Gastrointestinal Uses of Botulinum Toxin

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Contents

Abstract

Botulinum toxin (BT), one of the most powerful inhibitors that prevents the release of acetylcholine from nerve endings, represents an alternative therapeutic approach for "spastic" disorders of the gastrointestinal tract such as achalasia, gastroparesis, sphincter of Oddi dysfunction, chronic anal fissures, and pelvic floor dyssynergia.

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BT has proven to be safe and this allows it to be a valid alternative in patients at high risk of invasive procedures but long-term efficacy in many disorders has not been observed, primarily due to its relatively short duration of action. Administration of BT has a low rate of adverse reactions and complications. However, not all patients respond to BT therapy, and large randomized controlled trials are lacking for many conditions commonly treated with BT.

The local injection of BT in some conditions becomes a useful tool to decide to switch to more invasive therapies. Since 1980, the toxin has rapidly transformed from lethal poison to a safe therapeutic agent, with a significant impact on the quality of life.

Keywords

Achalasia · Autonomic nervous system diseases · Biliary diseases · Botulinum toxin · Cholinergic nerve ending · Enteric nervous system · Esophageal diseases · Fissures · Gastric emptying · Hirschsprung · Motility · Neuromuscular agents · Obesity · Spasm · Therapeutic agents

Local injection of botulinum toxin A (BT) is an effective treatment for many different diseases of the gastrointestinal tract because it inhibits contraction of smooth muscles and sphincters by blocking cholinergic nerve endings in the autonomic nervous system (ANS). Normal gastrointestinal (GIT) motility depends on intrinsic neurons contained in the enteric nervous system (ENS), with significant modulatory input being provided by the central nervous system (CNS) via autonomic sympathetic and parasympathetic nerves (Civelek et al. 1985; Albanese et al. 2000). Immediate control of muscle tone in the gut reflects a balance between both excitatory (predominantly cholinergic) and inhibitory (predominantly nitrinergic). In some disease states, this balance is disrupted, usually due to a relatively selective loss of inhibitory neurons (Poulain et al. 1988; Grumelli et al. 2010; Akaike et al. 2013). In this setting, BT, by blocking excitatory neurotransmitter release, can restore the balance and cause a decrease in the resting tone of the muscle involved.

The ENS provides the intrinsic innervation. It is a highly complex system, responsible for the coordination of motility in the GIT. A deficiency of enteric neurons causes obstruction and lack of intestinal propulsion (Miftakhov and Wingate 1993). The ENS is composed of two main ganglionated plexuses (Auerbach's myenteric plexus and Meissner's submucous plexus) and non-ganglionated plexuses (the longitudinal muscle plexus, the circular muscle plexus, the plexus of the muscularis mucosae, and the mucosal plexus) (Kuhn and Belafsky 2013). Intraparietal neurons encompass motor excitatory and inhibitory neurons, interneurons, and intrinsic sensory neurons. Sympathetic and parasympathetic neurons also innervate the GIT. ACh is the primary excitatory transmitter. Inhibitory motor neurons relax smooth muscles; these neurons release a combination of at least three transmitters: NO, adenosine triphosphate (ATP), and VIP (Albanese et al. 2000). At cellular level, smooth muscle contraction and relaxation are regulated by changes in cytosol calcium levels (Hansen 2003). These functions depend on the

intrinsic electrical and mechanical properties of GIT smooth muscles and are regulated by the ENS and by sympathetic and parasympathetic influences (Albanese et al. 2000). Hormones also influence GIT motility (Lourenssen et al. 2009). Interstitial cells of Cajal act as local pacemakers to generate the rhythmic activity of the circular muscle layer throughout the GIT. Motor neurons control the musculature indirectly, through their action on the Cajal cells. Substances, such as histamine, serotonin, adenosine, and eicosanoids, produced by nonneural cells, can influence smooth muscle activity (Walzer and Hirano 2008).

At esophageal level, muscle tone of the lower esophageal sphincter (LES) results from the interaction of neurogenic and myogenic conditions. Neurogenic tone in humans is partly due to cholinergic innervation. The modulation of LES tone is largely mediated through the vagus nerve. Acetylcholine (ACh) is the presynaptic neurotransmitter; postsynaptic transmission is mediated by NO, but vasoactive intestinal polypeptide (VIP) is also thought to contribute (Walzer and Hirano 2008).

At anal level, the sphincter complex consists of two overlapping sphincters (Brisinda et al. 2004b). The external anal sphincter (EAS) that forms the outer layer is composed of voluntary, striated, skeletal muscle. The internal anal sphincter (IAS) is the inner, involuntary, smooth muscle component. It is in a state of continuous maximal contraction, due to a combination of intrinsic myogenic and autonomic neurogenic properties. Being of visceral origin, IAS is supplied both by sympathetic and parasympathetic nerves; in addition, the ENS modulates its tonic activity (Albanese et al. 2000). Noradrenergic sympathetic nerves are considered excitatory and the parasympathetic inhibitory to the IAS. Vagal neurons do not act directly but rather form synaptic connections with neurons whose cell bodies are in the intrinsic GIT ganglia. This transmission is principally mediated by ACh acting on nicotinic receptors (Brisinda et al. 2007b). Recently, it has been shown that the longitudinal layer and the circular smooth muscle in the human rectum receive an intrinsic NO-mediated inhibitory innervation.

Although BT can clearly inhibit the release of acetylcholine, little else is known about its effects in GIT muscle. Thus, while nitric oxide (NO) release is not affected – which is to be expected, since this is not a vesicular process – the specific effects on other potentially important neurotransmitters have not been well documented (Mariotti and Bentivoglio 1996; Lepiarczyk et al. 2015). Further, there is some suggestion that it may also inhibit the responsiveness of smooth muscle to exogenous stimuli, an effect that is quite unique to the GIT.

