Botulinum Toxin A Use in the Gastrointestinal Tract: A Reappraisal After Three Decades

إعادة تقييم استخدام البوتوكس في الأنبوب الهضمي بعد ثلاث عقود

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Introduction

- Botulinum toxin A (BTX) is produced by Clostridium botulinum and is a neurotoxin that causes flaccid paralysis by inhibiting the release of acetylcholine from axonal endings at the neuromuscular junction.
- Since its first clinical use in 1973, the discovery of BTX as a therapeutic option has led to several advances in treating a multitude of neuromuscular, urologic, gastrointestinal (GI), and dermatologic disorders, among others.

- Over the past 30 years, research on BTX use in the GI tract for a variety of disorders has continued to grow, particularly in areas of motility and spastic disorders such as achalasia, diffuse esophageal spasm (DES), gastroparesis, sphincter of Oddi disorders, chronic anal fissures (CAFs), and pelvic floor dysfunctions.
- It has also garnered much interest in disorders such as obesity.
- This presentation reviews the current literature on the use of BTX in different regions of the GI tract.

Cricopharyngeal Dysphagia

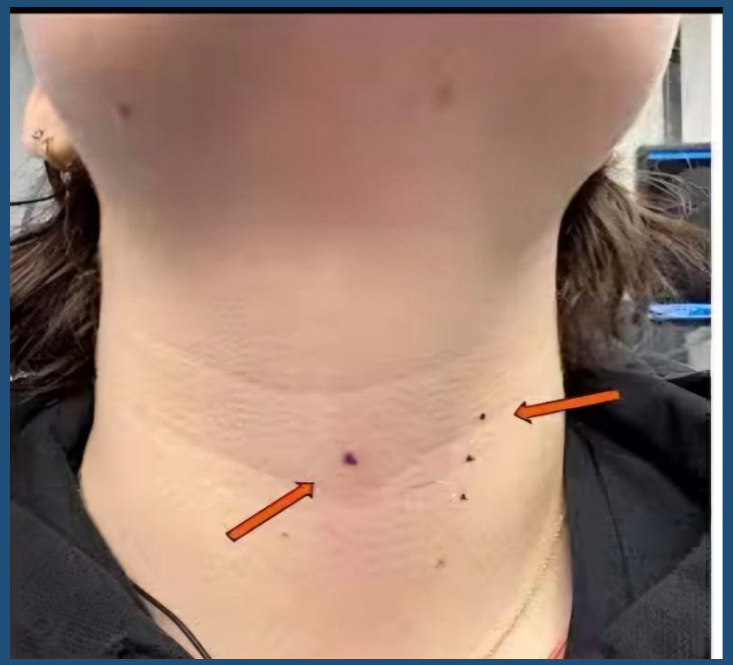
BTX use in Cricopharyngeal Dysphagia

- BTX has been shown to have efficacy in treating cricopharyngeal dysphagia in several small case series.
- Techniques :

