups; group A (28 patients) underwent surgical knife excision of the fibrotic fissure edges and associated sentinel pile then was injected with 20 unit per side BTA injection. Meanwhile, for group B (23 patients), also underwent similar fissurectomy procedure but followed with 2.0 cm – 2.5 cm 2% DTC which was applied to the perianal margin and into anal canal twice daily for nine weeks. Patients in both groups were discharged on the same day with Fybogel and lactulose. The patients were followed-up at a median of 12 weeks after surgery and the assessment involved direct question on persistence or resolution of pain and / or bleeding at defaecation and gentle eversion of the anal margin to assess the fissure healings. At initial followed-up, no statistically significant difference between group A and group B for complete symptom free; group A (25 / 28 patients; 89.3%) and group B (19 / 23; 82.6%) with p value of 0.77. In the symptomatic patients, three patients in group A had persistent symptoms of anal pain and / or bleeding and all of them were observed to have unhealed fissures. In the meantime, 4 patients in group B also had unhealed fissures.^{11, II-1}

Scholz TH et al. (2007) conducted a pre- and post-intervention study in 40 patients. The aim of the study was to determine the outcome of combined fissurectomy and injection of BTA. The procedure involved fissurectomy followed-by 10 unit in 2 ml of 0.09% NaCl of BTA injection which were injected each side of the fissure into the internal anal sphincter. The patients were enrolled from January 2001 to August 2004. They were followed-up six weeks after the treatment procedure. The outcomes were

observed on the improvement of the fissure healing and symptom relief were grade in four different stages. Those stages were stage I (fissure healed/symptoms resolved/no surgery required), stage II (fissure unhealed/symptoms resolved/no surgery required), stage III (fissure unhealed/symptoms satisfactory improved/no surgery required) and stage IV (fissure unhealed/symptoms not satisfactorily improved/surgery required). After one year of the procedure, the patients will be contacted for further assessment. After six months followed-up, the author found that 10 patients (25%) were at stage I with complete fissure healing and symptoms resolved, 26 patients (65%) at stage II where the fissure still presents but no complaints of any symptoms, four patients (10%) were at stage IV where the patients presented with persistent symptoms and unhealed fissures which was successfully treated with second fissurectomy and BTA injection. Overall the primary short-term success concerning fissure healing was 90% (36 out of 40 patients). For long term outcome (after median of one year followed-up), all patients were sent a detailed questionnaire and the response rate was 93% (37 out of 40 patients). The findings showed that, there was reduction of typical fissure symptoms compared to the pre-operative baseline values. Post defecate pain also significantly improved by 92% ($p < 0.01$). Overall, patients were satisfied with the procedure, with a median visual analogue score of nine. Mild incontinence reported which improved with dietary measures and completely disappeared as evaluated during long-term followed up.^{12, level II-2}

Lindsey I et al. (2004) conducted a pre- and post-intervention study to assess whether a combination of fissurectomy and BTA injection may improve the healing rate of medically resistant fissures over that achieved with BTA alone. This study used high-concentration of BTA injection, which was 25 units. Thirty (30) patients having persistence anal pain and sign of chronic fissure and failed with previous treatments were enrolled from April 2001 to January 2004. Their previous treatments were GTN, combination BTA injection and GTN, and combination of fissurectomy and BTA injection at dose of 20 units. The primary outcome of the study was fissure healing at end of followed-up which was eight weeks and secondary outcome was symptomatic improvement. However, for those who were unhealed, they were also seen at 16 weeks. Initially, at eight weeks followed-up, most patients were not completely healed. At 16 weeks, 28 patients (93%) were completely healed with complete symptoms resolution and two patients remained unhealed but with significant improvement in symptoms and no further treatment required. Only one unhealed patient came to surgery for lay-open of an unrelated subcutaneous fistula-in-ano. For incontinence, two male patients (6.7%) had transient flatus incontinence symptoms that resolved within one and six weeks. The incontinence score for both of them were six and eight.^{13, level II-2}

5.2.2 Botulinum Toxin Type A Injection versus Other Treatments

Ebinger SM et al. (2017) conducted SR and network meta-analysis (MA) in order to analyse the established invasive and non-invasive treatments for primary CAF in adults with respect to heal, incontinence and long-term treatment failure rates and to compare the treatments for CAF by incorporating indirect comparisons using the network MA. The SR included 44 RCTs which involved several CAF treatments; lateral internal sphincterotomy (LIS), anal dilatation (DILA), anoplasty and / or fissurectomy (FIAP), BTA and non-invasive treatment [(oral or local application of isosorbide dinitrate, isosorbide mononitrate (NIT), calcium channel blocker (CCB) and local anaesthesia and hydrocortisone)]. Total patients included were 3,268 with median followed-up of two months. The primary outcome for the included studies was healing and incontinence rates after the interventions and the secondary outcome was number of failure rates. Out of 44 studies, 31 studies reported healing rates as the primary outcome. The healing rates reported for each treatment were as follows; the LIS healing rates varied from 37.8% to 100%, the conservative treatment and / or placebo healing rates ranges from 13.3% to 88.9%, the BTA healing rates ranged from 25% to 96% and the FIAP healing rates ranged from 68% to 100%. The authors found that the low healing rates after LIS probably due to bias in the study and the higher healing rates for conservative treatment probably due to the inclusion of acute fissure as the definition was not given in the study. For incontinence rate, the results for each treatment showed that LIS rate varied from 0% to 44.4%, the conservative treatment and / or placebo had 0% rate and one study reported incontinence rate of 12.1%, the DILA ranged from 5.1% to 39.3% and FIAP was 0% to 11.1%.^{4, level I}

Meta-analysis was conducted based on 2,883 patients in 42 trials with 2,190 events of healing. The direct comparisons of LIS against all other treatment were available and FIAP direct comparisons were only conducted against LIS. Comparison of FIAP against BTA, DILA and NIT were based on indirect comparisons. Based on random effect model of MA, there was significant higher healing rate for anal fissure after LIS than other treatment groups (93.1%, with 95% CI 88.9%, 95.7%) and the lowest healing rate was NIT. Meanwhile, the healing rates of other treatments were summarised in Figure 3. Then, for network MA the authors observed moderate inconsistencies of healing rates among the treatments. The authors ranked the treatment with p score of 0 meaning worst treatment and 1 meaning best treatment. The results were LIS (0.898), DILA (0.814), FIAP (0.483), BTA (0.296) and NIT (0.010). The network MA model confirmed that healing rate was significantly higher in LIS compared to other treatment groups (91.2%, with 95% CI 85.8%, 94.5%). Meanwhile, the other treatments were DILA (85.0%, 95% CI 73.9%, 92.0%), FIAP (80.6%, 95% CI 62.6%, 91.45), BTA (62.8%, 95% CI

50.2%, 73.9%) and NIT (56.5%, 95% CI 46.7%, 65.8%). Next for incontinence rate, the meta-analysis was based on 2,393 patients in 35 trials with 144 incontinence events. For FIAP and DILA, direct comparisons were only conducted with LIS. Based on the random effects of MA, DILA had highest incontinence rate which was 18.2%, and the lowest was NIT; 3.0%. Then with network MA, the DILA treatment also had the highest risk of incontinence as shown in Figure 4.4, level I

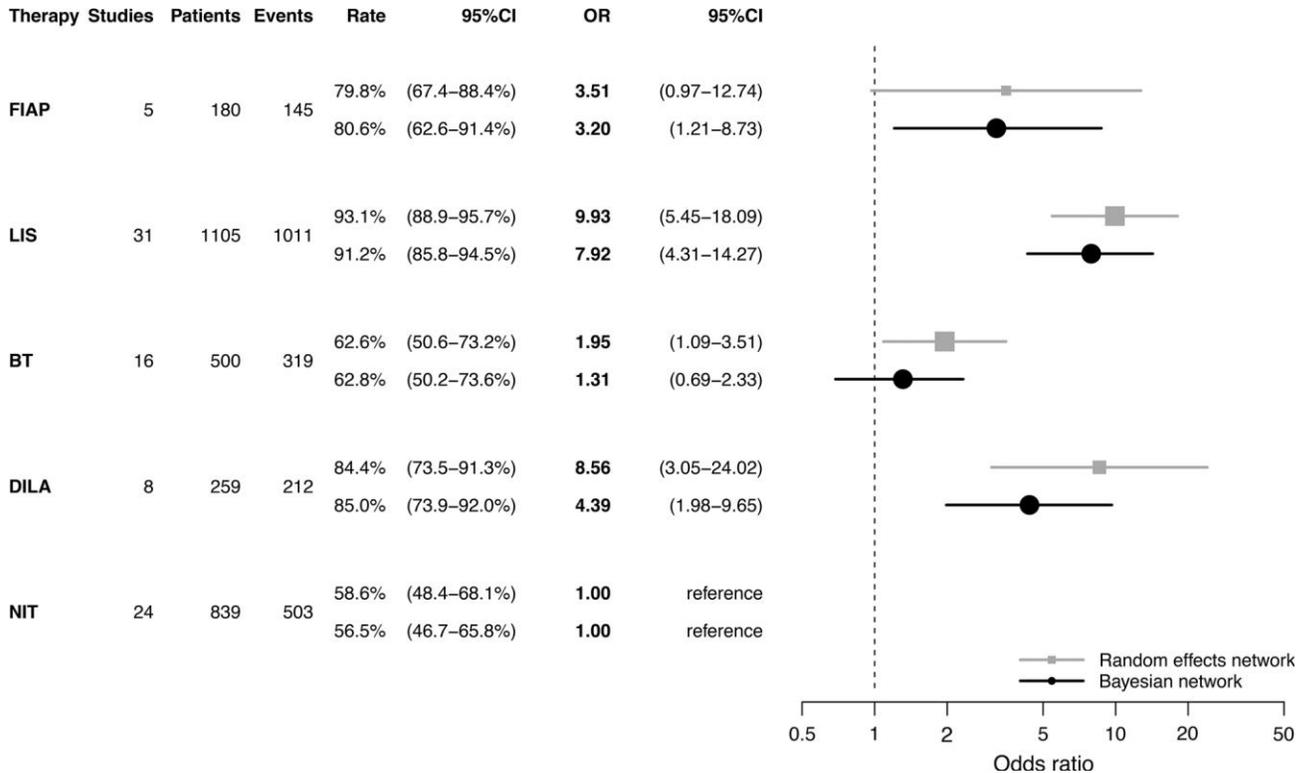


Figure 3: Healing rate in random effects and Bayesian network meta-analysis. OR Odds ratio, CI confidence interval

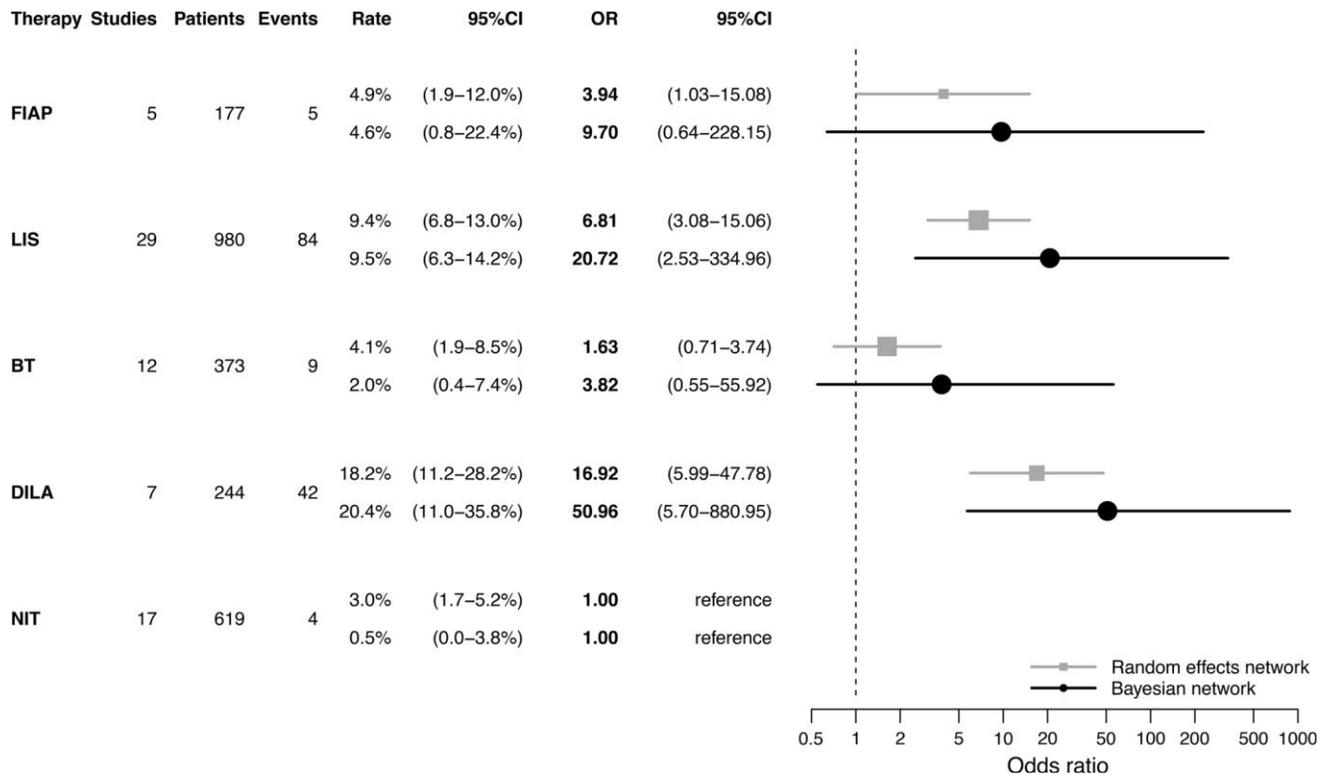


Figure 4: Incontinence rate in random effects and Bayesian network meta-analysis

Sahebally SM et al. (2018) conducted an SR and MA of RCT to compare the effectiveness of BTA and topical nitrates in the management of CAF. The study included six RCTs with total patients of 393 where 194 patients underwent BTA and 199 patients with topical nitrates. The total dose of BTA injection used in the included studies were 20 units, 30 units, 40 units and 60 units and the topical bitrates was at concentrations of 0.2% to 1.0%. The primary outcome observed was unhealed fissures and the secondary outcomes were transient anal incontinence and fissure recurrence. The study found that incomplete fissure healing was observed in five studies with total patients of 313 with 28.6% in BTA groups compared with 42.1% in the topical nitrates group. However, the difference was not statistically significant (pooled OR = 0.47 95% CI 0.13, 1.67; $p = 0.24$). The transient anal incontinence was higher in BTA group (10.4%) compared with 4.4% in topical nitrates group. The difference was also not significant with pooled OR of 2.53, 95% CI 0.98, 6.57, $p = 0.06$. In fissure recurrence, the recurrence rate was lower in BTA group (18.5%) compared with 25.1% in topical nitrates group. However, the difference was also not significant (pooled OR = 0.70, 95% CI 0.39, 1.25; $p = 0.22$).^{14, level I}