1 Esophageal Applications

1.1 Cricopharyngeal Dysphagia

Dysphagia associated with failed relaxation of the upper esophageal sphincter (UES) has been observed in patients suffering from different types of neurological disease. The absent relaxation of the cricopharyngeal (CP) muscle during bolus swallowing prevents the UES from opening; consequently, the bolus cannot progress into the

esophagus. This may result in penetration or aspiration of ingested food into the airways. Many reports in the literature demonstrate that neurogenic dysphagia associated with UES spasms or dyskinesia can be effectively treated by injecting BT into the CP muscle (Alberty et al. 2000; Haapaniemi et al. 2001; Moerman 2006; Krause et al. 2008; Alfonsi et al. 2010; Regan et al. 2014) (Table 1). Most of these reports are case series formed by a low number of patients, and randomized control trials are lacking. Moreover, because of different methodological approaches, study designs, and outcome measures, the results obtained by different authors are not absolutely comparable. Indeed patient selection criteria vary greatly from study to study, and the same is also true for follow-up times: some authors have focused only on short-term safety and efficacy of BT treatment, while others have investigated long-term effects (Haapaniemi et al. 2001; Shaw and Searl 2001; Zaninotto et al. 2004a). A number of injection techniques have been employed including rigid endoscopy with electromyographic control, flexible endoscopy, and an open technique with various doses (10–50 units Onabotulinumtoxin A, Ona-A). Endoscopically, 3–4 injections of BT can be delivered to the dorsomedial and bilateral ventromedial compartments of CP muscle. CP injection of BT has distinct appeal in patients who are not ideal candidates for longer general anesthesia or in whom the temporary nature of BT injection is warranted. It may be advantageous to pursue CP injection of BT in patients in whom multilevel dysphagia is suspected and in whom the clinician suspects that there may be some detriment to treatment directed at the UES. Additionally, CP injection of BT is a diagnostic tool used to identify patients who may potentially benefit from CP myotomy (Kelly et al. 2013; Regan et al. 2014; Kuhn and Belafsky 2013; Blitzer and Brin 1997).

Only two series included more than 20 patients; the largest study included 34 patients. The causes of CP dysfunction in these published series encompassed several diagnoses, including neurological diseases, diabetic neuropathy, external-beam radiation treatment, cerebrovascular accident, and others. The dosage and administration techniques of BT were also quite variable (Kelly et al. 2013). There were also different types of BT administered (Kelly et al. 2013; Moerman 2006).

In general, the majority of patients reported improved swallowing function, approximately 75% in combined analysis. Complications were infrequent and included transient vocal fold paresis, temporary worsening of dysphagia, neck cellulitis, and aspiration pneumonia. There were no reported deaths in the literature that were directly related to CP injection of BT. Kelly and coworkers demonstrated that CP injection of BT is a well-tolerated treatment for dysphagia related to CP dysfunction, with good efficacy in the majority of their 49 patients (Kelly et al. 2013).

Alfonsi et al. enrolled 67 patients with neurogenic dysphagia associated with incomplete or absent opening of the UES (24 with brain stem or hemispheric stroke, 21 with parkinsonian syndromes, 12 with multiple sclerosis, and 10 with spastic-dystonic syndromes secondary to post-traumatic encephalopathy), and they were treated with the injection of incobotulinumtoxin A (Inco-A, Xeomin) (dose 15–20 U) into the CP muscle under electromyographic guidance. The patients were assessed at baseline and after the first and second treatment through clinical

Table 1 Review of the literature on the treatment of cricopharyngeal dysphagia with BT injection

Authors	Pts	Ona-A (Unit)	Abo-A (Unit)	Improvement	Method of delivery	Causes	Complications
Schneider et al. (1994)	7	80–120		5/7 (71%)	GA, EGD	Stroke, CN palsies, supraglottic or oropharyngeal cancer, reflux disease	None
Atkinson and Rees (1997)	5	5–20		4/5 (80%)	CT-guided injection	Stroke, CN palsies, bulbar palsy	Left vocal fold paresis, aspiration pneumonia
Blitzer and Brin (1997)	6	10		6/6 (100%)	Percutaneous injection	CVA, partial pharyngectomy, small Zenker's diverticulum	None
Brant et al. (1999a)	1	100		1 (100%)	Flexible EGD	CVA	None
Alberty et al. (2000)	10	30		10/10 (100%)	GA, EGD	CVA, idiopathic polymyositis	None
Shaw and Searl (2001)	12	25–50		10/12 (83%)	GA, EGD, open technique	Progressive neuropathy, oculopharyngeal dysphagia, skull base tumor resection, total laryngectomy, CVA, partial pharyngectomy, CNS neuropathy	Pharyngeal tear, worsening dysphagia
Haapaniemi et al. (2001)	4	14–50		3/4 (75%)	GA, EGD	Brain stem stroke, inclusion body myositis, peripheral motor neuropathy, CVA	None
Moerman et al. (2002)	4	100		4/4 (100%)	GA	Head and neck cancer resection including total laryngectomy, radiation	None
Parameswaran and Soliman (2002)	12	10–30		11/12 (92%)	EGD with mask ventilation and apneic technique	Idiopathic, radiation, CVA, total laryngectomy, ALS, Parkinson's disease	Neck cellulitis (concurrent thyroglossal duct excision)

(continued)

Table 1 (continued)

Authors	Pts	Ona-A (Unit)	Abo-A (Unit)	Improvement	Method of delivery	Causes	Complications
Zaninotto et al. (2004a)	21	4–10		9/21 (43%)	Percutaneous with EMG	CNS disease, peripheral neuropathies, idiopathic	Death of aspiration (attributed to underlying disease)
Liu et al. (2004)	2	100		2/2 (100%)	Flexible EGD under sedation	Inclusion body myositis	None
Chiu et al. (2004)	1		120	1/1 (100%)	GA and direct laryngoscopy	Brain stem stroke	None
Murry et al. (2005)	13	100		11/13 (85%) 2/13 improvement after second injection	EMG-guided transcutaneous approach	Stroke, head and neck surgery, cranial neuropathies, MVC, chemical inhalation, radiation therapy or lymphoma	None
Kim et al. (2006)	8	100		5/8 (62.5%)	Flexible endoscopy	CVA	None
Masiero et al. (2006)	2	25, 30		2/2 (100%)	Percutaneous injection	CVA	None
Restivo et al. (2006)	12		60	12/12 (100%)	EMG-guided transcutaneous approach	Diabetic neuropathy	None
Suzukia et al. (2007)	1	5		1/1 (100%)	Percutaneous injection	Spinal muscular atrophy type 2	Transient worsening of dysphagia
Krause et al. (2008)	1		180, 150	1/1 (100%) 0/1 (0%)	Endoscopic injection with propofol sedation	Spasticity secondary to SAH	None
Alfonsi et al. (2010)	34	15		17/34 (50%)	EMG-guided transcutaneous approach	MS, multiple system atrophy, Parkinson's disease, progressive supranuclear palsy, ataxia-telangiectasia	None