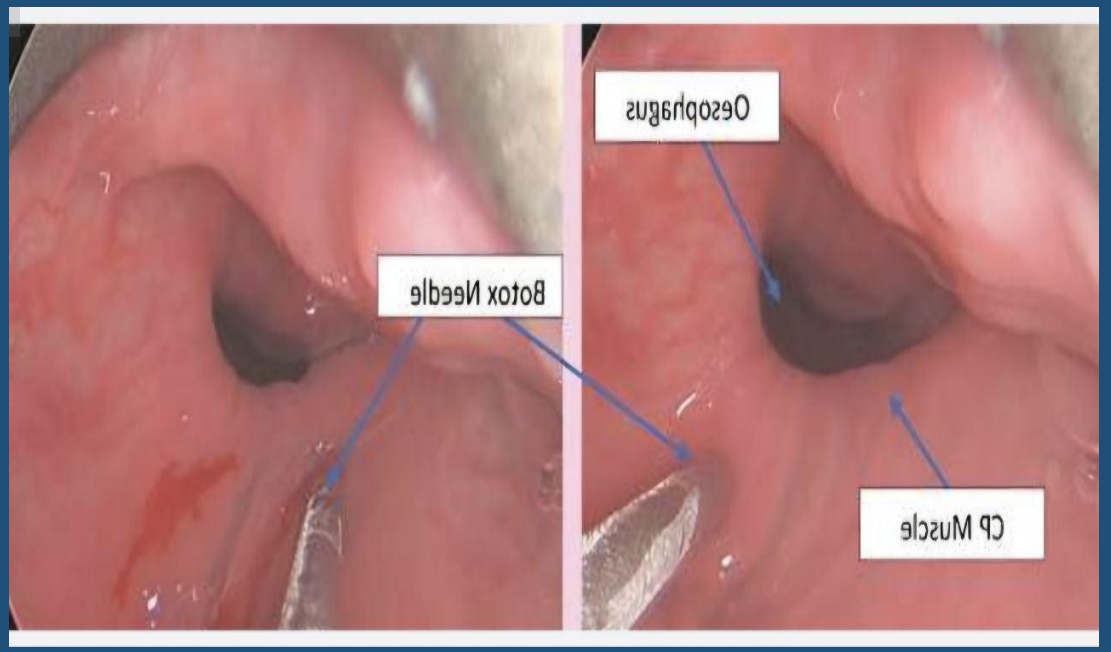
✓The endoscopic technique uses a standard adult flexible upper endoscope with a 5-mm sclerotherapy needle to deliver 3 to 4 injections of BTX 25 units (U)/mL or more into the cricopharyngeus muscle ..

✓In office BTX injection with differing doses .

In office injection



Endoscopic injection



BTX use in Cricopharyngeal Dysphagia VS Myotomy

- Using BTX in cricopharyngeal dysphagia was intended to be an alternative to myotomy, as BTX appears to have a lower risk of complications and decent success.
- A comprehensive systematic review published in2016 examined more than 500 studies on the use of myotomy, BTX, and dilation in cricopharyngeal dysphagia.

✓Logistic regression analysis of patient-weighted averages found that the success rate of BTX injection was 69%, but the success rate of myotomy was higher (78%; P=.042) .

✓ The success rate of dilation was not statistically different from that of myotomy or BTX (P values of .37 and .42, respectively).

BTX use in Cricopharyngeal Dysphagia VS Myotomy

- Ultimately, BTX injections can be considered as

✓An alternative to surgical myotomy in patients who are not optimal surgical candidates or who seek only temporary relief of symptoms.

✓ BTX can also be used as a potential diagnostic test to predict response to surgical myotomy. if patients had good clinical response they would likely benefit from repeat BTX injections or cricopharyngeal myotomy. However, if there was no radiographic or clinical improvement, a stricture would be suspected and surgery considered.

Achalasia

Achalasia : Treatments

- Treatments for achalasia include surgical myotomy, per-oral endoscopic myotomy (POEM), endoscopic pneumatic dilation (PD), and BTX injection.

✓Although surgical myotomy is a durable option, it is associated with a higher likelihood of complications in patients who are high-risk surgical candidates.

✓ POEM is also durable but can be associated with iatrogenic gastroesophageal reflux disease.

✓ PD has shown to be cost-effective, although it is less durable than POEM or

✓Heller myotomy (HM), and has a small risk of causing esophageal perforation.

✓ In patients with achalasia who are not ideal candidates for invasive procedures, BTX injections can be a viable option, particularly for type 2 achalasia. It was less effective in types 1 and 3 achalasia.

BTX in Treatment of Achalasia

- Many studies showed that, in the short term, BTX can have equitable outcomes in comparison with other modalities with a lower incidence of complications; however, BTX has a higher rate of relapse in symptoms, and PD, HM, and POEM have more long-lasting efficacy.
- Patients older than 50 years have higher response rates to BTX injections compared with younger patients for unclear reasons (82% vs 43%, respectively). Thus, in this age range, BTX can be a safe and
- effective alternative that yields a good quality of life in a large portion of patients without risks of major complications.
- In patients who failed prior PD or HM, BTX injections resulted in improvement in 75% of patients. Although the duration of symptom relief was shorter , repeat injections of 100 U into the LES increased remission time.