Brady JT et al. (2017) conducted a cross-sectional study to assess patients that underwent BTA compared to LIS whether the treatments able to prevent incontinence, the recurrence rates of both procedures and satisfaction rate after the procedures. The study involved 94 patients; 73

patients underwent LIS and 21 patients underwent BTA injection. The dose of BTA varied between 50 units and 100 units. Patients' treatment chart was reviewed retrospectively, and they were also contacted through phone. Cleveland Clinic Faecal Incontinence (CCFI) score was used to assess the incontinence and whereby 0 represent as perfect continence and 20, complete incontinence. From the CCFI score, the authors found statistically significant difference between BTA and LIS; $p = 0.007$. Preoperatively, the CCFI score for BTA was 2.1 with 50% of perfect continence and CCFI score for LIS was 0.4 with 88% perfect continence. Secondary procedure was the same in both groups; BTA patients underwent endoscopy more often (29%) than LIS (8%), LIS patients were more likely to have fissurectomy (23%) than BTA (5%) and sentinel / skin tag removed more in LIS (21%) than BT (14%). Postoperative assessment on the incontinence found that overall CCFI score was higher in BTA group compared to LIS group; $p = 0.04$. The CCFI score after BTA procedure was 29% showed improvement, 36% unchanged and 36% worsened. On the other hand, CCFI score after LIS was 9% improvement, 67% unchanged and 23% worsened. In terms of patient satisfaction, 78% of patients in both groups were very satisfied with the treatments, three patients (7%) in the LIS group were dissatisfied with the treatment, two patients (14%) in the BTA group were dissatisfied and one patient (7%) were very dissatisfied. No significant differences in both group for satisfaction towards treatments; $p = 0.1$. The recurrence of anal fissure was significantly higher in BTA group than LIS group; $p = 0.03$. However, those patients were manageable with non-operative procedure and laxatives and topical analgesic.^{15, level II-2}

Yiannakopoulou E. et al. (2012) conducted a SR to investigate the efficacy and safety of BTA in the treatment of anal fissure. The study included 21 studies which involved BTA compared with placebo, lidocaine, nitrates or surgery. Two included studies that compared BTA and placebo showed inconsistent results which was caused by underpowered sample size calculation and different BTA dose. One study that compared BTA and lidocaine pomme showed that BTA was more effective than lidocaine pomme with healing rate of 70.58% versus 21.42% ($p = 0.006$). Five RCTs compared BTA and nitrates (either in topical or injection). The findings were inconsistent as two studies showed BTA was more effective than topical; one study found that topical nitrates more effective than BTA and two studies showed no difference. Then eight trials that consisted of five RCTs and three non-RCTs were comparing BTA and LIS. The result showed that healing rate was significantly higher in LIS compared to BTA. Botulinum toxin A was used especially in cases of medical treatment resistant anal fissure. Only two trials compared BTA either alone or in combination with other means of chemical or minimally invasive surgical interventions versus LIS. The patients were previously treated with nitrates or anal dilators for eight weeks. The study found that the healing rate of

LIS was 98.7% and BTA was 83.3%. The recurrence of anal fissure after successful healing with BTA was reported in 18 trials. The followed-up period ranged from six months to five years. Overall, the recurrence ranged from 0% to 52.5%. Temporary incontinence to flatus was reported in approximately 10% of patients, and to liquids and faeces in approximately 5% of patients. Long term incontinence was reported in one study.^{5, level I}

5.2.3 Botulinum Toxin Type A Injection and Dose Effect

Bobkiewicz A et al. (2016) conducted an SR and MA to assess the dose dependent efficiency of BTA for CAF. The study involved a total of 1,577 patients from 34 prospective studies. Two different manufactured BTA injections were used which was Botox formulation with dose of 5 to 80 units and Dysport injection with dose of 10 to 150 units. Out of 34 studies included, 30 studies used Botox formulation and the other four studies used Dysport formulation. The efficiency of the formulation showed that there was no correlation between the types of formulation and the efficiency. Botox formulation 33% to 96% and Dysport formulation 67% to 94%. Total mean volume of injected both BT types also showed no statistical correlation between total volume of BT injection and efficiency based on Spearman's rank correlation. The authors also observed the area of BTA injection and its efficiency; they found that there was no significant difference in efficiency concerning the site of injection. Transient faecal incontinence also reported, where 79 patients (5.0%) experienced transient faecal incontinence, those were 51 patients in the Botox formulation group and 28 patients in the Dysport formulation group. All those cases were resolved within one to eight weeks after treatment.^{8, level I}

Lin JX et al. (2016) conducted an SR and MA to systematically analyse the efficacy of BTA for treatment of CAF to identify an optimum dosage and injection regimen. The SR included 18 studies which consisted of 11 RCTs and seven non-RCTs. The SR involved a total of 1,158 patients with 661 in BTA treatment arms. The outcomes were observed for healing, incontinence and recurrence. Based on meta-regression analysis, every increased in dosage will reduced the healing rate by 0.34% (95% CI 0.00, 0.68; $p = 0.048$). Progressive decrease in efficacy in BTA over time with healing up to 60% at six months dropping to close to 30% after three years. In term of incontinence, meta-regression analysis found that each increase in dosage increase in odds of developing incontinence by 1.02 (95% CI 1.000, 1.049; $p = 0.048$). The incontinence was transient and resolved spontaneously within a few weeks. The recurrence rate was reported in 14 studies and they found that there was variability in the timeframe for reporting recurrences between the different doses. For Low-dose (< 20 Unit), the followed-up was short which was within three to six

months. Meanwhile for high-dose (40-50 Units) the followed-up was up to a year. The meta-regression found that each increase in dosage, increased the odds of fissure recurrence by 1.037 (95% CI 1.018, 1.057; $p = 0.0002$). The authors concluded that lower doses of BT were as effective as higher doses for the treatment of chronic anal fissures in adults, resulting in higher rates of reepithelization and resolution of symptoms. Lower doses also result in lower rates of incontinence and recurrence in the longer term. Thus, further research with longer-term follow-up is needed to assess the efficacy of different dosages over time.^{16, level I}

Yiannakopoulou E. et al. (2012) also looked at an optimal dosage regimen for BTA in CAF, three studies were assessed. However, the results were not consistent as in one RCT the result showed that high dose significantly increased the efficacy of BTA and in two non-RCTs the results were vice versa. Difference in types of BTA formulations was also reported in one RCT and the result showed no significant difference between Botox formulation and Dysport. Site of injection also did not show any significant difference as BTA injection at internal sphincter either anteriorly or posteriorly did not show any difference in earlier healing.^{5, level I}

5.3 SAFETY

United State of Food and Drug Administration (USFDA) approved the use of BTA injection for cosmetic. Meanwhile, BTA is indicated for focal dystonia, hemifacial spasm and spasticity including cerebral palsy in MOH formulary.

Barnes TG et al. observed post-operative complications after the combination treatment of fissurectomy and BTA. Ninety-five (95) patients out of the total 102 patients (93.1%) experienced no post-operative complications. No local complications such as bleeding, perianal sepsis, thrombosis or haematoma were reported. No keyhole deformity at the fissurectomy site was observed.⁷

Patti R et al. also evaluated immediate and long-term complications after combination treatment of fissurectomy and BTA injection such as incontinence, anal stenosis, keyhole deformity, urinary retention and any related side effects of botox in their study. At the followed-up period there was no case of urinary retention, anal stenosis, keyhole deformity or necrosis of transposed flap. The post-operative complications observed slight entity and no case required further surgery. There were two infections (20.0%) in donor site and partial break down in one case. At 12 months followed-up, no recurrences and requirement of further surgery recorded.⁹

Arthur JD et al. also reported complications in their study. In BTA group (Group A), two patients (7.1%) complained of minor passive post-defecator faecal soiling that lasted about two weeks during the treatment. Meanwhile, in DTC group (Group B), three patients (13.0%) complained of pruritus ani that resolved on completion of treatment. There was no incidences of perianal sepsis or haematoma following the BTA injection and no headaches or dizziness with DTC used were reported.¹¹

Scholz Th et al. also observed any complications during combination of fissurectomy and BTA injection in CAF treatment. Out of a total of 40 patients involved, five patients (12.5%) had some complications that need no pharmacological treatment or surgical, endoscopic, and radiological interventions. The complications were ongoing anal bleeding that spontaneously resolved on the first post-operative day and small abscess that drained and healed spontaneously. On long-term followed-up which was after median of one year, post-defecatory pain was significantly improved by 92% ($p < 0.01$) and bleeding also significantly improved by 100% ($p < 0.001$).¹²

Sahebally SM et al. reported in the SR that the rate of total side effects was 6.4% in the BTA group compared with 33.1% in the topical nitrates group. On random effects analysis the difference was statistically significant with pooled OR of 0.12, 95% CI 0.02, 0.63; $p = 0.01$. The most common side effect in both groups was headache; 4.8% in BTA group and 27.9% in topical nitrates group. The finding was statistically significant (pooled OR = 0.10, 95% CI 0.01, 0.60; $p = 0.01$).¹⁴

Bobkiewicz A et al. reported in the SR and MA, the complications occurred after the BTA injection was local post-operative complications. The most common local post-operative complications were haematoma, perianal thrombosis or perianal abscess. Comparing between two types of BTA formulation, there was no significance difference in the complications incidence in both formulations.⁸

Yiannakopoulou E. et al. included 10 articles in their SR regarding the safety of BTA for CAF treatment. Generally, they found low frequencies of adverse events reported. The common complication was perianal haematoma and perianal thrombosis. One fourriere gangrene has been reported after BTA injection in one study and the patient had diabetes mellitus. The authors also reported some contraindications to BTA which were hypersensitivity case, pregnancy, neurological disease including myasthenia, Lambert Eaton syndrome and amyotrophic lateral sclerosis and co-administration with amino-glycosides which may enhanced the action of BTA.⁵

5.4 COST/COST-EFFECTIVENESS

In Ministry of Health, no botulinum toxin was used for CAF treatment. The local price is around RM 500 per 100 units / vial.

Brisinda G et al. (2014) conducted a study to look at cost implications in the treatment of anal fissures. The authors assessed the CAF treatments which included effectiveness of surgery (LIS, anal dilatation), chemical sphincterotomy, nitrite oxide, CCB, and BTA. In term of cost, the authors came out with two approaches; first was Brisinda approach that used BTA injection in all cases and surgery used for failures only and second approach was used of LIS to cure all CAF patients. Cost analysis for both approaches was conducted based on multistep approach in one prospective trial of 67 anal fissure patients who were symptomatic for longer than three months and was treated using multi-step approach. The trial showed that nitroglycerin application was successful in 43.2% patients where three of them required surgery. Subsequently, BTA injection was effective in 28 of 33 patients (84.8%) while the overall surgery rate was 11.9%. The cost of treating CAF in the trial was nitroglycerine ointment US\$10 per patient, BTA vial of 100IU US\$528 with injection procedure cost of US\$148 per patient and the surgery procedure was US\$1,119 per patient. Thus, total cost for 67 patients was US\$33,282 which included US\$290 for nitroglycerine, US\$20,580 for nitroglycerine with BTA and finally US\$9,025 for nitroglycerine ointment plus BTA plus LIS, considering that a BTA vial was used for every patient. Based on the findings, Brisinda and Nelson approach were applied. The analysis was simplified in table 6. Compared with all approaches, Brisinda approach was cost saving than multistep approach if low dose of BTA used which was 20IU or 30IU, the total cost may decrease US\$29,300 to US\$32,837 than multistep approach.¹⁷ Previous studies which previously discussed showed that there was no significant different in efficacy of BTA injection either in low-dose or high-dose. However, Brisinda G et al. not taken into account the complications of each treatment in their cost-analysis. The analysis also stated that, the approach will be more cost saving if Dysport formulation was used as the preparation was 500 IU per vial which enough to treat eight or five patients with 60IU or 90 IU respectively.¹⁷

Table 6: Cost Analysis of 3 Treatment Approaches

Treatment Cost. Approach	Procedures	Healing/ successful rate	BTA Injection			Nitroglycerine (US\$)	LIS / Surgery	Total Cost for 67 Patients
			100IU/ vial	40IU	20IU/ 30IU			
Multistep Approach	Nitroglycerine + BTA inj. + LIS	Nitroglycerine (successful rate) - 46.2% BTA (successful rate) - 28 of 33 patients (84.8%) Overall surgery rate - 11.9%	BTA cost: US\$ 528 Procedure cost: US\$ 148 for toxin injection (BTA Cost + Procedure Cost: US\$676 per patient)			US\$10	Procedure cost: US\$ 1,119	Total Cost: US\$ 33,282 - Nitroglycerine US\$ 290 - Nitroglycerine + BTA inj. US\$ 20,580 - Nitroglycerine + BTA inj. + LIS US\$ 9,025 (Considering that all patients received BTA inj.)
Brisinda Approach	BTA inj. For all cases LIS only for pts that failed the BTA inj	BTA Inj for 67 patients and LIS in 15.2% cases	BTA cost + Procedure Cost for 67 patients: US\$ 45,292	40IU BTA cost + Procedure Cost for 67 patients: US\$24,066	20IU BTA cost + Procedure cost for 67 patients: US\$: 16,991 30IU BTA cost + Procedure cost for 67 patients: US\$: 20,529		LIS cost in 15.2% cases: ~11,190 - US\$12,309	100IU/BTA: Total cost: US\$ 56,688 (70.3% increase than multistep approach) 40IU BTA: Total cost US\$45,292 (36% increase compared with the multistep approach) 20IU / 30IU: Total cost US\$29,300 / US\$32,837
Nelson Approach	Exclusive use of LIS to cure all 67 patients						Procedure cost: US\$ 1,119 per patient	Total cost: US\$74,973 (125.3% increase compared to multistep approach)

5.5 LIMITATIONS

This technology review has several limitations. Although there was no restriction in language during the search, but only English full text articles were included in this report. The studies included in this review have several limitations including small sample size.