Restivo et al. (2011)	14	20		14/14 (100%)	Percutaneous injection with EMG guidance	MS	None

ALS amyotrophic lateral sclerosis, *CN* cranial nerve, *CNS* central nervous system, *CT* computed tomography, *CVA* cerebrovascular accident or stroke, *EGD* esophagogastroduodenoscopy, *EMG* electromyography, *GA* general anesthesia, *MVC* motor vehicle collision, *SAH* subarachnoid hemorrhage, *MS* multiple sclerosis, *Ona-A* onabotulinumtoxin A (Botox), *Abo-A* abobotulinumtoxin A (Dysport)

evaluation and fiber-optic endoscopy of swallowing, while their dysphagia was quantified using the Dysphagia Outcome and Severity Scale (DOSS). An electrokinesiographic/electromyographic study of swallowing was performed at baseline. Most patients responded to the first BT treatment: 35 patients (52.2%) were classified as high responders (DOSS score increase >2 levels), while other 19 patients (28.4%) were low responders (DOSS score increase of ≤2 levels). The effect of the first treatment usually lasted longer than 4 months (67%) and in some cases up to a year. The treatment efficacy remained high also after the second injection: 31 patients (46.3%) qualified as high responders, and other 22 patients (32.8%) showed a low response. Only in the parkinsonian syndrome group, they observed a reduction in the percentage of high responders as compared with the first treatment. Side effects were mostly mild and reported in non-responders following the first injection. A severe side effect, consisting of ingestion pneumonia, was observed following the second BT injection in two patients who had both been non-responders to the first (Alfonsi et al. 2017).

On the basis of these results, CP injection of BT appears to be effective in patients with UES dysfunction. Response to BT injection may select out a group of patients with higher likelihood of a more durable response to surgical myotomy (Allen et al. 2010). Further work, however, is needed to define the population of patients who might have a poor response to BT treatment. Furthermore, non-response may indicate another etiology of dysphagia, i.e., stricture.

1.1.1 Cricopharyngeal Achalasia (CPA) in Children

CPA is a condition characterized by an incomplete relaxation of the UES or by a lack of coordination of the UES opening with pharyngeal contractions (Drendel et al. 2013; Hussain et al. 2002). Both etiologies can lead to choking, cough, and aspiration. CPA is a different entity than the CP dysphagia that was seen in adults. Although an exact cause of CPA is unknown, it is considered to be associated with an immature neuromuscular system. Immaturity of the interstitial intraparietal cells of Cajal may explain why there have been reports of spontaneous resolution of CPA seen in infants (Scholes et al. 2014). CPA has also been associated with gastroesophageal reflux disease and CNS abnormalities (Kuhn and Belafsky 2013; Drendel et al. 2013; Hussain et al. 2002; Scholes et al. 2014; Shogan et al. 2014; Huoh and Messner 2013).

Recently, six children were identified with CPA (Drendel et al. 2013). The decision to proceed with BT therapy was based on ongoing severe symptoms, the necessity of altered feeds, and parent preference over a surgical myotomy. The number of injections ranged from 1 to 3 per patient. The mean dose was 5.6 units/kg of Ona-A, with a range of 1.6–7.9 units/kg and a median of 6.0 units/kg. In those patients with multiple injections, the mean time between injections was approximately 13 months. The mean time to return to normal radiographic swallow study was 8.2 weeks. Two of the children benefited from BT injections and went on to have CP myotomy, while four of the children did not require myotomy, and their symptoms resolved after one or two injections. The authors concluded that BT injection of CP muscle is a useful tool to help diagnose and treat CPA (Drendel

et al. 2013). It is a feasible alternative to more invasive surgical procedures. However, more research is needed to elucidate the optimal dosing, frequency of injections, and when to move on to surgical intervention.

1.2 Achalasia

The major pathophysiological lesion in achalasia results from a relatively specific loss of nitrergic inhibitory neurons of the LES, resulting in an inability of the sphincter to relax after swallowing (Woltman et al. 2005). This results in a functional obstruction and dysphagia. Although no cure exists for achalasia, there are a number of palliative treatments available including surgical myotomy, pneumatic dilation (PD), and BT injections into the LES (Tack and Zaninotto 2015; Maradey-Romero et al. 2014; Marjoux et al. 2014; Vela 2014; Mabvuure et al. 2014; Patti and Fisichella 2014). Surgical myotomy has proven durable but is associated with increased morbidity and mortality in high-risk surgical patients. Pneumatic dilation of the sphincter results in an initial symptomatic improvement in 60–90% of patients, but repeated dilations are often necessary. Furthermore, the procedure carries a small but significant risk of esophageal perforation (Leyden et al. 2014; Jung et al. 2014; Kim do and Jung 2014). Thus, BT provides a potentially attractive alternative to the above treatment methods (Vela 2014).

Endoscopic injection of 25 units of Ona-A BT in four LES quadrants is generally the standard of care. The efficacy of BT in achalasia has been proven by the results of several randomized trials comparing it to either placebo or pneumatic dilation. Table 2 summarizes the response rates to BT in patients with achalasia.