BTX in Treatment of Achalasia

- Techniques of BTX injecting :

✓Injecting 100 U in 4 quadrats .

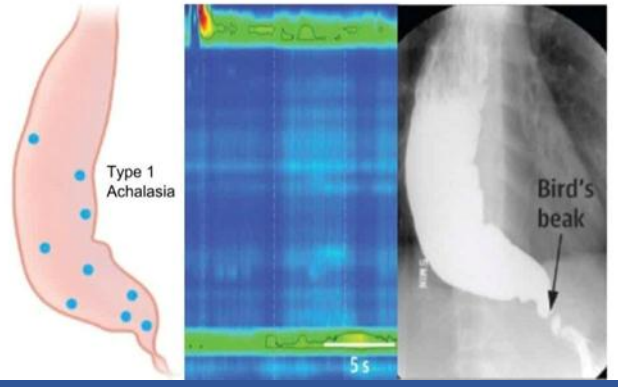
✓ injections into 4 quadrants at 2 different levels in the lower esophageal sphincter (LES) region and below the gastroesophageal Junction.

✓ endoscopic ultrasound–guided injections .

✓manometry-guided injections.

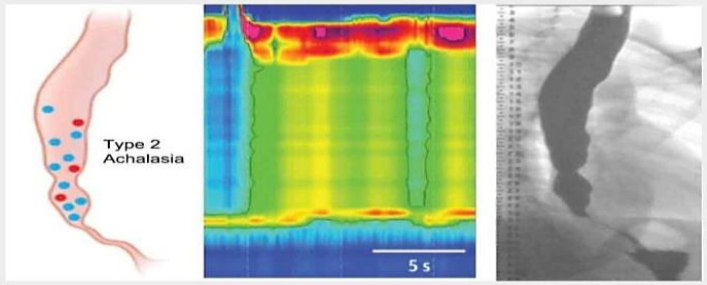

Botox Injection
تمّ تكبير الفيديو لملء الشاشة بأكملها
G. S. Raju, MD

Type 1 shows no motility in the oesophagus and the presence of a high-pressure band near the lower oesophageal sphincter level.



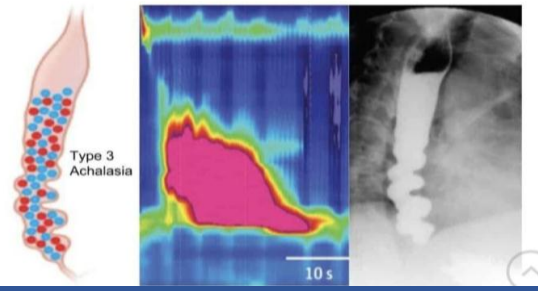
Type 1

In type 2, the lower oesophageal sphincter is always non-relaxed and simultaneous contractions occur throughout the body of the oesophagus while a person swallows. This type is the one that responds best to endoscopic therapy.



Type 2

Type 3 achalasia is typically characterised by high-pressure spasms in the oesophagus. This type is also most commonly prone to chest pain that can be difficult to control. The new POEM procedure might have particular value in treating this type of achalasia.



Type 3

BTX in Treatment of Achalasia

- Overall, in achalasia, BTX is recommended for patients who are
- Poor medical candidates for definitive treatment (eg, patients who are elderly, with multiple comorbidities, previous therapeutic failure) .
- Or as a transient treatment for very acute cases (eg, total outlet
- obstruction).
- BTX can help predict who may respond well to alternative treatments such as PD or HM .
- when used synergistically with other therapies, it does not increase remission time significantly.
- It is also not effective in type 3 achalasia.

Nonachalasia Motility Disorders

BTX in Nonachalasia Motility Disorders

- The use of BTX has been explored in nonachalasia motility disorders such as DES, hypertensive peristalsis (previously known as nutcracker esophagus), and isolated hypertensive LES .