6. CONCLUSION

Efficacy / Effectiveness

- Combination of BTA and fissurectomy for CAF showed an improvement in CAF
- LIS surgery was more effective in healing and preventing recurrence of anal fissure compared with BTA but incontinence was lesser with BTA compared with LIS
- There was no significant difference in healing, recurrence rate and incontinence rate among BTA injection and topical nitrates
- BTA injection was significantly more effective than lidocaine
- Different doses of BTA, different injection sites and different types of BTA formulation, did not significantly affect the efficacy and effectiveness of BTA injection for CAF treatment

Safety

- Common complication in the combination treatment was anal bleeding that resolved spontaneously few days after treatment
- Other reported complications that occurred after combination treatment were perianal sepsis, recurrence anal fissure, pruritus ani, delayed healing, and headache
- Comparing BTA injection with topical nitrates, there was more significant complications especially headache occurred in topical nitrates group compared to BTA injection
- The systematic reviews reported BTA injection had low frequencies of adverse events which were mostly local post-operative complications such as hematoma, perianal thrombosis, perianal abscess and temporary incontinence that consisted of liquid and faeces
- One case of fourniere gangrene was reported in patient with diabetes mellitus
- Contraindications included hypersensitivity case, pregnancy, neurological disease including myasthenia, Lambert Eaton Syndrome and Amyotrophic lateral sclerosis and co-administration with amino-glycosides may enhanced the action of BTA

Cost

- No local cost analysis was retrieved on the management of CAF with BTA injection
- One cost analysis from United State of America showed that combination of treatment (BTA injection and surgery for any fail BTA case) was cost saving compared to only surgery (LIS) approach

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9. APPENDIX

9.1. Appendix 1: LITERATURE SEARCH STRATEGY

Ovid MEDLINE® In-process & other Non-Indexed citations and OvidMEDLINE® 1946 to present

- 1 anal fissure.mp. or Fissure in Ano/
2. (anal adj (fissure# or ulcer#)).tw.
3. fissure# in ano.tw.
4. 1 or 2 or 3
5. Botulinum Toxins, Type A/ or Botulinum Toxins/
6. (botulinum toxin# adj type A).tw.
7. (Botulinum adj toxin#).tw.
8. Meditoxin.tw.
9. Neuronox.tw.
10. Oculinum.tw.
11. Botulin.tw.
12. (clostridium botulinum adj toxin#).tw.
13. (Botulinum a adj toxin).tw.
14. (Botulinum adj neurotoxin a).tw.
15. clostridium botulinum toxin type a.tw.
16. clostridium botulinum a toxin.tw.
17. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
18. 4 and 17
19. limit 18 to (english language and humans and yr="2010 -Current")

OTHER DATABASES	
EBM Reviews - Cochrane database of systematic reviews	
EBM Reviews - Health Technology Assessment	
PubMed	
NHS economic evaluation database	
INAHTA	
FDA	
Others (Google Scholar, Google)	

9.2. Appendix 2

HIERARCHY OF EVIDENCE FOR EFFECTIVENESS STUDIES

DESIGNATION OF LEVELS OF EVIDENCE

- I Evidence obtained from at least one properly designed randomised controlled trial.
- II-1 Evidence obtained from well-designed controlled trials without randomization.
- II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.
- II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.
- III Opinions or respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

SOURCE: *US/CANADIAN PREVENTIVE SERVICES TASK FORCE (Harris 2001)*

9.4. Appendix 3 EVIDENCE TABLE

Evidence Table: Efficacy/Effectiveness

Question: Is it COMBINATION of fissurectomy and Botox Injection effective for anal fissures treatment?

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
1. Barnes TG, Zafrani Z, & Abdelrazeq AS. Fissurectomy Combined with High-Dose Botulinum Toxin is Safe and Effective Treatment for Chronic Anal Fissure and a Promising Alternative to Surgical Sphincterotomy. 2015; 58: 10	Retrospective study (pre & post intervention study) Obj: to determine the efficacy, safety and durability of using a combination of fissurectomy and BTA in the management of CAF Methods: - Patients treated with combination of fissurectomy and BTA injection between Sept 2008 and March 2012 - Fissurectomy and BTA injection were conducted as described - The procedure was performed as a day-case - All patients were prescribed a 7 day course of non-opioid analgesics as required with 8-week supply of laxative - All patients were evaluated in the outpatient clinic approximately 12		102 (62 women and 40 men) - Mean age: 41 years (21-70 years) - Mean BMI: 27 (16-45kg/m ²)	Fissurectomy + BTA Patients treated with same method: 500mg of i.v Metronidazole Fissurectomy was conducted Total dose of 100 units of BTA was diluted with 1 ml isotonic saline BTA was injected directly into the internal sphincter at the base of the fissure Local anaesthesia 20ml of 0.5% bupivacaine was infiltrated into the fissure Indication: a. CAF symptoms	None	12 to 54 months (mean 33 months) (all patients were contacted via phone and asked whether they having any recurrence	Outcomes assessed: resolution, improvement or persistence of symptom (healing → complete epithelialization of the fissure area) or persistence of fissure and complications of post-operative period RESULTS Types of Fissure - Posterior fissure: 70.6% (72/102 patients) - Anterior fissure: 6.7% (7/102 patients) - Both fissures (posterior and anterior): 2.5% (23/102 patients) Indications of treatments a. 40.2% (42/102 patients) failed to respond to topical therapy b. 26.5% (27/102 patients) CAF with signs of chronicity c. 33.3% (34/102 patients) having both a & b At 12-weeks postoperative review - 95% (97/102 patients): showed resolution or improvement of symptoms - 68/97 patients: reported resolution of their symptoms, complete fissure healing → discharge - 29/97 patients: symptoms improved but fissure healing was incomplete - 25/29 patients: prescribed topical	

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
	<p>weeks</p> <p>Definition of Chronic Anal Fissure (CAF):</p> <ul style="list-style-type: none"> - Based on appearance of any features of chronicity, sentinel tag at the distal pole of the fissure, a hypertrophied anal papilla at its proximal extent, a fibrotic edge and the appearance of circular fibers of the internal sphincter muscle at its base - Symptoms persistent for more than 8 weeks despite topical treatment with GTN or diltiazem <p>Clinical records of all recruited patients were reviewed in March 2013</p> <p>Comparison of fissure healing between groups was evaluated using the Fisher exact test</p>			<p>that failed to respond to topical therapy</p> <ul style="list-style-type: none"> b. CAF with signs of chronicity c. Both a & b <p>CCFIS = Cleveland Clinic Faecal Incontinence Score → to assess incontinence</p>			<p>diltiazem and Fybogel for 8 weeks</p> <ul style="list-style-type: none"> - 4/29: declined topical therapy → opting for repeat treatment with BTA ± fissurectomy if signs of chronicity were found - Fissures in all 29 patients had subsequently healed and discharged following their 12-week post-operative assessment - 5/102 patients: no improvement (3 men, 1 women with posterior anal fissure and 1 women with anterior anal fissure) → declined to repeat fissurectomy and BTA injection → opted for alternative surgery → fissures in all 5 patients healed at the 12-week postoperative review <p>At 12-months (phone interview)</p> <ul style="list-style-type: none"> - All patients were asymptomatic with normal continence - No evidence of recurrence of patients previously treated anal fissure - Clinical records were reviewed in March 2013 equating follow-up period ranging between 12 and 54 months → no patients had anal-fissure related concerns or received anal fissure-related treatment since being discharged <p>Healing</p> <ul style="list-style-type: none"> - No significant difference in fissure healing between posterior and anterior anal fissures (95% vs 86%), $p = 0.38$ - No difference between males and female (97% vs 93%), $p = 0.38$ <p>Conclusion</p>	

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
							- Combination of fissurectomy and high dose BTA injection should be considered as 2 nd line therapy for CAF that fails to heal with use of topical therapy or even as a 1 st line therapy for those patients who have signs of chronicity at presentation	

Evidence Table: Efficacy/Effectiveness

Question: Is it COMBINATION of fissurectomy and Botox Injection effective for anal fissures treatment?

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
<p>2. Patti R, Fama F, Tornambe A, Asaro G & Di Vita G. 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. Coloproctol. 2010; 14: 31-36</p>	<p>Pre- & post-intervention study?</p> <p>Obj: To evaluate the efficacy of fissurectomy with advancement flap and IAS injection of botulinum toxin in healing the chronic anterior anal fissure (CAAF) with hypertonia of internal anal sphincter (IAS) resistant to medical therapy</p> <p>Methods Treatment procedure - After fissurectomy and anoplasty, Botox A (diluted in saline to 50UI/ml) was injected into IAS</p> <p>Observation - Pain intensity was scored with VAS from 0 to 10 - Anal incontinence was assessed preoperatively and after 1, 6 and 12 months from the surgical operation using Pescatori grading system: A = incontinence for</p>		<p>10 patients</p> <p>Patients affected with hypertonia of IAS unresponsive to medical therapy and who refused further medical treatment were enrolled in this studies from January 2002 to January 2008</p>	<p>Fissurectomy an Anoplasty + botulinum toxin A</p> <p>Total dose of Botox received: 30 UI equally divided on either side of posterior midline</p>	<p>None</p>		<p>Primary Outcome: - Complete healing and maximum resting pressure (MRP) changes of anal sphincter</p> <p>Secondary Outcome: - Symptoms relief (bleeding, pain, pruritus) - Immediate and long term complications (incontinence, anal stenosis, keyhole deformity, urinary retention, related side effects of botox)</p> <p>RESULTS Baseline Characteristics of patients - 7 women and 3 men - Age range 18-56 years - 3 patients had normal bowel habits and 7 had constipation</p> <p>Fissure Characteristics - Mean duration of symptoms: 9.5 ± 6.8 months - 4 patients failed a therapeutic course of glycerine trinitrate alone → 2 were treated with botox injection 40 UI ad 2 patients had past topical CCB - 2 patients previously failed only botox therapy at dosage of 40 UI</p> <p>Healing Fissure and Relief of Symptoms - All patients healed completely within 30 days from operation - Intensity and duration of pain post-defecation was reduced significantly compared to the</p>	

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	<p>flatus and mucus, B = Liquid stool, C = solid stool and 1 = for occasional, 2 = for weekly and 3 = for daily</p> <ul style="list-style-type: none"> - Patients were as outpatients discharged 24 – 48 h after surgery - Follow-up examination at 1, 6 and 12 months following the surgical operation <p>Statistical analysis</p> <ul style="list-style-type: none"> - MRP values in median and range - Student's t-test with Welch correction was used to analyse the differences of pain score and pain duration at each registration point - $P < 0.05$ = statistically significant 						<p>preoperative values starting from the 1st defecation ($p < 0.0001$ and $p < 0.0001$, respectively)</p> <ul style="list-style-type: none"> - None of patients complained of pain, bleeding or pruritis 30 days after surgery - Analgesic used decreased significantly after the 1st defecation <p>MRP and Anal Incontinence</p> <p>MRP</p> <ul style="list-style-type: none"> - Preoperatively, MRP values : median of 99 mmHg with range of 88 to 120 - At 6 months revision, MRP values were a median of 79.5 mmHg with range of 68 to 98 mmHg (significant difference, $p < 0.001$) - In all patients, preoperative MRP value was lower at 6 months of surgery and the overall reduction was 20.5% <p>Anal Incontinence</p> <ul style="list-style-type: none"> - Preoperatively: 2 patients reported anal incontinence → both were classified as A2 according to Pescatori grading system - 1 month after surgery: anal incontinence were reported in 3 patients → 2 were complained preoperatively → 1 patient were classified as A1 and 2 were classified as A2 <p>Conclusion</p> <ul style="list-style-type: none"> - Randomized trials comparing fissurectomy alone vs fissurectomy combined with graft and fissurectomy with grafts and drugs to reduce sphincter tone are needed 	

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<p>3. Witte ME, Klaase M & Koop R. Fissurectomy Combined with Bolutinum Toxin A Injection for Medically Resistant Chronic Anal Fissures. Colorectal Disease. 2010; e163-e169</p>	<p>Pre- and Post-intervention study</p> <p>Obj: To evaluate the effect of the combination of fissurectomy and Botulin Toxin A in treatment of CAF</p> <p>Methods: Treatment; - Fissurectomy was performed by minimal excision of the fibrotic edges with a scalpel or cutting diathermia until normal, non-fibrotic, bleeding anodermal tissue was reached - Then 80 IE (0.4ml) botox (Dysport) was injected in the visible internal sphincter fibres</p> <p>Follow-up - Standardized with plan visit at 6 and 12 weeks post-operatively and longer when necessary - Recorded any changes in continence → incontinence was</p>		<p>21 patients (10 male patients, median age 48 years)</p> <p>All patients at least had undergone 1 botox A injection (11 patients had 60 IE (0.3ml) injection and 10 patients had 80 IE (0.4ml) → as 1st injection dosage</p>	<p>Fissurectomy + Botulinum Toxin A (80 UI) under regional anaesthesia in day care</p>	<p>None</p>		<p>RESULTS</p> <ul style="list-style-type: none"> - 16/21 healed with complete resolution of symptoms at follow-up - 3/21 fissures healed at physical examination and symptoms improved but not completely resolved → 2 patients were referred to dermatologist because of perianal dermatitis, 1 patients become symptoms free after treatment of co-existing haemorrhoids by rubber band ligation - 2/21 patients were not improved in symptoms and the fissure had not healed at physical examination → treated with GTN, diltiazem and 1 botox injection before the combined treatment → both underwent LIS → 1 patient become symptom free and the other patient had co-existing haemorrhoids so haemorrhoids artery ligation procedure were performed and became symptom free thereafter - From 4 patients with co-existing haemorrhoids, only 1 patient became symptom free after combination treatment → the other 3 patients needed treatment of their haemorrhoids to become symptom free → patient with Crohn disease was treated successfully with fissurectomy an botox injection 	

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	<p>defined as any episode of loss of control of flatus, liquid or solid stool → Wexner incontinence score</p> <ul style="list-style-type: none"> - Physical examination: fissure healing → complete epithelialization of the fissure base - Symptoms Improvement graded: symptom persistent, slightly better, requiring further surgery, symptom improved or symptoms completely resolved 						<p>Changes in Continence</p> <ul style="list-style-type: none"> - 1 male patient complained of incontinence of fluids after defecation a few times a week during 3-4 weeks → become normal then - 1 female patient experienced incontinence of gas more than once a week but less than once a day (Wexner score 3) - 1 female patient experienced incontinence of liquids more than once a week but less than once a day (Wexner score 3) - Remaining 18 patients experienced no changes in continence - No other complications were encountered - Within median follow-up of 16 (9-30) months, none of the healed fissures recurred <p>Conclusion</p> <ul style="list-style-type: none"> - Combination of fissurectomy and botox injection in the treatment of medically resistant CAFs was promising - High resting pressure of the internal anal sphincter and fibrotic nature of chronic fissure - Effective in 90% of patients with low morbidity and no reported complications in the study - The combination may further reduced the need for lateral internal sphincter (LIS) so avoiding the risks of permanent sphincter damage due to incontinence 	