Most patients (75–100%) show an initial response, but more sustained improvement (beyond 6 months) is seen in about two-thirds. For unclear reasons, it appears that patients older than 50 years of age respond at a higher rate (82% vs 43% in younger patients). Similarly, patients with so-called vigorous achalasia (with the esophagus retaining some contractile ability) respond at a higher rate (100% vs 52% with classic achalasia).

Several studies have compared BT to pneumatic dilation with most reporting similar initial clinical or manometric responses. However, the 1-year remission rate after a single injection is markedly inferior for BT, which is to be expected given its pharmacological properties. In the only study comparing the two modalities in a head-to-head comparison, 80 patients were randomized to receive 100 BT Ona-A units or laparoscopic surgical myotomy with fundoplication. After 6 months, symptom scores improved more in surgical patients (82% vs 66%, $P < 0.05$). The drop in LES pressure was similar in the two groups; the reduction in esophageal diameter was greater after surgery (19% vs 5%, $P < 0.05$). The only complication in the surgical group was one patient bled at the trocar site. The probability of being symptom-free at 2 years was 87.5% after surgery and 34% after BT ($P < 0.05$). The same group investigated the cost-effectiveness of the two modalities and concluded that BT was more cost-effective in the short term, but at 2 years, cost between the two groups was similar. The results of a recent meta-analysis suggest

Table 2 Review of experience using BT for the treatment of esophageal achalasia

Authors	Description	Patients	Results/conclusions
Pasricha et al. (1995)	BT vs placebo	21	67% were improved at 6 weeks
Annese et al. (1996)	BT vs placebo vs PBD	16	100% were improved at 1 month, 88% required repeated injections. BT is as effective as pneumatic dilatation
Fiorini et al. (1996)	BT vs placebo	13	72% were improved at 3 months
Pasricha et al. (1996)	BT	31	60% (82% of those aged >50) were improved at 3 months
Fishman et al. (1996)	BT	65	60 idiopathic cases: BT treatment improved symptoms of dysphagia, chest pain, and regurgitation in the majority of patients. Five secondary cases: there was no response to BT in four patients. Patients, who respond to a first BT injection but relapse, may respond to a second treatment
Cuilliere et al. (1997)	BT	55	60% were improved at 6 months
Brant et al. (1999b)	BT in Chagas' disease	3	Clinical improvement occurred in all patients. Mean LES pressure drop by 29%
Kolbasnik et al. (1999)	BT	30	Symptomatic improvement for >3 months was seen in 77% of patients. 7 patients had a sustained response after a single injection; 16 relapsed and required re-treatment
Annese et al. (1999)	Ona-A vs Abo-A	78	Comparable efficacy in esophageal achalasia after up to 6 months after treatment
Muehldorfer et al. (1999)	BT vs PBD	24	The two treatments had equal initial success rate (dilatation 83%, BT 75%). In the long term, the efficacy of BT injection was statistically significant and shorter than that of balloon dilatation
Panaccione et al. (1999)	BT vs PBD	NR	Intrasphincteric BT injection was more costly than pneumatic dilatation (USD 5,033 compared to USD 3,608). BT treatment may be less costly if life expectancy is less than 2 years
Greaves et al. (1999)	BT	11	The relapse rate was 73% within 2 years from treatment. There were a beneficial effect on dysphagia and no improvement in chest pain or regurgitation scores, and no reduction of mean LES pressure was improved at 6 weeks
Wehrmann et al. (1999)	BT in high-risk patients	20	80% were improved at 6 weeks. Mean cardiac diameter was increased from 2.1 to 3.2 mm. The patients who initially had a symptomatic relapse after an average of 5 months. BT reinjections were efficacious
Hurwitz et al. (2000)	BT in children	23	The mean duration of effect in 19 responders was 4.2 months. 50% of the patients required

(continued)

Table 2 (continued)

Authors	Description	Patients	Results/conclusions
			an additional procedure (PD, surgery) on average 7 months after the first treatment
Annese et al. (2000)	BT dose raging study	118	82% of the patients were responders at 1 month. No dose-related effect was observed. Vigorous achalasia was the main determinant of BT response
Ip et al. (2000)	BT in children	7	100% were improved at 4 months. Sustained response beyond 6 months occurred in 43% of patients
Hep et al. (2000)	BT plus PBD	3	Propulsive peristalsis of the esophagus was restored in all patients
Mikaeli et al. (2001)	BT vs PBD	40	Cumulative 12-month remission rate was significantly higher after a single PD (53%) compared to a single BT injection (15%, $P < 0.01$). The 12-month estimated adjusted hazard for relapse and need for re-treatment for BT group was 2.69 times that of the PD group
Allescher et al. (2001)	BT vs PBD	37	After 24 months a single PD was superior to a single BT injection, and after 48 months, all patients treated for BT injection had experienced a symptomatic relapse
Ghoshal et al. (2001)	BT vs PBD	17	Both therapies resulted in a significant reduction in LES pressure
Zarate et al. (2002)	BT	17	The effect of BT injection wanes with time in elderly patients, necessitating repeated injections to keep the patients symptom-free
D'Onofrio et al. (2002)	BT	37	Of the 35 patients followed, 12 had a relapse and were treated; 4 out of 12 did not respond after treatment. One or two BT injections result in a clinical and objective improvement in about 84% of achalasia patients and are not associated with serious side effects; patients over 50 years showed better benefit than younger patients
Neubrand et al. (2002)	BT	25	Good results after 2.5 years of median follow-up in 9 of 25 patients that were significantly older than 14 patients for whom BT treatment was unsuccessful
Brant et al. (2003)	BT in Chagas' disease	24	Over a period of 6 months, clinical improvement of dysphagia was statistically significant ($P < 0.001$) in patients receiving BT when compared with the placebo. Esophageal emptying time in BT group was significantly lower than in the placebo ($P = 0.04$) after 90 days
Bansal et al. (2003)	BT vs PBD	32	After 12-month follow-up, 16 of 18 patients of PBD were in clinical remission despite 6 of 16 of BT group

(continued)

Table 2 (continued)