BTX in Nonachalasia Motility Disorders

- In 2013, a prospective controlled trial of 22 patients with DES or hypertensive peristalsis compared BTX injection (100 U) vs placebo for improvements in dysphagia and noncardiac chest pain. The BTX group had significant improvement with sustained results in 50% of patients at 1-year follow-up, compared with the placebo group.
- In other studies, BTX injections showed improvement in dysphagia but not in heartburn or chest pain. There has been variable response with esophagogastric junction outlet obstruction and noncardiac chest pain in small retrospective studies.
- Some case reports describe the benefits of BTX injections in the management of hypertensive LES , showed a 50% reduction in noncardiac and nonreflux chest pain in 75% of patients for an average of 7.3 months.

BTX in Nonachalasia Motility Disorders

- 2016 RCT of 67 patients evaluated BTX injections as a prophylactic way of preventing esophageal strictures after endoscopic submucosal dissection (ESD) of esophageal squamous cell carcinoma. BTX significantly reduced the development of strictures compared with ESD alone (6.1% vs 32.4%, respectively; P<.05). Thus, BTX injections may be effective in preventing post-ESD esophageal strictures.
- These findings are promising; however, they need to be substantiated with larger RCTs.

Gastroparesis

BTX in Gastroparesis :

- Classifications include idiopathic gastroparesis (IG), diabetic gastroparesis (DG), and postsurgical states. Injection of BTX into the pylorus was hypothesized as a way to improve gastric emptying.
- Early open-label trials showed a significant reduction in symptoms in patients with DG and improvements in gastric emptying at varying intervals from 4 to 12 weeks. However, these trials tended to be low-powered and lacked randomization or control groups.
- In 2007 and 2008, 2 randomized, double-blinded, placebo-controlled trials compared BTX injections with placebo saline injections and showed no statistical significance in the difference between the 2 groups in symptom improvement or solid-phase gastric emptying time.

BTX in Gastroparesis : which subgroups ?

- Studies have attempted to identify which subgroups of gastroparesis patients may be more responsive to intrapyloric BTX injections.
- A large retrospective analysis consisted of 179 patients who received intrapyloric BTX injections for gastroparesis over a 7-year period (DG, n=81; IG, n=76; BTX dose, 100-200 U).
- More than half (51.4%) had symptom relief and weight improvement, whereas 32% had no benefit.
- Factors for better response included higher doses of injection, female sex, age less than 50 years, and etiologies not involving diabetes or surgery ($P<.05$).
- Response to repeat injections (87 total) was similar between patients who responded to the first injection and those who did not

BTX in Gastroparesis : which subgroups ?

- In 2017, Wellington and colleagues evaluated 33 gastroparesis patients with a suspected etiology of pylorospasms with normal gastric myoelectric activity.
- BTX 100 U was injected intrapylorically, and symptomatic improvement was seen in 78% of patients (P<.04).
- This could suggest that there is a subset of gastroparesis patients that may respond well to BTX injections, but further studies are needed.

Obesity

BTX in Obesity

- It is hypothesized that BTX injection into the gastric antrum can relax gastric smooth muscle, thereby delaying propulsion of food into the duodenum, which leads to early satiety and thus reduces dietary take and causes weight loss.
- Multiple RCTs have had mixed results. Studies have evaluated injection of BTX in varying locations of the stomach (ie, gastric angulus, antrum, or a combination of antrum and fundus) at differing doses(100-500 U) vs placebo.
- Many RCTs evaluating injection into the antrum or angulus found weight loss to be comparable between the BTX and placebo groups.

- Injection into the fundus could reduce gastric emptying and gastric accommodation, thereby increasing early satiety and decreasing oral intake.
- In summary, the limited number of studies investigating the effects of BTX on weight loss in obese patients have at best shown equivocal results. The variability maybe owing to small sample sizes and differences in location of injection, dosing, or operator skill.
- A higher-powered, randomized, double-blind, controlled trial is needed to evaluate this possibility.
- With no apparent serious adverse effects related to its use, BTX still appears to be an attractive option to some doctors, but currently cannot be routinely recommended.