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<p>4. Baraza W, Boereboom C, Shorthouse A & Brown S. The Long-Term Efficacy of Fissurectomy and Botulinum Toxin Injection for Chronic Anal Fissure in Females. The ASCRS. 2008; 51: 239-243</p>	<p>Pre & Post Intervention Study</p> <p>Obj: To determine whether botox injection and fissurectomy is an effective, safe and lasting treatment modality in the population and further add to the data on the novel technique</p> <p>Methods:</p> <ul style="list-style-type: none"> - Patients undergoing combination treatment (fissurectomy and botox injection) for CAF <p>Follow-up Assessment</p> <ul style="list-style-type: none"> - Initial follow-up after 6 – 8 weeks in surgical outpatient clinic - Vaizey Continence score - Physical assessment on fissure <p>Complications</p> <ul style="list-style-type: none"> - Resolution symptoms of pain and bleeding - Post-operative complications, 		<p>46 patients (mean age 42 (range 24 – 66 years)</p> <p>Consisted of consecutive female underwent fissurectomy and botox injection for primary CAF in UK teaching hospital between August 2003 and October 2005</p>	<p>Fissurectomy + Botox (25 to 100 units)</p>	<p>None</p>	<p>6 to 8 weeks after procedures</p>	<p>Primary Outcome: Fissure healing and incidence of incontinence</p> <p>Secondary Outcome: need for further surgical intervention</p> <p>RESULTS</p> <p>Demographics</p> <ul style="list-style-type: none"> -46 patients -42/46 (89%) had undergone previous topical therapy in form of 0.2% GTN or 2% diltiazem paste for at least 6 weeks before the procedure - 1/46 had undergone previous latera sphincterotomy -No patient had incontinence symptoms on specific questioning pre-operatively (Vaizey score 0) <p>Primary Outcome</p> <ul style="list-style-type: none"> -9 patients: delayed healing at 1st follow-up at approximately 2 months - At median follow-up of 11 months: <ul style="list-style-type: none"> •2 patients: defaulted follow-up •36 of 44 patients (82%): asymptomatic - At median follow-up of 22 (range 6 – 26) months: <ul style="list-style-type: none"> •11 patients: lost to follow-up •16 of 32 patients (50%): asymptomatic from their fissure •1 patient had lateral sphincterotomy that cured the fissure 	

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	recurrence rates and need for further surgical interventions						<ul style="list-style-type: none"> •2 patients had symptom resolution •5 patients require further surgical intervention → lateral sphincterotomy in 2 patients and flap procedure in 3 patients → successful in all 5 with no recurrence fissure •8 patients with recurrence symptoms neglected to seek further specialist intervention •1 incontinence case at final assessment and the patient complained of urge incontinence (Vaizey score = 8/24) → persisted more than 18 months •No other patient reported any incontinence <p>Conclusion</p> <ul style="list-style-type: none"> - Fissurectomy and botulinum toxin effective in chronic fissure in ano among female sample but have high rate of late recurrence - Required RCT to look at long term advantages 	

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<p>5. Arthur JD, Makin CA, El-Sayed TY & Walsh CJ. A Pilot Comparative Study of Fissurectomy/Diltiazem and Fissurectomy/botulinum Toxin in the Treatment of Chronic Anal Fissure. Tech Coloproctol. 2008; 12: 331-336</p>	<p>Retrospective Study (Fissurectomy + BTA vs Fissurectomy + topical 2% DTC)</p> <p>Methods</p> <ul style="list-style-type: none"> - Outcomes of treatments in all patients with medically resistant chronic anal fissures who had undergone either fissurectomy followed by 8 weeks of topical perianal DTC or fissurectomy combined with BTA injection was studied retrospectively - Patients in both group were discharged home the same day with Fybogel and lactulose - Clinic followed-up: at a median of 12 weeks after surgery - Outcome: assessed by consultant surgeon or a supervised senior registrar in the clinic → direct questioning (persistence or resolution of pain and/or bleeding at 		<p>51 patients</p> <ul style="list-style-type: none"> - All included patients had failed previous treatment for at least 6 weeks with either topical GTN or 2% DTC - All patients underwent day-case general anaesthetic procedures between January 2005 and June 2006 - Group A (28 patients): underwent surgical knife excision of the fibrotic fissure edges and associated sentinel pile. Then, was injected with BTA - Group B (23 patients): similar fissurectomy as group A followed with 2% DTC 	<p>Fissurectomy + BTA injection (40 U: 20 U per side)</p>	<p>Fissurectomy + topical 2% DTC → 2-2.5cm DTC and applied to the perianal margin and into anal canal twice daily for 8 weeks</p>	<p>8- 20 weeks</p>	<p>RESULTS</p> <ul style="list-style-type: none"> - Demographic: no statistically significant difference between group A & B with respect to age, gender or fissure characteristics <p>Symptoms Free</p> <ul style="list-style-type: none"> - At initial followed-up: no statistically significant difference between group A & B for complete symptom free: Group A 25/28 (89.3%) and Group B 19/23 (82.6%) → p = 0.7739 - Symptomatic patients: <ul style="list-style-type: none"> • Group A (3/28) persisting symptoms of anal pain and/or bleeding → all were observed to have unhealed fissures → 2 patients were underwent topical 2% DTC treatment for further 6 weeks → 1 of the patients completely symptom free at the end of the period → the other 2 unhealed patients underwent lateral sphincterotomy • Group B (4/23): all 4 had unhealed fissures → all 4 received further topical 2% DTC → 2 patients had complete symptom free after further 6 weeks of treatment → the other 2 omit clinic follow-up session <p>Conclusion</p> <ul style="list-style-type: none"> - Larger prospective RCT of these treatment modalities, powered to detect significant differences was need with long-term follow up to 	

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	<p>defaecation→gentle eversion of the anal margin to assess fissures healing</p> <ul style="list-style-type: none"> - Grade of degree of fissure healings was not included - All patients with symptoms and signs of failed treatment were offered further treatment with either DTC for a further 6 weeks of lateral sphincterotomy <p>Statistical Analysis</p> <ul style="list-style-type: none"> - Mann-Whitney, Chi-squared and Fischer's exact test 						<p>assess recurrence</p>	

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<p>6. Scholz Th, Hetzer FH, Dindo D, Dermatines N, Clavien PA & Hahnloser D. Long-Term Follow-up After Combined Fissurectomy and Botox Injection for Chronic Anal Fissures. Int J Colorectal Dis. 2007; 22: 1077-1081</p>	<p>Retrospective (pre- & post-intervention study)</p> <p>Obj: to determine the outcome of combined fissurectomy and injection of BTA</p> <p>Methods: Inclusion Criteria -Patients with CAF and treated with fissurectomy + BTA were enrolled from January 2001 to August 2004 -Older than 16 years old -Persistent sign and symptoms of CAF lasted more than 6 weeks</p> <p>Morphological signs of CAF: present fibrosis, induration of fissure edges and visible muscle fibres</p> <p>Followed-up: 6 weeks after the operation - Improvement of fissure healing and symptoms relief were graded in 4 different Stages: 1. Stage I: Fissure</p>		<p>40 patients (21 women, 19 men)</p> <p>Median age 37 years (range 18 – 57 years)</p> <p>Definition Fissure healing: completely resolved symptoms according to stages I and II below</p>	<p>Fissurectomy + BTA injection (10 UI in 2 ml of 0.09% NaCl were injected on each side of the fissure into the internal anal sphincter)</p> <p>Other: treated with stool regulation (Macrogolum) and topical Lidocaine for 6 weeks</p>	None	6 months 12 months	<p>RESULTS: Fissures Sites</p> <ul style="list-style-type: none"> - Posterior Fissure: 34 patients (85%) - Anterior fissure: 6 patients - Sentinel skin tag: 26 patients (65%) - During study period, 152 patients were conservatively treated for acute anal fissure in the hospital → 30 patients (20%) were not responding to the combined treatment after 3 months (range 2 – 6 months) and were enrolled into the study → 12 patients were primarily seen for CAF with median duration of symptoms of 16 months (range 15 to 19 months) <p>Short-term Outcome (after 6 months follow up)</p> <ul style="list-style-type: none"> - All 40 patients were evaluated and interviewed - Stage I: 10 patients (25%): completely healed fissure and resolved symptoms - Stage II: 26 patients (65%): fissure still present but no complaints of any symptoms at all - Stage IV: 4 patients (10%): presented with persistent symptoms and unhealed fissures → 2 were successfully treated by a 2nd fissurectomy and BTA injection - The primary short-term success concerning fissure healing was 90% (36/40) 	

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	<p>healed/symptoms resolved/no surgery required</p> <p>2. Stage II: Fissure unhealed/symptoms resolved/no surgery required</p> <p>3. Stage III: Fissure unhealed/symptoms satisfactory improved/no surgery required</p> <p>4. Stage IV: Fissure unhealed/symptoms not satisfactorily improved/surgery required</p> <ul style="list-style-type: none"> - Incontinence: - Wexner Score 1 year after surgery - Patients need to answered detailed questionnaires - 2 classical symptoms of CAF (post-defecatory pain and bleeding) were compared with baseline parameters preoperatively - Overall satisfaction toward treatment were assessed using VAS score - Mc Nemar Test - $p < 0.05$ 						<p>Long-term Outcome (after median of 1 year followed-up → range 0.9 to 1.6 years)</p> <ul style="list-style-type: none"> - All patients were sent a detailed questionnaire for evaluation of long-term follow-up - Response rate was 93% (37/40) - Figure 1: shows the reduction of typical fissure symptoms compared to the preoperative baseline values - Post-defecatory pain significantly improved by 92% ($p < 0.01$) <p>Patients' Satisfaction</p> <ul style="list-style-type: none"> - With questionnaires: evaluated the overall satisfaction of the treatment using visual analogue scale → median of 9 (range 7 to 10) → among 37 patients <p>Conclusion</p> <ul style="list-style-type: none"> - Combination of fissurectomy and BTA injection was promising for the treatment of CAF with high success rate and low morbidity. - However, RCT comparing the combination and fissurectomy is required to ensure the effectiveness of the treatment 	

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<p>7. Lindsey I, Cunningham C, Jones OM, Francis C & Mortensen NJM. Dis Colon Rectum. 2004; 47: 1947-1952</p>	<p>Pre and Post Intervention Study</p> <p>Obj: To assess whether a novel procedure, fissurectomy-BTA, improves the healing rate of medically resistant fissures over that achieved with BTA alone</p> <p>Methods:</p> <ul style="list-style-type: none"> - Patients were having persistence of symptoms of anal pain and sign of chronic fissure despite an appropriate course of medical therapy → GTN, topical 0.2% GTN paste and GTN and subsequent BTA injection alone → all failed - Primary end point: fissures healing at last followed-up - 2nd end point: symptomatic improvement, need for lateral internal sphincterotomy and side effects - Patients were followed-up by interview and 		<p>30 patients</p> <p>[(17 female (57%) and 13 male)]</p> <p>Median age 39 years (range 19.1-16.8)</p> <p>Patients were enrolled from April 2001 to January 2004</p>	<p>Fissurectomy + BTA injection – high-concentration (25UI)</p>			<p>RESULTS:</p> <p>Fissure Site and Others:</p> <ul style="list-style-type: none"> - Posterior fissure: 24 patients (80%) - Anterior fissure: 4 patients - Both site fissure: 2 patients - Sentinel pile: 20 patients (67%) - Median preoperative duration of symptoms was 11 months (range 3 to 60 months) - 29 patients: no specific condition associated with fissure - 1 patient: fissure appeared post-milligan Morgan Hemorrhoidectomy <p>Previous Treatment:</p> <ul style="list-style-type: none"> - 19 patients: failed GTAN alone and no history of underwent either BTA injection or LIS - 11 patients: previously failed BTA injection and GTN - BTA dose that failed: 20 UI BTA (2 patients), 25 UI (6 patients); 20 UI followed with 25 UI (1 patient) - 2 patients: failed combination of fissurectomy and BTA injection (at 20 UI and 20 UI followed with 25 UI dose) <p>Fissure Healing and Symptoms Relief</p> <ul style="list-style-type: none"> - 28/30 fissure (98%) completely healed with complete symptoms resolution - 2/30 fissure: remained unhealed but with significant improvement in symptoms (no further treatment 	

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	<p>physical examination at 8 weeks</p> <ul style="list-style-type: none"> - If fissure was not completely healed, patients were seen at 16 weeks - Definition of fissure healing: complete epithelialization of the fissure base - Symptoms were graded as: <ul style="list-style-type: none"> •symptoms same or worst; •symptoms better but not significant (further surgery required); • symptom significantly better, further surgery not required; •symptoms completely resolved - Incontinence: any episodes of loss of control of flatus, liquid, or solid stool and scored with CCIS (Cleveland Clinic Incontinence Score) 						<p>required)</p> <p>Time to Healing and Follow-up</p> <ul style="list-style-type: none"> - Follow-up range from 6.4 to 53.0 (median 16.4) weeks - In most patients, fissure was not completely healed at initial review at 8 weeks - At 16 weeks: complete fissure healing achieved in 28 of 30 fissures (93%) <p>Fissure Healing vs Predictive Factors for Healing (Table 1)</p> <ul style="list-style-type: none"> - No differences in healing rates between male and females ($p = 0.18$) - No differences in healing rates between those with or without sentinel pile ($p > 0.99$) - No differences in healing rates between those with shorter history of fissure symptoms rather than longer ($p = 0.48$) - No differences in healing rates between those with anterior or posterior fissure ($p = 0.25$) - No differences in healing rates between those treated previously with GTN alone or GTN then BTA ($p = 0.13$) <p>Need for LIS</p> <ul style="list-style-type: none"> - No patient required LIS - 1 patients who failed to heal but had significant improvement in symptoms came to surgery for lay-open of an unrelated subcutaneous fistula-in-ano → at examination under anaesthetic, further gentle curettage of his 	