Authors	Description	Patients	Results/conclusions
Martinek et al. (2003)	BT vs PBD	41	16 patients had BT injection from the antegrade angle only (group A), 15 both from antegrade than retrograde (group B) and 10 had subsequent PD (group C). 93% had an immediate clinical response after 1 month, and 49% were in remission after 22 months. Better responders were older and with lower LES pressure. Patients in group C had better results at 1 and 2 years
Martinek and Spicak (2003)	Modified BT	16	After a single BT injection, 11 responders reported a relapse with a median symptom-free interval of 17 months. After reinjection the median symptom-free interval was 16 months
Vela et al. (2004)	PBD vs HM vs BT PBD vs HM in patient with prior surgery	232	111 patients underwent PBD, 72 HM, and 39 elderly patients BT injection. 48 patients had already surgical treatment and underwent to PBD or redo-HM. PBD and HM are the best treatments for untreated achalasia and are less successful after surgery. BT group needed repeated injections, and their symptoms improving lasted for a mean period of 6.2 months
Zaninotto et al. (2004b)	BT vs HM	80	After 6 months similar results were reported in the 2 groups of 40 patients, but after 2 years, 87.5% of patients of surgical groups were symptom-free vs 34% of BT group ($P < 0.05$)
Mikaeli et al. (2004)	BT + PBD vs PBD	24	BT + PBD (case group) had a significant higher cumulative remission rate compared to control (PBD) group (24.6 vs 12.6 months $P < 0.01$) and a significant reduction in symptom score (76% vs 53% $P < 0.001$). Control group needed a 35 mm PBD vs 30 mm of case group
Dughera et al. (2005)	BT elderly	12	After 12 months of follow-up, up to 70% of patients were considered responders. They underwent 2 BT injection (time 0 and after 1 month). Average age 86 y.o. ASA 3 or 4
Bassotti et al. (2006)	BT elderly	33	Patients underwent 2 BT injections (time 0 and after 1 month). 78% were considered responders after 1 year and 54% after 2 years. No relationship was found between baseline LES pressure and symptom score
Mikaeli et al. (2006)	BT + PBD vs PBD	54	77% of patients of BT + PBD group were in remission after 1 year vs 62% of PBD group and showed a significant reduction in barium volume at the various time intervals post-treatment

(continued)

Table 2 (continued)

Authors	Description	Patients	Results/conclusions
Zhu et al. (2009)	BT vs PBD vs BT + PBD	90	LES pressure and symptom score in group C (BT + PBD) were significantly lower compared with those in group A (BT) or group B (PBD) ($P < 0.05$). At 2 years after treatment, the response rate in group C remained 56.67% vs 35.71% (group B) and 13.79% (group A) ($P < 0.05$)
Kroupa et al. (2010)	BT + PBD vs PBD	91	The mean duration of follow-up was 48 months (12–96 months). 41 of 51 patients were followed up more than 2 years. Effect of therapy lasted in 75% (31/41) of them. The cumulative 5-year remission rate in combined treated patients was higher than in controls but not statistically significant ($P = 0.07$). Injection of BT followed by PD seems to be effective for long-term results, but the combined therapy is not significantly superior to PD alone
Gutschow et al. (2010)	BT vs PBD vs PBD-HM vs HM	41	Patients of BT group ($n = 7$) had the lower mean LES pressure (18.1 mmHg) and higher recurrence rate (71.4%) compared to patients of PBD group ($n = 16$, 34.8 mmHg – 50%), PBD-HM group ($n = 14$, 22.2 mmHg – 35.7%), and HM group ($n = 6$, 36.4 mmHg – 16.7%)
Bakhshipour et al. (2010)	BT + PBD vs PBD	34	Patients of study group already underwent two initial PBD with a low response. They were randomized to receive another PBD or BT injection and PBD by 4 weeks interval. BT + PBD group had higher remission rate at 1, 6, and 12 months compared to PBD group (87.5% vs 67.1%, 87.5% vs 61.1%, 87.5% vs 55.5%, respectively). Difference was not statistically significant
Porter and Gyawali (2011)	BT	36	Response lasted a mean of 12.8 months, and symptom relief for >6 months was seen in 58.3% of patients. Chest pain, younger age, and contraction amplitudes >180 mmHg independently predicted <6 months relief ($P < 0.05$ for each)
Ciulla et al. (2013)	BT	68	36 patients who underwent echo-guided BT injection had complete relief of obstruction compared to 32 patients who underwent blind treatment
Cai et al. (2013)	BT vs SEMS	110	Improvements in global symptom, in dysphagia scores, and in LES pressure were significantly more marked in the SEMS group ($n = 59$) than in the BT group ($n = 51$). Remission rate in the SEMS group was

(continued)

Table 2 (continued)

Authors	Description	Patients	Results/conclusions
			statistically significantly higher than that in the BT group at 12 and 36 months [81.28 vs 64.58 ($P < 0.05$) and 49.1 vs 4.2 ($P < 0.01$)]. No side effects were reported in BT group vs 26 in SEMS group
Jung et al. (2014)	BT vs PBD	37	A significant difference was observed in the mean remission duration between the BT injection ($n = 25$) and PBD ($n = 12$) (13 months vs 29 months). Independent factors predicting long-term remission included treatment type and the difference in the initial LES pressure
Marjoux et al. (2014)	BT	45	22 patients had achalasia, 8 jackhammer esophagus, 7 distal esophageal spasm, 5 esophagogastric junction outflow obstruction, 1 nutcracker esophagus, and 2 unclassified cases. 71% were significantly improved after 2 months, and 57% remained satisfied for more than 6 months. No clear difference was observed in terms of response according to manometric diagnosis. Type 3 achalasia had the worst outcome with none of these patients responding to the endoscopic BT injection

BT botulinum toxin, *HM* Heller myotomy, *LES* lower esophageal sphincter, *NR* not reported, *PBD* pneumatic balloon dilatation, *PD* pneumatic dilatation, *SEMS* self-expanding metal stent

that PD is the more effective endoscopic treatment in the long term (greater than 6 months) for patients with achalasia (Leyden et al. 2014).