Sphincter of Oddi Disorders

- According to the Rome IV criteria, there are 2 subtypes: functional biliary sphincter of Oddi disorder and functional pancreatic sphincter of Oddi disorder.
- In functional biliary sphincter of Oddi disorder, there is biliary pain associated with either elevated liver enzymes or a dilated bile duct (not both) and there are no biliary stones or structural abnormalities.
- In functional pancreatic sphincter of Oddi disorder, there must be recurrent episodes of pancreatitis, exclusion of other causes of pancreatitis, negative endoscopic ultrasound findings, and abnormal sphincter manometry.

Table 1.
Modified Milwaukee Classification System (13)

SOD Type	*Definition*
Type I	Pain + abnormal hepatic or pancreatic enzymes on 2 occasions + dilated common bile duct/pancreatic duct
Type II	Pain + either abnormal enzymes or dilated common bile duct/pancreatic duct
Type III	Pain alone

Sphincter of Oddi Disorders : TREATMENTS

- Endoscopic sphincterotomy is the standard of treatment but is considered a high-risk procedure that is not consistently effective.
- Thus, BTX, hypothesized to be a safer alternative .
- Additionally, the role of BTX in predicting response to sphincterotomy has been evaluated.

BTX in Sphincter of Oddi Disorders : TREAT.& PREDICTING

- A large study of 22 patients looked at BTX's effectiveness in type III SOD (using previous Milwaukee criteria) . A single injection of BTX 100 U was inserted at the sphincter of Oddi,

✓ 55% of patients responded to treatment with 92% remaining asymptomatic at 6months.

✓Eleven of 12 patients who had a recurrence of symptoms were treated with sphincterotomy and had long-term resolution of symptoms at 15 months.

- Of the 10 patients who did not respond to initial BTX injections,

✓ 5 had normal sphincter pressures and did not respond to sphincterotomy,

✓ 2 of the 5 with sustained sphincter hypertension benefited from subsequent sphincterotomy .

BTX in Sphincter of Oddi Disorders : post– (ERCP) pancreatitis

- Patients with SOD who underwent biliary sphincterotomy had a higher risk of developing post– (ERCP) pancreatitis thought to be secondary to residual pancreatic sphincter hypertension.
- A study in 2004 looked at BTX injection injection into the pancreatic sphincter of patients after biliary sphincterotomy :

✓ found some reduction in post-procedure pancreatitis.

✓ However, it was not statistically significant (P=.34).

✓ Although these data may support a proof of concept for BTX, type III SOD is no longer a recognized entity for which ERCP is indicated.

BTX in Sphincter of Oddi Disorders : recurrent pancreatitis

- A study looked at the efficacy of BTX in preventing recurrent pancreatitis owing to SOD in 15 women with recurrent pancreatitis with manometric evidence of SOD. Patients were treated with a single injection of BTX 100 U into the ampulla of Vater, and the effectiveness of treatment was monitored over 3 months.

✓ Twelve patients (80%) remained asymptomatic at 3-month follow-up; however,

✓11 patients developed recurrent symptoms at 8 months and underwent pancreatic or biliopancreatic sphincterotomy with long-term remission at 15 months.

✓ Of the 3 patients who did not respond to therapy, 1 showed manometric evidence of elevated pancreatic sphincter pressure and benefited from pancreatic sphincterotomy.

- However, 3 months for follow-up is a short time frame for making substantial conclusions given that recurrent acute pancreatitis may occur as often as every 2 years.

BTX in Sphincter of Oddi Disorders : acalculous biliary pain

- In acalculous biliary pain, BTX injections have been used for relaxing the sphincter of Oddi.
- One study found that in 25 patients with acalculous biliary pain,

✓44% had a positive response to injection of BTX 100 U into the sphincter of Oddi.

✓All of these patients who underwent sphincterotomy had resolution of pain.

✓ Of those who did not respond to BTX, only 80% improved with sphincterotomy.

- BTX injections into the sphincter of Oddi may help direct therapy for patients with acalculousbiliary pain.

BTX in Sphincter of Oddi Disorders : postoperative pancreatic fistula after distal pancreatectomy.