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							<p>unhealed but symptomatically improved fissure was undertaken</p> <p>Conclusion - Fissurectomy and BTA address both the established fibrosis of chronic fissures and internal sphincter spasm resulted in improved healing of medically resistant fissure Larger RCT for this treatment is needed to confirm the pilot study findings</p>	

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Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
<p>8. Ebinger SM, Hardt J, Warschkow R, Schmied BM, Herold A, Post A & Marti L. Operative and Medical Treatment of Chronic Anal Fissure-a Review and Network Meta-Analysis of Randomized Controlled Trials. J Gastroenterol. 2017;52(6):663-676</p>	<p>Review & Network Meta-analysis</p> <p>Obj: To analyse the established invasive and non-invasive treatments for primary chronic anal fissures in adult with respect to healing, incontinence and long term treatment failure rates</p> <p>To compare the treatments for chronic anal fissures by incorporating indirect comparisons using network meta-analysis</p> <p>44 RCTs</p> <ol style="list-style-type: none"> 1. Iswariah H et al 2005 2. Marby M 1979 3. Parellada C 2004 4. Mousavi SR 2009 5. Leong AF 1995 6. Jensen SL 1984 7. Hiltunen KM 1986 8. Oettle GJ 1997 9. Libertiny G 2002 10. Katsinelos P 006 11. Siddique MI 2008 12. Giridhar CM 2014 13. Maria G 1998 14. Abd Elhady HM 2009 15. Festen S 2009 		<p>3,268 patients</p>	<p><u>Invasive</u></p> <p>Lateral Internal sphincterotomy (LIS),</p> <p>Anal dilatation (DILA),</p> <p>Anoplasty and/or fissurectomy (FIAP),</p> <p>Botulinum toxin (BT)]</p> <p><u>Non-invasive treatment (NIT)</u></p> <p>Oral or local application of isosorbide mononitrate, isosorbide dinitrate (GTN), calcium channel blocker (CCB) and conservative treatment (local anesthesia, local hydrocortisone</p>		<p>Median follow-up of 2 Months</p>	<p>Results</p> <p>Primary Outcome: - Healing and incontinence rates after all the interventions</p> <p>Secondary Outcome - No – success rate</p> <ul style="list-style-type: none"> • Healing Rates: Number of studies - 31 studies with healing rate as primary endpoint - 1/31 study had 1 arm study received LIS - 24/31 studies received conservative treatment and / or placebo - 16/31 studies received BT injections - 8/31 studies received anal dilatation - 5/31 received anoplasty and/or fissurectomy • Healing Rates: Results - LIS healing rates: varied from 37.8%² to 100%³⁻¹² - Low healing rates after LIS (the difference probably due to bias in the study)² - Conservative treatment and/or placebo healing rate: ranges from 13.3%¹³ to 88.9%³ - Higher healing rates (85%) for conservative treatment however the definition of chronic fissure was not given – possibly patients with acute fissure¹⁴ and 90% patients²⁰ were women were 	

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	16. Brisinda G 1999 17. Magdy A 2012 18. Fischer M 1978 19. Wang ZY 2005 20. Berkel AE 2014 21. Weaver RM 1987 22. Ram E 2007 23. Renzi A 2008 24. Boshetto S 2004 25. Saad AM 1992 26. Hancke E 2003 27. Olsen J 1987 28. Richard CS 2000 29. Evans J 2001 30. Colak T 2002 31. Mentis BB 2003 32. Siproudhis L 2003 33. Arroyo A 2005 34. Ho KS 2005 35. Mishra R 2005 36. De Nardi P 2006 37. Fruehauf H 2006 38. Brisinda G 2007 39. Suknaic S 2008 40. Nasr M 2010 41. Samim M 2012 42. Valizadeh N 2012 43. Arslan K 2013 44. Aslam MI et al 2014			or ointment)]			included - BT healing rates: ranged from 25% ¹⁵ to 96% ¹⁶ - FIAP healing rates: ranged from 68% ¹⁷ to 100% ⁴ • Incontinence Rate - LIS: varied from 0 ¹ , 4-5, 8, 12, 16, 18,19 to 44.4% ³ - Conservative Treatment and/or placebo: ➤ 16 studies had incontinence rate of 0% and ➤ 1 study had 12.1% ²⁰ - DILA: ranged from 5.1% ²¹ to 39.3% ⁶ ➤ Lowest incontinence rate 5.1% was reported after anal dilatation with 4 fingers for 4 minutes and another study 14.5% ²² incontinence rate ➤ 2 studies using pneumatic balloon dilatation (4cm): incontinence rate ranged up to 12.5% ²³ ➤ Wider DILA (7-8cm): higher incontinence rate 24.3% ²⁵ - FIAP: 5 studies ➤ 3 studies reported no incontinence at all ➤ 2 studies reported incontinence rate of 6.7% ⁴ and 11.1% ²⁶ Meta-analysis of Healing Rate • Network Description • Based on 2883 patients in 42 trials with 2190 events of healing • LIS: direct comparisons against all other treatment were available • FIAP: direct comparisons were	

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							<p>only conducted against LIS. Comparison FIAP against BT, DILA and NIT were based on indirect comparisons only</p> <ul style="list-style-type: none"> • Meta-analysis of single event rates <ul style="list-style-type: none"> ✓ Healing Rate • Fixed-effect and random-effects meta-analysis for healing rate for each intervention group showed relevant heterogeneity <ul style="list-style-type: none"> ➢ LIS: $I^2 = 75.6\%$, $Q = 123.1$, $p < 0.001$; ➢ DILA: $I^2 = 68.0\%$, $Q = 21.9$, $p < 0.003$; ➢ BT: $I^2 = 81.6\%$, $Q = 81.5$, $p < 0.001$; ➢ FIAP: $I^2 = 55.9\%$, $Q = 9.1$, $p < 0.060$; • Random effect model showed: <ul style="list-style-type: none"> ➢ Significant higher healing rate for anal fissures after LIS than other treatment groups (93.1%, 95% CI 88.9,95.7%) ➢ DILA: (84.4%, 95% CI 73.5,91.3%) ➢ FIAP: (79.8%, 95% CI 67.4,88.4%) ➢ BT: (62.6%, 95% CI 50.6,73.2%) ➢ NIT: (58.6%, 95% CI 48.4,68.1%) <p>(All the findings were confirmed with fixed-effects)</p> • Fixed and Random Effects Network Meta-analysis (NMA) <ul style="list-style-type: none"> ✓ Healing Rate 	

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
							<ul style="list-style-type: none"> •For NMA of the healing rate, significant heterogeneity and inconsistency were observed ($I^2 = 59.6\%$, $Q = 94.1$, $p < 0.001$) •Moderate inconsistencies observed: <ul style="list-style-type: none"> ➢ LIS: Random [OR = 9.93 (95% CI 5.45,18.09)]; Fixed [OR = 9.30 (95% CI 6.37,13.57)] ➢ DILA: Random [OR = 8.56 (95% CI 3.05, 24.02)]; Fixed [OR = 10.66 (95% CI 5.76,19.75)] ➢ FIAP: Random [OR = 3.51 (95% CI 0.97,12.74)]; Fixed [OR = 3.59 (95% CI 1.67,7.71)] ➢ BT: Random [OR = 1.95 (95% CI 1.09,3.51)]; Fixed [OR = 1.74 (95% CI 1.26,2.41)] •The authors ranked the treatment with p score of 0 meaning worst treatment and 1 meaning best treatment) <ul style="list-style-type: none"> ➢ LIS: 0.898 ➢ DILA: 0.814 ➢ FIAP: 0.483 ➢ BT: 0.296 ➢ NIT: 0.010 •Bayesian Random Effects Network Meta-Analysis <ul style="list-style-type: none"> ➢ The model confirmed that healing rate significantly higher in LIS compared to other treatment groups (91.2%, 95% CI 85.8%, 94.5%) ➢ DILA: (85.0%, 95% CI 73.9%, 92.0%) ➢ FIAP: (80.6%, 95% CI 62.6%, 	

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
							<p>91.4%)</p> <ul style="list-style-type: none"> ➤ BT: (62.8%, 95% CI 50.2%, 73.6%) ➤ NIT: (56.5%, 95% CI 46.7%, 65.8%) <ul style="list-style-type: none"> • Compared with NIT, <ul style="list-style-type: none"> ➤ LIS: had highest OR 7.92 (95% CI 4.31, 14.27) ➤ DILA: OR 4.39 (95% CI 1.98, 9.65) ➤ FIAP: OR 3.20 (95% CI 1.21, 8.73) ➤ BT: OR 1.31 (95% CI 0.69, 2.33) • Ranking through Bayesian analysis showed: <ul style="list-style-type: none"> ➤ LIS: ranked 1st in 90.1% of the models ➤ DILA: ranked 2nd and 3rd in 64.8% and 28.4% of the models respectively ➤ FIAP: ranked 2nd and 3rd in 25.8% and 66.5% of the models respectively ➤ BT: ranked 4th in 76.3% of the models ➤ NIT: ranked last in 79.8% of the models <p>Meta-analysis of post-interventional incontinence rate</p> <ul style="list-style-type: none"> • Network Description <ul style="list-style-type: none"> - Based on 2393 patients in 35 trials with 144 events of incontinence - For FIAP and DILA direct comparisons were only conducted with LIS - LIS is represented with comparisons to all other treatment groups 	

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
							<ul style="list-style-type: none"> • Meta-analysis of single event rates - Heterogeneity Fixed effect and random effects meta-analysis for post-interventional incontinence rate for each treatment groups revealed heterogeneity: <ul style="list-style-type: none"> ➤ LIS: ($I^2 = 52.1\%$, $Q = 60.6$, $p = 0.01$) ➤ DILA: ($I^2 = 60.1\%$, $Q = 15.1$, $p = 0.020$) ➤ NIT: ($I^2 = 0\%$, $Q = 14.9$, $p = 0.600$) ➤ BT: ($I^2 = 33.3\%$, $Q = 19.5$, $p = 0.108$) ➤ FIAP: ($I^2 = 21.6\%$, $Q = 5.1$, $p = 0.277$) - Random Effects model for Incontinence rate: <ul style="list-style-type: none"> ➤ DILA: (18.2% 95% CI 11.2, 28.2%) ➤ LIS: (9.2%, 95% CI 6.7, 12.7%) ➤ FIAP: (4.9%, 95% CI 1.9, 12.0%) ➤ BT: (4.1%, 95% CI 1.9, 8.5%) ➤ NIT: (3.0%, 95% CI 1.7, 5.2%) (the findings were confirmed by fixed effect models) • Fixed and Random Effects Network Meta-Analysis (NMA) - No significant heterogeneity or inconsistency observed for NMA of Incontinence rate ($I^2 = 0\%$, $Q = 2.41$, $p = 0.842$) - Random Effects NMA: <ul style="list-style-type: none"> ➤ DILA: highest risk for incontinence [OR = 16.92 (95% CI 5.99, 47.78%)] 	

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
							<ul style="list-style-type: none"> ➤ LIS: [OR = 6.81 (95% CI 3.08, 15.06%)] ➤ FIAP: [OR = 3.94 (95% CI 1.03, 15.08%)] ➤ BT: [OR = 1.63 (95% CI 0.71, 3.74%)] ➤ NIT: was the reference with an OR of 1 <p>(fixed effect NMA yielded similar results)</p> <p>- Ranking of treatment in frequentist analysis further supported these results:</p> <ul style="list-style-type: none"> ➤ NIT: P = 0.963 ➤ BT: P = 0.717 ➤ FIAP: P = 0.487 ➤ LIS: P = 0.289 ➤ DILA: P = 0.004 <p>• Bayesian Random Effects NMA</p> <ul style="list-style-type: none"> ➤ Found significantly higher incontinence rates for DILA compared with other treatment groups (20.4%, 95% CI 11.0, 35.8%) ➤ LIS: 9.5%, 95% CI 6.4, 14.2% ➤ FIAP: 4.6%, 95% CI 0.8, 22.4% ➤ BT: 2.0%, 95% CI 0.4, 7.4% ➤ NIT: 0.5%, 95% CI 0.0, 3.8% <p>- Compared with NIT</p> <ul style="list-style-type: none"> ➤ DILA: highest OR = 50.96 (95% CI 5.70, 880.95) ➤ LIS: OR = 20.72 (95% CI 2.53, 334.96) ➤ FIAP: OR = 9.70, (95% CI 0.64, 228.15) ➤ BT: OR = 3.82 (95% CI 0.55, 55.92) <p>- Ranking in Bayesian analysis for lowest risk on incontinence:</p>	

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
							<ul style="list-style-type: none"> ➤ NIT: 1st; 87.4% ➤ BT: 2nd; 70.7% & 3rd 20.0% ➤ FIAP: 2nd; 18.1% & 3rd 58.3% ➤ LIS: 4th; 78.1% ➤ DILA: last; 93.8% (highest risk for post-interventional incontinence) <p>•Meta-Analysis of No-Success Rate - Random effects model for no-success rate supported the findings of the MA for the healing rate in an inversely arranged ranking</p> <p>Conclusion Additional RCTs are needed especially concerning the long-term incontinence rates after fissurectomy and/or BT and the combined effect of these 2 treatments</p>	

Evidence Table: Efficacy/Effectiveness

Question: Is it BOTOX INJECTION effective for anal fissures treatment?

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
<p>9. Sahebally SM, Meshkat B, Walsh SR & Beddy D. Botulinum Toxin Injection vs Topical Nitrates for Chronic Anal Fissure: an Updated Systematic Review and Meta-Analysis of Randomized Controlled Trials. <i>Colorectal Dis.</i> 2018; 20(1): 6-15</p>	<p>Systematic Review and meta-analysis</p> <p>Obj: To compare the effectiveness of BT and TN in the management of CAF</p> <p>- Directly compared local BT injection vs TN application for treatment of CAF</p>		<p>6 RCTs 393 patients (194 BT and 199 TN)</p> <p>i. Brisinda et al, 1999 ii. De Nardi et al, 2006 iii. Brisinda et al, 2007 iv. Festen et al, 2009 v. Berkel et al, 2014 vi. Abd Elhady et al, 2009</p>	<p>Botulinum toxin (BT) Injection</p> <p>Total of 20U / 30U / 60U / 40U</p>	<p>Topical nitrates</p> <p>0.2% to 1.0%</p>		<p>Results Primary Outcome: a. Unhealed fissures</p> <ul style="list-style-type: none"> - Incomplete fissures healing in 5 studies (n = 313) (28.6% in BT groups compared with 42.1% in the TN group) - On random effects: the difference was not statistically significant (pooled OR = 0.47, 95% CI 0.13, 1.67, p = 0.24). There was statistically significant heterogeneity among the trials [(τ² = 1.62 (df = 4) p = 0.0005; I² = 80%)] <p>Secondary Outcomes a. Transient anal incontinence</p> <ul style="list-style-type: none"> - 5 studies reported rate of transient anal incontinence (n = 313) (10.4% in the BT group compared with 4.4% in the TN group) - On random affects analysis: the difference (pooled OR = 2.53, 95% CI 0.98, 6.57, p = 0.06). There was no statistical heterogeneity among the trials [(τ² = 0 (df = 2) p = 0.63; I² = 0%)] <p>b. Fissure Recurrence</p> <ul style="list-style-type: none"> - 6 studies reported recurrence rate (n = 393) (18.5% in BT group compared with 25.1% in TN group) - On random effects analysis, the difference was not statistically significant (pooled OR = 0.70, 	

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							<p>95% CI 0.39, 1.25, p = 0.22). There was no significant heterogeneity among the trials [($\tau^2 = 0.02$ (df = 4) p = 0.39; $I^2 = 4\%$)]</p>	

Evidence Table: Efficacy/Effectiveness

Question: Is it BOTOX INJECTION effective for anal fissures treatment?