BT injections into the upper GIT appear to be quite safe with very few, if any, reports of serious adverse effects. The incidence of gastroesophageal reflux has not been well characterized in most studies but has been reported to be about 20%, by symptoms at least. There has also been some question in recent years whether BT prior to PD or myotomy complicates the more invasive procedures possible secondary to LES fibrosis. However, although previous BT injection (or PD for that matter) may make myotomy more challenging technically because of obliteration of tissue planes, this does not appear to affect the final outcome after myotomy.

Given its favorable safety profile, BT injection is a reasonable option for the short-term treatment of achalasia; it cannot be recommended as a long-term solution for patients who are candidates for more definitive therapies. Thus, this treatment is currently reserved for patients in whom PD or myotomy is precluded by patient-related risk.

HRM (high-resolution manometry) has enabled identification of achalasia subtypes that have important prognostic implications. Pneumatic dilatation is a commonly used and cost-effective method of treating achalasia but has shown poor longevity of symptom relief compared with other modalities and carries a

risk of esophageal perforation. LHM (laparoscopic Heller myotomy) is often the preferred, most effective treatment modality; however new studies may show that outcomes are equivalent or even inferior to POEM (peroral endoscopic myotomy). Botulinum toxin injection of the lower esophageal sphincter has a waning and short duration of efficacy and is used primarily for patients unsuitable for more definitive invasive procedures. POEM is considered the most effective treatment for type III achalasia but carries a high risk of iatrogenic gastroesophageal reflux disease that might predispose to the development of Barrett's esophagus (Zaninotto et al. 2019).

1.3 Other Esophageal Disorders

BT has also been used in a variety of less well-characterized esophageal conditions including diffuse esophageal spasm (DES) and patients with non-cardiac chest pain suspected to be on the basis of a dysfunctional esophagus. DES is a condition that is related to achalasia and may be associated with LES dysfunction as well (Marjoux et al. 2013; Burmeister 2013; Achem and Gerson 2013; Sharata et al. 2013; Vaezi 2013; Vanuytsel et al. 2013; Roman and Kahrilas 2013; Spector et al. 2013). In a clinical trial assessing the effect of BT in DES (Storr et al. 2001a, b), each of the nine patients was given 100 Ona-A BT units diluted in l0 mL of saline solution and injected endoscopically at multiple sites along the esophageal wall beginning in the LES region and moving proximally in 1- to 1.5-cm intervals and into endoscopically visible contraction rings. At week 4, eight patients had a significant reduction in symptom score, and four patients required subsequent injections over a 2-year period. A recent study examined 22 patients with DES or nutcracker esophagus who had primarily dysphagia and gave them blinded saline or BT injections in a crossover study design (Vanuytsel et al. 2013). Results showed that symptom scores and weight loss improved after BT treatment, not the saline injections, and this benefit was sustained for over a year in almost half of the patients.

In addition to dysphagia and regurgitation, chest pain can be associated with achalasia, DES, ineffective esophageal motility (IEM), and isolated LES dysfunction which may respond to BT administration as shown in previous studies. A study, with improvement of chest pain as the primary end-point, evaluated 29 patients with non-cardiac chest pain who received 100 Ona-A BT units injection into the LES, same as the treatment regimen for achalasia. Seventy-two percent of the patients responded with at least 50% reduction in chest pain (Miller et al. 2002a).

The response rates of BT injection therapy vary depending on the esophageal motility disorder. Studies have shown that response is transient in achalasia patients, and given the more effective therapies available, it is only recommended in patients who are not surgical candidates. In nonachalasia patients, studies of BT injections have demonstrated improvement in dysphagia symptoms in patients with spastic disorders, though studies are small and largely retrospective. The available literature showed a variable response to BT in esophagogastric junction outlet obstruction (EGJOO) and non-cardiac chest pain patients. Despite advances in diagnosing esophageal motility disorders, there is a need for further research in patient selection for esophageal BT, dose and injection location, and disease-specific outcomes.

Placebo-controlled trials are crucial to evaluate BT efficacy and duration of response. Esophageal-directed BT injections are beneficial in improving dysphagia in spastic motility disorders and in achalasia patients who are elderly or have multiple comorbidities. There is a lack of evidence to support use in patients with EGJOO and non-cardiac chest pain or for young or healthy achalasia patients (Sterling et al. 2018).

2 Gastric Applications

2.1 Gastroparesis

Gastroparesis or delayed gastric emptying resulting in nausea, vomiting, dyspepsia, and abdominal bloating can occur as a result of poorly controlled diabetes mellitus, postsurgical manifestations, or idiopathic causes (Lacy et al. 2004; Friedenberg et al. 2004; Rayner and Horowitz 2005; Bromer et al. 2005). It has been hypothesized that one of the clinical causes of gastroparesis is pylorospasm partially from impaired relaxation and unopposed cholinergic stimulation, thus decreasing pylorospasm may increase gastric emptying. In recent years, BT injection into the pylorus has been investigated as a treatment option in this otherwise debilitating disorder.

The initial study evaluating the BT efficacy in patients with diabetic gastroparesis assessed six patients with abnormal solid phase gastric emptying studies (Ezzeddine et al. 2002). Each patient received 100 BT Ona-A units into the pyloric sphincter, and symptom scores and gastric emptying were assessed after 6 weeks. There was an improvement of subjective symptom scores of 55%, which was maintained at 6 weeks. In addition, there was a 52% improvement in gastric emptying at 6 weeks. Another study investigated the BT use in cases of idiopathic gastroparesis (Miller et al. 2002b). Ten patients were given 80–100 Ona-A BT units, and a 38% reduction in symptom scores were seen at 4 weeks which correlated with findings of increased gastric emptying. A recent study evaluated the effects of BT on diabetic gastroparesis for 12 weeks (Lacy et al. 2004). Eight patients received 200 Ona-A BT units into the pyloric sphincter, and seven patients completed the 12-week follow-up. Mean symptom scores declined from 27 to 12.1 ($P < 0.01$). Furthermore, six of the seven patients gained weight ($P = 0.05$), and gastric emptying scan time improved in four patients (Lacy et al. 2004). The largest study to address this issue retrospectively evaluated 63 patients who met the study criteria (Bromer et al. 2005). Gastroparesis was secondary to diabetes in 26 patients (41.2%), after surgery in two (3.2%), and idiopathic in 35 (55.6%). Twenty-seven of 63 (43%) patients experienced a symptomatic response to treatment (100–200 units Ona-A) with a mean duration of 5 months. Male gender was associated with response to therapy. However, vomiting as a major symptom was predictive of no response to BT (Bromer et al. 2005).