- In a prospective clinical phase 1/2 trial in 2017, preoperative BTX injection into the sphincter of Oddi was used as a novel approach to reduce the incidence of postoperative pancreatic fistula after distal pancreatectomy.
- None of the 29 patients injected with BTX had clinically relevant fistulas, compared with 33% of the case-control patients (P<.004).

Chronic Anal Fissures

Chronic Anal Fissures : TREATMENTS

- . Treatments can include topical nitroglycerine, oral nifedipine, BTX injections, or lateral internal sphincterotomy (LIS).
- Many studies have looked at the effectiveness of BTX injections vs placebo or alternative non invasive treatments for CAFs

BTX FOR CAF : LOCATIONS , NUMBERS , DOSAGES

- location impacts the effectiveness of healing has also been studied. One theory is that the internal anal sphincter (IAS) has fibrosis at these site of posterior fissures that may delay healing. Patients who received anterior injections of BTX had lower resting IAS pressures and faster healing compared with patients who received posterior injections (88% vs 60%, respectively; P=.025).
- Increasing the number of injections (bilateral injections vs a single injection) did not significantly affect outcomes.
- The optimal dosage for BTX injections remains unsettled for symptom improvement despite multiple small studies.
- A 2016 meta-analysis analyzed dose-dependent efficiency of BTX (5-150 U) among 1577 patients over 34 prospective studies and found no significant difference in terms of effectiveness, postoperative complications, or healing rates. There was no significant correlation between dose and recurrence of symptoms or between dose and long-term efficacy of treatment.

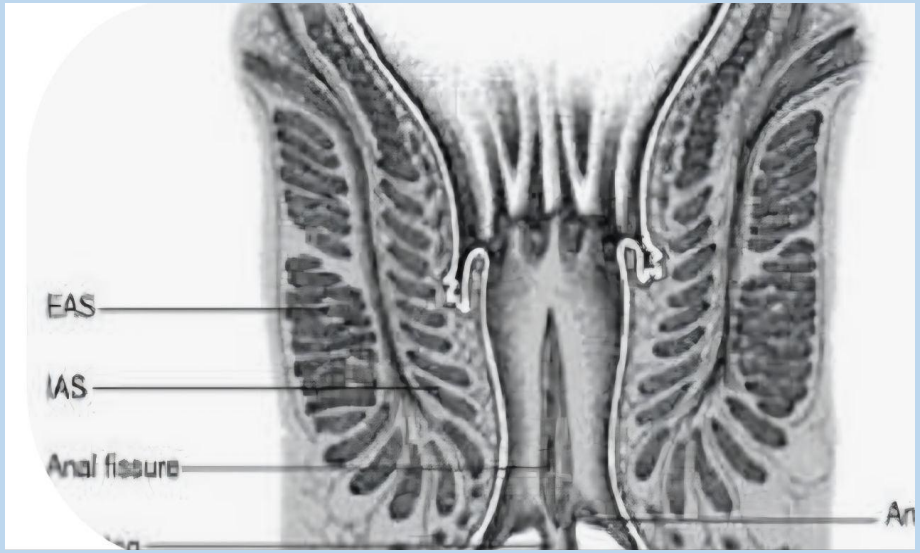
BTX VS. LIS IN CAF

- Although the gold standard for CAFs is LIS, BTX can be a safer alternative with lower risk of side effects (eg, anal incontinence, bleeding, pain, abscess, fistula) and faster healing times. ;however, long-term efficacy is lower.
- In patients with a history of LIS and recurrent anal fissures, BTX can be used therapeutically and diagnostically to identify those who would not be suitable for further surgical LIS if transient fecal incontinence developed