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
<p>10. Bobkiewicz A, Francuzik W, Krokowicz L, Studniarek A, Ledwosinski W, Paszkowski J, Drews M & Banasiewicz T. Botulinum Toxin Injection for Treatment of Chronic Anal Fissure: Is There Any Dose-Dependent Efficiency? A Meta-Analysis. World J Surg. 2016; 40: 3064-3072</p>	<p>- Meta-Analysis</p> <p>Inclusion:</p> <ul style="list-style-type: none"> • Diagnosis of chronic anal fissure • Prospective character of the study • Simple botulinum toxin injection without any other interventions • No previous treatment with botulinum toxin 		<p>1577 patients from 34 prospective studies</p>	<p>Botulinum Toxin (BT) injection</p> <p>2 types of formulation:</p> <p>Botox formulation or</p> <p>Dysport Injection</p>	<p>none</p>	<p>Mean time of followed up 4 to 156 weeks after BT injection</p> <p>Botox formulation vs Dysport formulation (28.9 ± 42.6 vs 10.2 ± 2.1 weeks)</p>	<p>RESULTS</p> <ul style="list-style-type: none"> - 34 studies (30 studies using Botox formulation and 4 studies using Dysport formulation) - 31 studies (91.2% prefer internal anal sphincter injection) - Results were evaluated based on <ul style="list-style-type: none"> ✓ Physical examination = 33 studies ✓ Questionnaire (self-evaluation of pain, bleeding and incontinence = 10 studies) ✓ Anorectal manometry in 19 studies <p>Total of BT units per session</p> <ul style="list-style-type: none"> - Botox formulation: 5 to 80 IU - Dysport formulation: 10 to 150 IU <p>Efficiency</p> <ul style="list-style-type: none"> - Botox formulation: 33% to 96% - Dysport formulation: 67% to 94% (no statistical correlation) <p>Total mean volume of injected both types BT;</p> <ul style="list-style-type: none"> - 0.2ml to 1.0ml per session (no statistical correlation between total volume of BT injection and efficiency based on Spearman's rank correlation) <p>Area of BT injection</p> <ul style="list-style-type: none"> - Within external anal sphincter: in 3 studies (133 patients) - Within internal anal sphincter: in 31 studies (no significant difference in efficiency concerning the site of 	

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
							injection Conclusion - No BT dose-dependent efficiency for CAF - Post-operative incontinence rate and complication rate is not related to the BT dosage - No difference in healing rate in regard to site of injection and number of injection per session - Further studies are required to determine the optimal dose of BT injection	

Evidence Table: Efficacy/Effectiveness

Question: Is it BOTOX INJECTION effective for anal fissures treatment?

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
<p>11.Lin JX, Krishna S, Su B, & Hill AG. Optimal Dosing of Botulinum Toxin for Treatment of Chronic Anal Fissure: A Systematic Review and Meta-Analysis. Dis Colon Rectum. 2016; 59: 886-894</p>	<p>Systematic Review and Meta-Analysis 18 studies (11 RCT, 7 Non-RCT)</p>		<p>1,158 of which 661 in BT treatment arm (From 18 included studies)</p>	<p>Botox toxin injection</p>		<p>Up to 36 months</p>	<p>RESULTS Outcome a. Healing (reepithelization on examination and resolution of symptoms) - 17 studies reported healing rates - Meta-regression analysis: each increased in dosage reduced the healing rate by 0.34% (95% CI 0.00, 0.68; p = 0.048) - Progressive decrease in efficacy of BT over time with healing up to 60% at 6 months dropping to close to 30% after 3 years b. Incontinence - 16 studies reported incontinence rates - Meta-regression analysis found that each increase in dosage increase in odds of developing incontinence by 1.02 (95% CI 1.0002, 1.049; p = 0.048) - Incontinence was transient and resolved spontaneously within a few weeks c. Recurrence - 14 studies reported recurrence rates - There was variability in the timeframe for reporting recurrences between the different doses - Low-dose (< 20 U) the follow-up was short (3 to 6 months) - Higher-dose (40 – 50 U) the follow-up was up to a year - Meta-regression found that each increase in dosage, increased the odds of fissure recurrence by</p>	

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
							<p>1.037 (95% CI 1.018, 1.057; p = 0.0002)</p> <p>Injection Sites</p> <ul style="list-style-type: none"> - Common used 2 injections, one each into the 3 o'clock and 9 o'clock position of internal anal sphincter (IAS) i. Injection into External Anal Sphincter (EIS) <ul style="list-style-type: none"> - 3 studies reported this - BT injected into the external anal sphincter (easier to find and less painful) - 2 studies injected each side of fissure and showed healing rates of 76% and 80% at 3 months and close to 80% even at 6 months - 1 study: injected BT into each lateral side of sphincter and only had healing rates of 29% and 38% after 3 and 6 months ii. Injection into IAS <ul style="list-style-type: none"> - Lateral Sides with 20 U dose (2 studies) <ul style="list-style-type: none"> • Samim et al: number of injection 1, 3 months healing rates of 43% • Asim et al: number of injections 2 3 months healing rates of 57% (not statistically significant p = 0.276) - 25 to 27 U dose <ul style="list-style-type: none"> • 2 studies used 2 injections (3 months healing rates of 75% (Sahakitrungruang et al) and 	

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
							<p>93% (Mehrota et al) → not statistically significant (p = 0.06)</p> <ul style="list-style-type: none"> • 2 studies used 3 injections (extra injection into anterior IAS) (Arroyo et al found similar healing rate at 2 months (88%) and at 6 months (88%)) <p>- Site of the Fissure (4 studies)</p> <ul style="list-style-type: none"> • 20 U dose (Nasr et al and Iswariah et al) <ul style="list-style-type: none"> ✓ Nasr et al: 2 injections with healing rate of 63% at 18 weeks ✓ Iswariah et al: 1 injections with healing rate of 41% at 26 weeks (not statistically significant; p = 0.139) <p>- Anterior/Posterior Midline of the sphincter (3 studies)</p> <ul style="list-style-type: none"> • All 3 used injected BT as 2 doses into both sides of the midline • 2 studies used 20 U of dose and only had patients with posterior fissure (De Nardi et al and Massoud et al) – injected BT into each side of anterior midline – at 6 months of follow-up the healing rates was 47% (De Nardi et al) and 88% (Massoud et al) (p = 0.005) – at 3 months the healing rates for De Nardi et al was 53% • Valizadeh et al used anterior or posterior midline with higher dose (50 U) 	

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
							Conclusion - Further research with longer-term follow-up is needed to assess the efficacy of different dosage - RCTs to determine the optimum injection also required	

Evidence Table: Efficacy/Effectiveness

Question: Is it BOTOX INJECTION effective for anal fissures treatment?

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
<p>12.Brady JT, Althans AR, Dosokey EMG, Jabir MA, Reynolds HL, Steele SR & Stein SL. Treatment for Anal Fissure: Is There a Safe Option. The American Journal of Surgery. 2017 doi:10.1016/j.amjsurg.2017.06.004</p>	<p>Cross-sectional study</p> <p>Methods:</p> <ul style="list-style-type: none"> - Retrospective chart review was performed for patients undergoing LIS or BTA injection for CAF between 2009 and 2015 - Patients identified from electronic medical record using ICD 9 dose - Exclusion: secondary anorectal procedure other than minor procedure, excision of anal skin tag, fissurectomy or colonoscopy, history of Crohn's disease - Data included: age, gender, surgeon, obstetric history, medical comorbidities and preoperative CCFI score (0 – 20) <p>Data collection</p> <ul style="list-style-type: none"> - In 2015 - Contacted through phone → specific questions on: satisfaction with procedure performed, 		<p>94 patients (73 patients LIS; 21 patients BTA)</p>	<p>BTA – single BT injection session</p> <p>Dose varied between 50 UI and 100 UI diluted in 5 to 10 ml of sterile saline based on surgeon preference</p> <p>Injection performed as 2 injections (left and right) or 4 quadrants injection into internal sphincter</p>	<p>LIS – using lateral incision overlaying internal anal sphincter or intersphincteric groove</p>		<p>RESULTS</p> <p>Demographic</p> <ul style="list-style-type: none"> - Not statistically different - Median age: 49 years (BT) and 52 year (LIS)(p = 0.1) - Median duration of symptoms: 4 months (BTA) and 6 months (LIS) (p = 0.2 - 90% patients had prior medical management: combination of stool softener, laxative, fiber and topical CCB - More woman had BT (71% of patients) than LIS (48% of patients) (p = 0.06) <p>CCFI</p> <ul style="list-style-type: none"> - Statistically difference between BTA and Lis (p = 0.007) - Mean CCFI score <ul style="list-style-type: none"> •BT patients preoperatively: 2.1 with 50% perfect continence (CCFI = 0) •LIS patients preoperatively: 0.4 with 88% perfect continence <p>Secondary Procedure</p> <ul style="list-style-type: none"> - Same in both groups; 52% but with different procedure <ul style="list-style-type: none"> •BT patients underwent endoscopy more often (29%) than LIS (8%) • LIS patients were more likely to have fissurectomy (23%) than BT (5%) •Sentinel/skin tag removed more in LIS (21%) than BT (14%) 	

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
	<p>subjectively felt the fissure had returned, fought treatment by physician, treated with any additional surgery or medications for their fissure</p> <ul style="list-style-type: none"> - CCI score were calculated at the time phone contact <p>Clinical Data</p> <ul style="list-style-type: none"> - Compared between groups - Student's t-test (mean) - Interquartile ranges (IQR) (median) - Wilcoxon Rank-sum test - Chi-squared - Fisher's exact test (frequencies and percentages) - STATA - p < 0.05 significant 						<p>Postoperative Study</p> <ul style="list-style-type: none"> - 57 patients (61%) responded to phone survey and consented to participant - No significant differences in surveyed group with respect to age, gender, preoperative CCFI score, duration of symptoms or other prior anal fissure treatments including prior BT or surgery (p > 0.07) - Mean time from procedure to survey 46±23 months in BT group and 44±23 months in Lis group (p = 0.8) <p>Postoperative Incontinence</p> <ul style="list-style-type: none"> - Overall CCFI score higher in BT group (2.4±3.2) compared to LIS group (0.9±1.9; p = 0.04) - Mean decline in CCFI score was lower in BT group (0.3) than LIS group (0.5) but not significant; p > 0.1 - CCFI score after BT procedure: Improvement 29%, unchanged (36%) and worsened (36%) - CCFI score after LIS procedure: Improvement (9%), unchanged (67%) and worsened (23%) - Preoperatively: <ul style="list-style-type: none"> • 50% of BT patients had preoperative CCFI score 0 (1 patient reported CCFI score 8-14) the number remained constant postoperatively • 88% of LIS had preoperative CCFI score 0 (1 patient reported CCFI score 8-14) but the number declined to 70% postoperatively 	

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
							<p>Patient Satisfaction</p> <ul style="list-style-type: none"> - 78% of patients in both groups were very satisfied with the treatments - 3 patients (7%) in the LIS group dissatisfied with their treatment - 2 patients (14%) in the BTA group were dissatisfied and 1 patients (7%) very dissatisfied <p>(no significant differences in both group; p = 0.1)</p> <p>Recurrence and Medical Management</p> <ul style="list-style-type: none"> - BTA (n = 5, 36%) patients believes that their anal fissure had returned compared to LIS group (n = 4, p = 0.03) - 2/5 BTA patients and 3/4 LIS patients had seen a physician regarding recurrence → 2 BTA patients were managed non-operatively, 1 LIS patient was managed non-operatively and another 1 received BTA treatment - At the item of survey, BT patients were more likely to be taking laxatives (BTA n = 6, 43% vs LIS n = 4, 9%; p = 0.01) and topical analgesics (BTA n = 4, 29% vs LIS n = 1, 2%; p = 0.01) <p>Conclusion-</p> <ul style="list-style-type: none"> - BTA and LIS patients experience decline in continence - Rate of recurrence higher in BTA patients than LIS patients - Further evaluation is needed to determine if these preferences are warranted 	

Evidence Table: Efficacy/Effectiveness

Question: Is it BOTOX INJECTION effective for anal fissures treatment?