Based on the current available literature, there is conflicting data regarding the efficacy of intrapyloric botulinum injections (IPBIs) for refractory gastroparesis. There have been many open-label trials showing good clinical response, but the only

two randomized controlled trials on the matter showed no objective improvement gastric emptying studies. However, both studies were likely underpowered, and changes in gastric emptying may not correlate with symptom improvement. As such, these discouraging findings should not be used to exclude BT from the armamentarium of therapies for refractory GP. More large-scale, double-blinded, multicenter randomized control trials are needed to further validate the long-term efficacy and safety of IPBI, as well as gastric peroral endoscopic myotomy (G-POEM), as compared to gastric electrical stimulation (GES) or surgical intervention (i.e., laparoscopic pyloromyotomy) for refractory gastroparesis (Thomas et al. 2018).

2.2 Obesity

BT injection into the gastric antrum may be used to transiently decrease gastric emptying as a treatment for obesity (Gui et al. 2000; Rollnik et al. 2003; Garcia-Compean et al. 2005; Coskun et al. 2005; Albani et al. 2005). Preliminary data in rats have shown a significant loss of body weight associated with a reduction of dietary intake in the BT-treated group. In a double-blind controlled study, 24 morbidly obese patients [mean body mass index (BMI) 43.6 $\pm$ 1.09 kg/m^2] were blindly randomized to receive 200 Ona-A BT units or placebo into the antrum and fundus of the stomach by intraparietal endoscopic administration (Foschi et al. 2007). The two groups were homogenous for anthropometric characteristics. Eight weeks after the treatment, BT patients had significantly higher weight loss (11 $\pm$ 1.09 kg vs 5.7 $\pm$ 1.1 kg, $P < 0.001$) and BMI reduction (4 $\pm$ 0.36 kg/m^2 vs 2 $\pm$ 0.58 kg/m^2, $P < 0.001$) than controls. No significant side effects or neurophysiologic changes were found. Similar results have been found in an open-label study of ten obese adults (BMI 31–54 kg/m^2) who received 100 units (four patients) or 300 units (six patients) of Ona-A BT and were followed for 16 weeks (Topazian et al. 2008).

Further results demonstrated that BT makes weight loss easier in obese patients (Foschi et al. 2008). It seems conceivable that BT acts by increasing the solid gastric emptying time and reducing the solid eating capacity of the stomach. However, the results in literature are controversial. In several other clinical experiences, intragastric BT injection did not seem to reduce body weight (Garcia-Compean et al. 2005; Cardoso et al. 2006; Mittermair et al. 2007; Topazian et al. 2013; Wiesel et al. 1997; Saliakellis and Fotoulaki 2013; Martin et al. 2009; Bai et al. 2010; Kent et al. 2007; Bagheri et al. 2013; Ballal and Sanford 2000; Shrestha and Pasricha 2001; Mandal and Robinson 2001; Gorelick et al. 2004; Wehrmann et al. 2000; Hackert et al. 2017; Murray 2011; Maria et al. 1999, 2000a, 2001, 2002, 2006; Brisinda et al. 2003a, 2006; Hallan et al. 1988; Joo et al. 1996; Ron et al. 2001; Madalinski et al. 2002; Albanese et al. 1997, 2003; Keshtgar et al. 2007, 2009; Irani et al. 2008; Farid et al. 2009a, b, c; Ahmadi et al. 2013; Zhang et al. 2014; Shafik and El-Sibai 1998; Cadeddu et al. 2005; Emile et al. 2016; Christiansen et al. 2001; Lund and Scholefield 1996; Madoff and Fleshman 2003; Shawki and Costedio 2013;

Lindsey et al. 2004a; Gui et al. 1994; Jost and Schimrigk 1994, 1995; Mason et al. 1996; Jost 1997; Minguez et al. 1999).

2.3 Other Gastropyloric Disorders

BT has been used to facilitate gastric emptying in patients who underwent pylorus-preserving duodenopancreatectomy (Wiesel et al. 1997). Initial studies suggest that BT injection into the pylorus improves both gastric emptying and symptoms.

Infantile hypertrophic pyloric stenosis is a congenital hereditary disorder characterized by a functional gastric outlet obstruction (Saliakellis and Fotoulaki 2013). Obstruction is the result of a gradual hypertrophy of the circular smooth muscle of the pylorus, and the neurons that innervate the circular muscle layer lack NO synthase. Recently lack of response to BT injection has been observed in two patients with pyloric stenosis. Studies have shown that BT injection helps patients suffering from postsurgical pyloric clogging. BT injection is also used as an alternative method for the treatment of gastric emptying disorders (Rayner and Horowitz 2005; Bromer et al. 2005; Ezzeddine et al. 2002). In a recent study, the authors compared the effect of BT injection and pyloroplasty in preventing delayed gastric emptying after esophagectomy for esophageal cancer (Bagheri et al. 2013). In the study 60 patients were included and were randomly divided into two groups. In group A, 30 patients underwent pyloroplasty, and in group B, injection of 200 BT units into the pyloric sphincter muscle was used in 30 patients. Isotope scan 3 weeks after surgery showed that five patients in group A and three in group B had delayed gastric emptying; there was no significant difference between the two groups, and the success rate of BT injection was 90% (Bagheri et al. 2013). BT injection may be used instead of pyloroplasty as a simple, effective, and complication-free method to prevent gastric emptying delay.