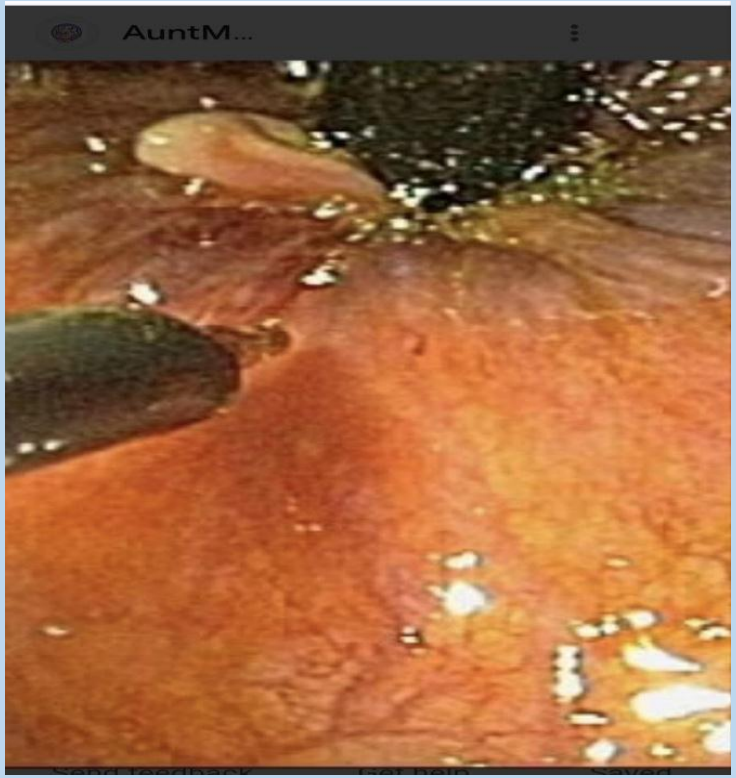
BTX VS LIS FOR CAF

- BTX may be an option in patients who are not optimal candidates for LIS or for those who prefer less-invasive forms of treatment.
- BTX is a viable treatment modality for elderly patients, those who have a higher risk of fecal incontinence with surgery, those who prefer to avoid surgical management, and those with a history of prior sphincterotomy.
- When BTX's effect wanes, repeat injections can be offered. Its short-term response rate is often greater than 60%, symptoms tend to improve with retreatment, and it can be more cost-effective given the unforeseen costs of treating potential complications of surgery.

Anatomy of anal canal



Endo . Injecting BTX for CAF



BTX VS. OTHER TREAT. IN CAF

- In several studies, BTX injections were more effective than placebo or nitroglycerine ointment Or 0ral nifedipine ,and had fewer side effects.
- . Results were also statistically better with a combination of BTX and oral nifedipine compared with nitroglycerine .

Chronic Idiopathic Anal Pain

BTX IN CHRONIC IDIOPATHIC ANAL PAIN

- BTX has been studied in chronic functional anorectal pain.
- In a study evaluating 113 patients at a tertiary proctology clinic, patients with hypertonia of the anal sphincter received 2 injections of BTX 30 U and patients with hypertonia of the levator ani received 2 injections of 40 U. If hypertonia was present in both areas, patients received both treatments.
- Of those patients who received both treatments, 47% had complete resolution of pain,20% had temporary resolution with relapse within 3 months, and 33% had poor or no response to therapy.

Anismus (pelvic floor dyssynergia)

- Anismus (also known as pelvic floor dyssynergia) can lead to chronic severe constipation via outlet Obstruction. defecation.
- Treatments :

✓ The mainstay of is typically biofeedback, which leads to improvement in up to 70% of patients.

✓ Surgery is not an effective treatment.

✓There is some evidence that BTX use in these patients can be effective.

BTX AS A TREATMENT OF ANISMUS

- In 2006, 15 patients with anismus received onabotulinumtoxinA 25 U into the EAS; improvement was seen in 87% of patients with an average remission time of 4.8 months.
- Similar results were seen in a prior study evaluating BTX injections into the EAS for non-relaxing puborectalis syndrome.

BTX AS A TREATMENT OF ANISMUS

- 5 studies used lateral EAS injections, whereas 2 studies used a combination of lateral and posterior injections. A median injection of 100 U resulted in improvement in 77.4% of patients at 1 month (measured via balloon expulsion test, EMG, and defecography).
- However, that number rapidly dropped to 46% at 4 months, with 7.4% developing complications after injection.
- Thus, although initial improvement can be seen, there tends to be a rapid deterioration of effect by 4 months.
- However, it may be possible to combat this with repeat injections.
- Larger studies are needed.