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
<p>13. Yiannakopoulou E. Botulinum Toxin and Anal Fissure: Efficacy and Safety Systematic Review. Int J Colorectal. 2012; 27:1-9</p>	<p>Systematic Review</p> <p>Obj: to investigate the efficacy and safety of BTA in the treatment of anal fissure</p> <p>Methods:</p> <p>Primary aims:</p> <p>i. Efficacy of BTA in healing of anal fissure compared to placebo</p> <p>ii. Efficacy of BTA in healing of anal fissure compared to other means of chemical sphincterotomy</p> <p>iii. Efficacy of BTA in healing of anal fissure compared to surgical sphincterotomy</p> <p>iv. Short term safety of BTA injections</p> <p>v. Long term safety of BTA injections</p> <p>Secondary aims:</p> <p>i. Recurrence rate of anal fissure treated with BTA injections</p> <p>ii. Optimal dosage regimen of BTA for the treatment of anal fissure</p> <p>iii. Appropriate site for</p>		<p>21 studies</p> <ol style="list-style-type: none"> 1. Siproudhis L et al 2003 2. Maria G et al 1998 3. Colak et al 2002 4. Brisinda G et al 2007 5. Fruehauf H et al 2006 6. Festen S et al 2009 7. De Nardi P et al 2006 8. Brisinda G et al 1999 9. Suknaic S et al 2008 (excluded – no fulltext) 10. Massoud BW 2005 11. Iswariah H 2005 12. Arroyo A et al 2005 13. Arroyo A et al 2005 14. Giral A et al 2004 15. Menten BB et al 2003 16. Algaithy JK et al 2008 17. Nasr M et al 2010 18. Sileri P et al 2007 19. Sileri P et al 2010 20. Arroyo A 2005 21. Jost WH 1997 22. Maria G et al 1998 23. Minguez M et al 2002 24. Abd Elhady HM et al 2009 25. Brisinda G et al 	<p>Botulinum Toxin A</p>	<p>Placebo Lidocaine Nitrates Surgery</p>		<p>RESULTS</p> <p>➤ <i>BTA vs Placebo</i></p> <p>- 2 RCTs (Siproudhis et al¹ and Maria et al²)</p> <ul style="list-style-type: none"> • 1st study¹: no difference → Healing rate: BTA 32% & placebo 32% - 2 months after injection • 2nd study²: BTA superior than placebo → Healing rate: BTA 73% and placebo 13% (p = 0.003) - 2 months after injection (the difference probably due to: underpowered in sample size calculation¹, methodological differences, different BTA preparations, volume BTA differ (0.4ml in Maria et al and 0.2 ml in Siproudhis et al)) <p>➤ <i>BTA vs Lidocaine</i></p> <p>- 1 RCT³ compared BTA with lidocaine pomme</p> <ul style="list-style-type: none"> • BTA more effective than lidocaine pomme → Healing Rate: BTA 70.58% & lidocaine 21.42% (p = 0.006) <p>➤ <i>BTA vs Nitrates</i></p> <p>- 5 RCTs⁴⁻⁸ compared BTA vs nitrates (4 studies on nitroglycerine ointment and 1 study on isosorbide dinitrate)</p> <p>- 5 RCTs = total patients 303 → almost equally distributed into 2 groups</p> <p>- Dosage ranged: 20 IU to 30 IU of</p>	

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
	<p>injection of anal fissure</p> <p>iv. Difference between different formulations in anal fissure treatment</p> <p>v. Efficacy of BTA in medical treatment resistant anal fissure</p> <p>Systematic Search:</p> <ul style="list-style-type: none"> - PubMed, Scopus - For efficacy: clinical trials, randomized or not, compared at least 2 treatments for anal fissure (1 of it BTA) and provided healing rates for each group - For safety: clinical trials of all study designs having at least 1 arm with BTA as the treatment of anal fissure and presenting data on safety were included → Case reports, case series, retrospective chart review, letters to the editor and trials investigating the effect of BTA in combination with other medical treatment vs BTA alone 		<p>2002</p> <p>26. Minguez M et al 1999</p> <p>27. Brisinda G et al 2004</p> <p>28. Maria G et al 2000</p> <p>29. Godevenos D et al 2004</p> <p>30. Jones OM et al 2006</p> <p>31. Charua GL et al 2007</p> <p>32. Witte ME et al 2006</p> <p>33. Radwan MM et al 2007</p> <p>34. Witte ME et al 2007</p> <p>35. Jost WH et al 1995</p> <p>36. Tilney HS et al 2001</p> <p>37. Tilney HS et al 2001</p> <p>38. Brown SE et al 2006</p> <p>39. Mallo-Gonzalez N et al 2008</p> <p>40. Durand A et al 2003</p>				<p>BTA (Botox) and 90 UI (Dysport)</p> <ul style="list-style-type: none"> - Injection site: anterior midline - 2 studies^{4,8}: BTA more effective than nitroglycerine ointment - 1 study⁹: nitroglycerine ointment more effective than BTA - 2 studies^{6,7}: no difference in both treatment → probably underpowered or power calculation based on wrong assumptions or large number of patients lost to follow up <p>➤ <i>BTA vs Surgery</i></p> <ul style="list-style-type: none"> - 8 trials (5 RCTs and 3 non-RCTs)⁹⁻¹⁷ compared BTA with LIS - Healing rate significantly higher in LIS compared to BTA <p>Randomized Controlled Trials</p> <ul style="list-style-type: none"> - Healing rate with BTA ranged from 10% to 73.8% - Superior efficacy of LIS^{11,12,15,17} <p>Non-Randomized Controlled Trials</p> <ul style="list-style-type: none"> - 3 studies found superior efficacy of LIS vs BTA^{10,14,16} <p>➤ <i>BTA in Medical Treatment Resistant Anal Fissure</i></p> <ul style="list-style-type: none"> - Trials^{18,19} comparing BTA either alone or in combination with other means of chemical or minimally invasive surgical interventions vs LIS - 1 study: Compared BTA + fissurectomy vs LIS in patients previously treated with nitrates or anal dilators for 8 weeks¹⁹ - 300 patients with CAF treated with 0.2% nitroglycerine ointment or 	

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
	<p>Study Quality Assessment:</p> <ul style="list-style-type: none"> - Randomization scheme - Allocation concealment - Blinding (patients and outcome assessors) - Study questions clearly described - Follow-up: duration and adequacy - Recurrence data - Lost to follow up description - ADRs included in the outcome - Mode of ADRs evaluated - Safety data properly reported or not 						<p>anal dilators for 8 weeks → if no improvement, patients were offered alternative treatment or combination of fissurectomy + BTA</p> <ul style="list-style-type: none"> - In case of symptom persistence or recurrence after 12 weeks, patients were submitted either to BTA + fissurectomy or LIS → Follow-up 2+ to 16 months - 102 patients underwent BTA or LIS - Healing Rate: LIA (98.7%) and BTA 83.3% <p>➤ <i>Recurrence of Anal Fissure after Successful Healing with Botulinum Toxin</i></p> <ul style="list-style-type: none"> - 18 trials provided recurrence --> *Table 4; other studies in other table - Follow-up ranged from 6 months to 5 years - Recurrence ranged from 0% to 52.5% - Jost et al: observed 8% recurrence of healed anal fissures in 6 month follow up - Maria et al: observed no recurrence of anal fissure after healing with BTA in follow up of 24 months - Minguez et al: analysed long term outcome of 57 patients that had been healed at 6 months after BTA injection → followed up every 6 months for a period of 42 months → fissure recurrence observed in 22 patients (41.5%) - Arroyo et al: prospective study in 50 consecutive patients with CAF 	

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
							<p>→ treated with 25UI BTA in the internal anal sphincter → recurrence or persistence was showed in 54% of patients</p> <p>- Abd Elhady et al: divided 164 patients into 4 equal groups → treated by LIS, diltiazem ointment, GTN ointment or BTA injection → patients were followed-up for 5 years → recurrence rate was 52.5% in BTA group</p> <p>➤ <i>Optimal Dosage Regimen</i></p> <p>- 1 RCT²⁵ and 2 non-RCTs^{22,26} → Table 5</p> <p>- Not consistent result → high dose: RCT significant difference but in non-RCT: no difference</p> <p>• RCT²⁵</p> <p>- Compared low and high dose of BTA</p> <p>- Patients were randomized into 2 groups (Group 1: 20 UI and if anal fissure persisted it will be retreated with 30 U BTA; Group 2: 30 UI BTA and if anal fissure persisted it will retreated with 50 UI BTA</p> <p>• Non-RCT</p> <p>- Maria et al²² divided the patients into 2 groups: Group 1 treated with 15 UI and retreated with 20 UI; Group 2 treated with 20 UI and retreated with 25 UI → higher healing rates with higher dose, even at 1 month or 2 month healing rate (p = 0.04)</p> <p>- Minguéz et al²⁷ divided the patients into 3 groups: Group 1 (10</p>	

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
							<p>UI BTA); Group 2 (15 UI) and Group 3 (21 UI) → Healing rates 83% (Group 1), 78% (Group 2) and 90% (Group 3) → not statistically significant; $p > 0.05$</p> <p>➤ <i>Effects of Formulation</i> - RCT by Brisinda et al²⁷ compared 2 different preparations of BTA; Botox vs Dysport in bioequivalent doses (1:3) → no difference in efficacy and tolerability; $p > 0.05$ (Table 5)</p> <p>➤ <i>Optimal Injection Site</i> - RCT by Maria et al²⁸ observed the optimal injection site for BTA (Table 5) - Patients were injected in internal sphincter (each side of posterior midline or on each side of anterior midline) → anterior midline improved lowering of resting anal pressure and produced earlier healing result compared to posterior ($p = 0.025$)</p> <p>Conclusion - BTA should be considered a minimally invasive therapeutic option for the treatment of CAF - Require well designed randomized trials for valid estimation</p>	

SAFETY

Evidence Table: Safety

Question: Is it Botox Injection SAFE for anal fissures treatment?

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
<p>14. Barnes TG, Zafrani Z, & Abdelrazeq AS. Fissurectomy Combined with High-Dose Botulinum Toxin is Safe and Effective Treatment for Chronic Anal Fissure and a Promising Alternative to Surgical Sphincterotomy. 2015; 58: 10</p>	<p>Retrospective study (pre & post intervention study)</p> <p>Obj: to determine the efficacy, safety and durability of using a combination of fissurectomy and BTA in the management of CAF</p>		<p>102 (62 women and 40 men)</p> <p>- Mean age: 41 years (21-70 years)</p> <p>- Mean BMI: 27 (16-45kg/m²)</p>	<p>Fissurectomy + BTA</p>	<p>None</p>	<p>12 to 54 months (mean 33 months)</p>	<p>RESULTS</p> <p>Complications of post-operative period</p> <p>Post-operative complications</p> <ul style="list-style-type: none"> - 95/102 patients (93%): no post-operative complications - 7/102 patients: reported a degree of incontinence in the immediate post-operative period; 4/7 to liquid stool and flatus (CCFIS = 2, 3 4 and 4) and 3/7 to flatus alone (CCFIS = 2, 2 and 3) → all patients returned to normal continence at 12-week follow-up (CCFIS = 0) - No local complications (bleeding, perianal sepsis, thrombosis or haematoma) - No keyhole deformity a the fissurectomy site 	

Evidence Table: Safety

Question: Is it Botox Injection SAFE for anal fissures treatment?

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
<p>15. Patti R, Fama F, Tornambe A, Asaro G & Di Vita G. 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. Coloproctol. 2010; 14: 31-36</p>	<p>Pre- & post-intervention study? Obj: To evaluate the efficacy of fissurectomy with advancement flap and combined with IAS injection of botulinum toxin in healing the chronic anterior anal fissure (CAAF) with hypertonia of internal anal sphincter (IAS) resistant to medical therapy</p>		<p>10 patients</p>	<p>Fissurectomy an Anoplasty + botulinum toxin A Total dose of Botox received: 30 UI equally divided on either side of posterior midline</p>	<p>None</p>		<p>Secondary Outcome: - Immediate and long term complications (incontinence, anal stenosis, keyhole deformity, urinary retention, related side effects of botox) Complications and Follow-Up - No cases of urinary retention, anal stenosis or keyhole deformity - No necrosis of transposed flap - Post-operative complications recorded: slight entity and no case required further surgery → 2 infections in donor site and partial break down in 1 case - At 12 months follow-ip, no recurrences and requirement of further surgery recorded</p>	

Evidence Table: Safety

Question: Is it Botox Injection SAFE for anal fissures treatment?

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
<p>16. Baraza W, Boereboom C, Shorthouse A & Brown S. The Long-Term Efficacy of Fissurectomy and Botulinum Toxin Injection for Chronic Anal Fissure in Females. The ASCRS. 2008; 51: 239-243</p>	<p>Pre & Post Intervention Study</p> <p>Obj: To determine whether botox injection and fissurectomy is an effective, safe and lasting treatment modality in the population and further add to the data on the novel technique</p>		<p>46 patients (mean age 42 (range 24 – 66 years)</p>	<p>Fissurectomy + Botox (25 to 100 units)</p>	<p>None</p>	<p>6 to 8 weeks after procedures</p>	<p>Complications</p> <ul style="list-style-type: none"> -9 patients: delayed healing at 1st follow-up at approximately 2 months -At median follow-up of 11 months: <ul style="list-style-type: none"> •2 patients: defaulted follow-up •36 of 44 patients (82%): asymptomatic •1 patient had perianal sepsis → resolved with antibiotics → recurrence pain and bleeding but opted not to get further intervention for the symptoms -At median follow-up of 22 (range 6 – 26) months: <ul style="list-style-type: none"> •11 patients: lost to follow-up •1 had inflammatory bowel disease •16 of 32 patients (50%): asymptomatic from their fissure •16 of 32 patients (50%): recurrence of pain or bleeding •3 patients: chronic perianal sepsis→ manage with antibiotic •1 patient had lateral sphincterotomy that cured the fissure •2 patients had symptom resolution •5 patients require further surgical intervention→lateral sphincterotomy in 2 patients and flap procedure in 3 patients → successful in all 5 with no recurrence fissure •8 patients with recurrence symptoms neglected to seek further specialist intervention 	

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
							<ul style="list-style-type: none"> •1 incontinence case at final assessment and the patient complained of urge incontinence (Vaizey score = 8/24) → persisted more than 18 months •No other patient reported any incontinence •Adverse outcome in Table 1 	

Evidence Table: Safety

Question: Is it Botox Injection SAFE for anal fissures treatment?

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
17. Arthur JD, Makin CA, El-Sayed TY & Walsh CJ. A Pilot Comparative Study of Fissurectomy/Diltiazem and Fissurectomy/botulinum Toxin in the Treatment of Chronic Anal Fissure. Tech Coloproctol. 2008; 12: 331-336	Retrospective Study (Fissurectomy + BTA vs Fissurectomy + topical 2% DTC)	-	51 patients	Fissurectomy + BTA injection (40 U: 20 U per side)	Fissurectomy + topical 2% DTC → 2-2.5cm DTC and applied to the perianal margin and into anal canal twice daily for 8 weeks	8- 20 weeks	<p>RESULTS</p> <p>Complication/patients complain</p> <ul style="list-style-type: none"> - Group A (2 patients): complained of minor passive post-defaecatory faecal soiling lasting about 2 weeks during treatment - Group B (3 patients): complained of pruritus ani → resolved on completion of treatment - No incidences of perianal sepsis or haematoma following BTA injection - No headaches or dizziness with DTC used 	

Evidence Table: Safety

Question: Is it Botox Injection SAFE for anal fissures treatment?

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
<p>18.Scholz Th, Hetzer FH, Dindo D, Dermatines N, Clavien PA & Hahnloser D. Long-Term Follow-up After Combined Fissurectomy and Botox Injection for Chronic Anal Fissures. Int J Colorectal Dis. 2007; 22: 1077-1081</p>	<p>Retrospective (pre- & post-intervention study)</p> <p>Obj: to determine the outcome of combined fissurectomy and injection of BTA</p>		<p>40 patients (21 women, 19 men)</p> <p>Median age 37 years (range 18 – 57 years)</p>	<p>Fissurectomy + BTA injection (10 UI in 2 ml of 0.09% NaCl were injected on each side of the fissure into the internal anal sphincter)</p> <p>Other: treated with stool regulation (Macrogolum) and topical Lidocaine for 6 weeks</p>	<p>None</p>	<p>6 months 12 months</p>	<p>RESULTS:</p> <p>Surgical Complications and Morbidity</p> <p>-Surgical complications were graded according to validated treatment-oriented score</p> <ul style="list-style-type: none"> •Grade I : 5 patients (any deviations from the normal post-operative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions <p>→ 1/5 patient: complained about mild incontinence 6 (Wexner score 5) weeks after surgery: improve by dietary measures and completely disappeared as evaluated during long-term followed-up</p> <p>→3/5 patients: with ongoing anal bleeding that spontaneously resolved on the 1st postoperative day</p> <p>→1/5 patient: developed small abscess that drained and healed spontaneously</p> <ul style="list-style-type: none"> •Grade II to III: no complications requiring surgical or pharmacological intervention were observed <p>Long-term Outcome (after median of 1 year followed-up → range 0.9 to 1.6 years)</p> <ul style="list-style-type: none"> - Post-defecatory pain significantly improved by 92% (p < 0.01) - Bleeding significantly improved by 100% (p < 0.001) 	

Evidence Table: Safety

Question: Is it Botox Injection SAFE for anal fissures treatment?

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
19. Lindsey I, Cunningham C, Jones OM, Francis C & Mortensen NJM. Dis Colon Rectum. 2004; 47: 1947-1952	Pre and Post Intervention Study Obj: To assess whether a novel procedure, fissurectomy-BTA, improves the healing rate of medically resistant fissures over that achieved with BTA alone		30 patients [(17 female (57%) and 13 male)] Median age 39 years (range 19.1-16.8) Patients were enrolled from April 2001 to January 2004	Fissurectomy + BTA injection – high-concentration (25UI)			RESULTS: Side Effects - 2 male patients (7%): transient flatus incontinence symptoms → 1 st patients: resolved within 1 week → 2 nd patient lasting for 6 weeks then resolved → the incontinence score for both patients were 6 and 8 respectively - No patient complained of either permanent incontinence or incontinence to liquid or solid stool	

Evidence Table: Safety

Question: Is it Botox Injection SAFE for anal fissures treatment?

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
<p>20. Sahebally SM, Meshkat B, Walsh SR & Beddy D. Botulinum Toxin Injection vs Topical Nitrates for Chronic Anal Fissure: an Updated Systematic Review and Meta-Analysis of Randomized Controlled Trials. <i>Colorectal Dis.</i> 2018; 20(1): 6-15</p>	<p>Systematic Review and meta-analysis</p> <p>Obj: To compare the effectiveness of BT and TN in the management of CAF</p> <p>- Directly compared local BT injection vs TN application for treatment of CAF</p>		<p>6 RCTs 393 patients (194 BT and 199 TN)</p> <p>vii. Brisinda et al, 1999 viii. De Nardi et al, 2006 ix. Brisinda et al, 2007 x. Festen et al, 2009 xi. Berkel et al, 2014 xii. Abd Elhady et al, 2009</p>	<p>Botulinum toxin (BT) Injection</p> <p>Total of 20U / 30U / 60U / 40U</p>	<p>Topical nitrates</p> <p>0.2% to 1.0%</p>		<p>Results</p> <p>Total Side Effects</p> <ul style="list-style-type: none"> - Rate of (total) side effects was 6.4% in the BT group compared with 33.1% in the TN group - On random effects analysis the difference were statistically significant (pooled OR = 0.12, 95% CI 0.02, 0.63, p = 0.01) - Statistical significant heterogeneity among the trials [($\tau^2 = 2.76$ (df = 5) p = 0.003; $I^2 = 72\%$)] <p>•Headache:</p> <ul style="list-style-type: none"> - Rate of headache was 4.8% in the BT group compared with 27.9% in the TN group - Random effects analysis the difference was statistically significant (pooled OR = 0.10, 95% CI 0.02, 0.60, p = 0.01) - Statistically significant heterogeneity among the trials [($\tau^2 = 3.38$ (df = 5) p = 0.006; $I^2 = 69\%$)] 	

Evidence Table: Safety

Question: Is it Botox Injection SAFE for anal fissures treatment?

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
<p>21. Bobkiewicz A, Francuzik W, Krokowicz L, Studniarek A, Ledwosinski W, Paszkowski J, Drews M & Banasiewicz T. Botulinum Toxin Injection for Treatment of Chronic Anal Fissure: Is There Any Dose-Dependent Efficiency? A Meta-Analysis. World J Surg. 2016; 40: 3064-3072</p>	<p>- Meta-Analysis Inclusion: • Diagnosis of chronic anal fissure • Prospective character of the study • Simple botulinum toxin injection without any other interventions • No previous treatment with botulinum toxin</p>		<p>1577 patients from 34 prospective studies</p>	<p>Botulinum Toxin (BT) injection 2 types of formulation: Botox formulation or Dysport Injection</p>	<p>none</p>	<p>Mean time of followed up 4 to 156 weeks after BT injection Botox formulation vs Dysport formulation (28.9 ± 42.6 vs 10.2 ± 2.1 weeks)</p>	<p>RESULTS Complications a. Local post-operative complications - Most common: Hematoma, perianal thrombosis or perianal abscess (No statistical correlation between amount of BT injections and number of complications) - No significant difference in post-operative complication rate between Botox and Dysport formulation b. Transient faecal incontinence - 79 patients (5.01%) (51 patients in Botox and 28 in Dysport formulation) - All cases resolved within a couple of weeks (1 to 8 weeks) - No statistical correlation between amount of BT injection and frequency of incontinence - No significant difference when compared Botox and Dysport groups regarding the incontinence rate</p>	

Evidence Table: Safety

Question: Is it Botox Injection SAFE for anal fissures treatment?

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
22. Yiannakopoulou E. Botulinum Toxin and Anal Fissure: Efficacy and Safety Systematic Review. Int J Colorectal. 2012; 27:1-9	Systematic Review Obj: to investigate the efficacy and safety of BTA in the treatment of anal fissure		21 studies	Botulinum Toxin A	Placebo Lidocaine Nitrates Surgery		<p>SAFETY</p> <p>Included 10 articles for safety²⁹⁻³⁹</p> <ul style="list-style-type: none"> - Generally low frequencies of ADR reported - Temporary incontinence to flatus in approximately 10% of patients and to liquids and feces in approximately 5% of patients - Perianal hematoma and perianal thrombosis →Jost et al: 5/26 female patients treated with BTA into external anal sphincter, perianal pain disappeared in 1st 2 days after injection but returned with greater intensity a few days later³⁵ - Thrombosis of external haemorrhoids, prolapse of internal haemorrhoids and perianal abscess - Long term incontinence in 2 studies³⁷⁻³⁸ - Fourniere gangrene has been reported after BTA injection in 1 patient that having DM³⁹ - Contraindications: hypersensitivity case, pregnancy, neurological disease including myasthenia, Lambert Eaton Syndrome and Amyotrophic lateral sclerosis and co-administration with aminoglycosides may enhanced the action of BTA 	

COST

Evidence Table: Cost

Question: Is it Botox Injection COST-EFFECTIVE for anal fissures treatment?

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
<p>23. Brisinda G., Bianco G, Silvestrini N & Maria G. Cost Consideration in the Treatment of Anal Fissures. Expert Rev. Pharmacoecon. Outcomes Res. 2014; 14(4): 511-525</p>	<p>Cost Analysis</p>						<p>Effectiveness of various treatment for anal fissure</p> <p>a) Surgery</p> <ul style="list-style-type: none"> - Lateral internal sphincterotomy (LIS) → Most common treatment for AF → although Eisenhammer's technique: simple and effective but potential to cause minor and often permanent, alterations in the control of gas, mucus and occasionally stool → Gold standard treatment → Healed and relieved symptoms in 96% of cases but incontinence occurred frequently → SR & MA showed overall incontinence disturbance rate after internal sphincterotomy was 14% → Weighted analysis showed flatus incontinence in 9% soilage/seepage in 6%, accidental defecation in 0.9%, incontinence to liquid stools in 0.6% and incontinence to solid stool in 0.8% of patients → Open or closed technique used, it does not seem to influence incontinence rate → Caution: for elderly patients or those with diarrhoea, irritable bowel syndrome, diabetes or recurrent fissure after previous surgery - Anal dilatation: non-standardized uncontrolled 	

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
							<p>procedure</p> <ul style="list-style-type: none"> → Disrupts and may lead to permanent damage of the sphincter mechanism → Healing rate of 40 – 70% → Recurrence rates of up to 56% → Reports of incontinence to flatus and soiling in 39% and fecal incontinence in 16% → Recent study found that LIS was superior to anal dilatation in terms of healing and poses less of a threat to continence <p>b) Chemical Sphincterotomy</p> <ul style="list-style-type: none"> - Accepted as 1st line treatment for CAF in many centres - 1st line surgical approach was difficult to justify - To lower anal pressure and heal fissures - Surgical approach to F was reserved for patients who have tried medical treatment for at least 1-3 months but have failed <p>c) Nitrite Oxide (NO) donors</p> <ul style="list-style-type: none"> - Promote AF healing by increasing local blood flow in 2 ways: <ul style="list-style-type: none"> → Reducing intra-anal pressure → Vasodilatory effect on anal vessels - GTN and isosorbide dinitrate are metabolized at cellular level to release NO and have shown to heal CAF - GTN 	

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
							<ul style="list-style-type: none"> • The dose of GTN has not been standardized → various effects with various dose (e.g. 0.2%GTN ointment 2-3 time daily for 8 weeks healed 2/3 CAF; 0.2% GTN ointment decrease resting pressure by 33% and induced an increase anodermal blood flow → high dose has no more efficacious • Not permanent benefit • GTN ointment significantly reduced pain within 5 minutes of application → healing rate of 33% - 68% • Adverse Event/Limitations: transient headache (19% - 58%), burning sensation in the anus, poor patient compliance (62%) because the adverse event interfered with quality of life, drug tolerance, and nitrates side effects such as headaches and tachyphylaxis • No correlation between plasma GTN concentration, resting anal pressure and the onset, duration of intensity of head ache - Isosorbide Dinitrate <ul style="list-style-type: none"> • If 1% ointment applied every 3 hr throughout the day → healing 30 of 34 patients • If 1.25 or 2.5mg applied 3 times daily →healing 34 of 41 patients <p>d) Calcium channel antagonists (CCB)</p>	

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
							<ul style="list-style-type: none"> - Diltiazem and nifedipine: block slow L-type calcium channels in vascular smooth muscle and recently has shown lowering resting anal pressure presumably by similar action on the IAS smooth muscle - Nifedipine <ul style="list-style-type: none"> • 20mg sublingual nifedipine (at 30 min) 32% (AF patients) and 24% (normal volunteers) reduction in anal pressure, without any significant effects on blood pressure or heart rate • Oral dose of 20mg nifedipine twice daily showed 36% fall in mean anal resting pressure and healing was achieved by 8 weeks in 9 of 15 treated patients - Diltiazem <ul style="list-style-type: none"> • Topical diltiazem (2 cm of 2% gel / 0.7g 3-times daily for 8 weeks): healed 65-75% of CAF <ul style="list-style-type: none"> → significant decrease in pain score; p = 0.002 → significant decrease in resting anal pressure; p = 0.0001 than baseline value → No headache are other side effect reported • Oral Diltiazem: • Side Effects: compared with GTN; GTN vs Diltiazem → headache more in GTN group; p = 0.01 → inconclusive results for healing rates and improvement rates in both group → no significant 	

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
							<p>difference</p> <ul style="list-style-type: none"> •Require multicentre RCT to further validate the studies conducted with small sample size <p>e) Botulinum Toxin A</p> <ul style="list-style-type: none"> - Difference study has difference finding •Double-blind study: success rate of 76% was achieved following a single treatment with 20 units •Prospective study: comparing 2 doses (15 units and 20 units) → healing rate higher in 20 units; negligible side effects and no complications •AF healing was induced more efficiently and IAS hypertonia alleviated more effectively by BT treatment than by GTN •Recent study found that healing rate did not significantly differ when the total dose of BT and number of injection sites varied •Site of injections: posterior AF have better results when BT injected anteriorly into IAS •Anteriorly placed injections include a higher fall in resting pressure and improve clinical outcome •Different BT formulations give similar efficacy and tolerability <p>Cost Saving Effect of Algorithm</p> <ul style="list-style-type: none"> - The authors come out with a few approaches 	

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
							<p>i. Brisinda Approach - Used BT injection in all cases, surgery for the failures</p> <p>ii. Nelson Approach - Used of LIS to cure all patients</p> <p>- Statistical examination were based on prospective trial of 67 AF patient symptomatic for longer than 3 months treated using multi-step approach</p> <p>→ Nitroglycerin application successful in 43.2%, → then 3 patients required surgery,</p> <p>→ subsequently BT effective in 28 of 33 patients (84.8%) while the</p> <p>→ overall surgery rate was 11.9%</p> <p>- Based on above data the cost for treating CAF was:</p> <ul style="list-style-type: none"> • Nitroglycerine ointment: US\$10 • BT vial US\$528 (meanwhile injection procedure cost US\$148) • Surgery procedure: US\$1119 • Total cost for 67 patients: US\$33,282 (included US\$290 for nitroglycerine, US\$20,580 for nitroglycerine + BT + LIS, considering that BT vial was used for all patients • Based on same healing rate, and Brisinda approach (injection for 67 patients and BT + surgery in non-responders that were 15.2% of cases), the total cost rises to US\$56,688 (70.3% increased comparing with the algorithm approach) → the calculation was performed by assuming that BT vial containing 	

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
							100units was used for every patient thus a cost US\$45,292 for BT treatment → if 40 IU of BT used for every patient, the BT cost reduced to US\$24,066 thus Brisinda approach will decreased to US\$45,292 → an increase of 36% compared with multistep approach	