BTX & BIOFEEDBACK IN ANISMUS

- The combination of BTX and biofeedback training can be effective.
- A 2014 study looked at 31 patients with anismus who failed simple biofeedback training .
- The researchers administered BTX 100 U into the puborectalis muscle and EAS consecutively during needle withdrawal and then provided biofeedback training 2 weeks after injection.
- Twenty-three of the patients had success and reported satisfaction throughout an 8-month period.

BTX in Outlet-type Constipation (exp.PARKINSON D.)

- In patients with Parkinson disease and outlet-type constipation secondary to focal dystonia of the pelvic floor.
- BTX injections led to improvement in 55% in terms of symptoms, anorectal manometry, and defecography.
- However, the study's results were weak in strength owing to its small size (N=18) and lack of a placebo group.

BTX in anterior rectoceles

- In 2001, an open-label study of 14 women with anterior rectoceles treated with ultrasound-guided BTX injections found that 64% had symptomatic improvement, and there was a significant reduction in rectocele depth (4.3 cm to 1.8 cm; P<.05).
- At 1 year, no patients required digital assistance to defecate and had evidence no of rectocele on digital examination, although 28.5% had defecographic evidence of a rectocele.

Postsurgical Haemorrhoidectomy Pain

- Postsurgical haemorrhoidectomy pain is thought to be secondary to spasms of the IAS , and last about 3 to 4 weeks .
- The purpose of BTX injection in postsurgical haemorrhoidectomy pain is to relax the IAS, thereby relieving pain.

BTX for Postsurgical Haemorrhoidectomy Pain

- In a double- blind RCT of BTX use in postsurgical hemorrhoidectomy pain, 50 patients were randomized into treatment and placebo groups for injection of BTX (20 U) vs saline.

On postoperative days 6 and 7, there was a significant improvement in pain compared with the placebo group ($P<.05$).

- Similar studies give the same results .

BTX for Postsurgical Haemorrhoidectomy Pain

- Overall, the use of BTX in postsurgical haemorrhoidectomy pain can be useful for decreasing symptoms up to 1 week after the procedure, including pain at rest and with defecation; however, there is some possibility of transient side effects, including flatus that may persist for up to 3 months.
- BTX may be a good option in patients with poor compliance to medical therapy postoperatively.

BTX VS. GTN. in Postsurgical Haemorrhoidectomy Pain

- When compared with topical glyceryl trinitrate (GTN), BTX is superior at 7 days for maximal relief of anal pain at rest and for overall analgesic required. Both are equally efficacious at reducing pain scores on defecation, and there was no significant difference in wound healing time.
- However, topical GTN had more side effects, including increased headaches.
- Complications related to BTX injections involved transient incontinence (0%-33%) and typically involved flatus lasting 3 to 12 weeks.

Conclusion

- For 30 years, BTX has been studied as a treatment modality in a variety of GI disorders with varying results.
- The appeal of BTX comes from its simplicity of administration, good safety profile, reliability in decreasing muscular tone, and effective response rate in patients who have failed conventional therapies.
- However, there are several drawbacks that limit its use, including the lack of long-term efficacy in many GI disorders, which leads to repeat administrations, additional costs associated with multiple procedures, and unclear effect in certain disorders such as gastroparesis and obesity.
- Overall, BTX has well-established efficacy in achalasia, CAFs, and cricopharyngeal dysphagia.

Future for BTX uses in GI tract disorders

- Establishing larger well-designed randomized trials with less eterogeneity among patients and intervention techniques may allow for stronger support for or against BTX use in these disorders.
- Methods that could potentially prolong the duration of action of BTX injections or combine them with therapies that could target additional neuronal pathways in the GI tract would be worth investigating.
- Methodologically rigorous prospective studies are needed to define the exact role of BTX for some indications.

Thank you