3 Duodenal and Biliary Applications

3.1 Sphincter of ODDI Dysfunction (SOD)

SOD is a poorly understood and controversial condition postulated to result in biliary pain, typically in the setting of a previous cholecystectomy. It has also been hypothesized that pancreatic SOD can result in pancreatic-type pain and/or recurrent pancreatitis. The standard of SOD treatment currently is endoscopic sphincterotomy, which is a relatively high-risk procedure that is not uniformly effective. Hence there is interest in the use of a simpler procedure such as BT to serve as a therapeutic trial; patients who respond to this treatment could then go on for more permanent relief using a sphincterotomy (Ballal and Sanford 2000; Shrestha and Pasricha 2001; Mandal and Robinson 2001). This was first suggested in a short report on two patients. Subsequently a larger study was reported evaluating 22 patients who had undergone cholecystectomy and had manometrically confirmed type III SOD

(Gorelick et al. 2004). Six weeks after 100 Ona-A units injected into the sphincter, 12 patients (55%) were symptom-free, but 10 patients (45%) were not. Of the ten patients who did not experience symptomatic benefit from BT injection, five had normal basal sphincter of Oddi pressures (<40 mmHg), and biliary sphincterotomy did not relieve the symptoms of these patients. Two of the remaining five patients with sustained sphincter hypertension after BT injection benefited from biliary sphincterotomy. Of the 12 patients who initially responded to BT injection, 11 patients remained symptom-free for a median duration of 6 months. These patients had recurrence of biliary hypertension and responded to biliary sphincterotomy. The authors concluded that response to BT injection may select a subset of patients who will respond to biliary sphincterotomy. BT has also been used with similar intent, although in an uncontrolled manner in patients with acute recurrent pancreatitis suspected to be due to pancreatic SOD (Wehrmann et al. 2000). Preoperative sphincter of Oddi botulinum toxin injection is a novel and safe approach to decrease the incidence of clinically relevant postoperative pancreatic fistula after distal pancreatectomy. The results of a recent trial suggest its efficacy in the prevention of clinically relevant postoperative pancreatic fistula and are validated currently in the German Federal Government-sponsored, multicenter, randomized controlled PREBOT trial (Hackert et al. 2017).

3.2 Other Biliary Disorders

BT-induced relaxation of the sphincter of Oddi may help to direct appropriate therapy for patients with acalculous biliary pain (Murray 2011). A protocol-based management of 25 patients with acalculous biliary pain who had 100 Ona-A BT units injected into their sphincter of Oddi musculature to relax the sphincter has been audited. Patients whose pain was temporarily relieved after BT injection were offered endoscopic biliary sphincterotomy, and patients who failed to experience benefit after BT injection were assessed for laparoscopic cholecystectomy. A total of 11 patients had a positive response to BT treatment. Of these patients, ten consented to undergo endoscopic biliary sphincterotomy, with relief of biliary pain in all cases. A total of 14 patients had a negative response to BT injection, with 10 of these patients progressing to laparoscopic cholecystectomy, which resulted in biliary pain relief in 8.

4 Pelvic and Anorectal Applications

4.1 Pelvic Floor Dyssynergia

Pelvic floor dyssynergia, also known as anismus, is a common cause of chronic constipation, hallmarked by inappropriate, paradoxical contraction or a failed relaxation of the puborectalis muscle and EAS during defecation (Maria et al. 2002; Brisinda et al. 2003a, 2006). In normal patients, the puborectalis muscle and the

EAS relax to straighten the anorectal angle and open the anal canal. Usually, this alteration in defecation is from maladaptive learning and responds to biofeedback in 60–70% of patients as demonstrated in mostly single group, uncontrolled trials. Surgery has not been shown to be effective and has been largely discouraged as a treatment option. There are a limited number of studies evaluating the BT use in pelvic floor dyssynergia (Table 3).

An initial trial evaluating seven patients with constipation and anismus received BT of unknown dose into the EAS (Hallan et al. 1988). Symptom scores improved significantly correlating with a reduction in the maximum voluntary and anal canal squeeze pressure and a significant increase in the anorectal angle on straining with subsequent fecal incontinence in two patients. In another study with a sample size of four patients with anismus, the dose of Ona-A BT ranged from 6 to 15 units injected into the EAS or puborectalis muscle under electromyography guidance (Maria et al. 2000a). All four patients, who had numerous failed biofeedback sessions, responded to BT with two patients having sustained responses for up to 1 year. A larger study evaluating 15 patients at a dose of 25 Ona-A BT units injected into the EAS showed improvement in 13 patients (87%) for a mean of 4.8 months (Maria et al. 2006). It is unclear whether BT should be injected into the EAS or the puborectalis muscle. Another study evaluated 25 patients who received 10 Ona-A BT units on each side of the puborectalis muscle or 20 Ona-A units in the posterior aspect of the muscle. Manometric relaxation was achieved after the first injection in 18 patients (75%), which endured throughout a 6-month follow-up. Seven of 16 patients who failed the first injection had an additional one. Symptom improvement of 29.2% in straining index was recorded during follow-up with an overall satisfaction rate of 58.3%. Twenty-four consecutive patients with chronic outlet obstruction constipation resulting from puborectalis syndrome were included in a recent study (Maria et al. 2006). The patients were treated with 60 units of Ona-A, injected into two sites on either side of the puborectalis muscle under ultrasonographic guidance. At 2 months, evaluation inspection revealed a symptomatic improvement in 19 patients. Anorectal manometry demonstrated decreased tone during straining from 98 $\pm$ 24 to 56 $\pm$ 20 mmHg at a 1-month evaluation ($P < 0.01$) and 56 $\pm$ 29 mmHg at a 2-month follow-up ($P < 0.01$). Pressure during straining was lower than resting anal pressure at the same time in all patients. Defecography after the treatment showed improvement in anorectal angle during straining, which increased from 98 $\pm$ 9° to 121 $\pm$ 15° ($P < 0.01$) (Mason et al. 1996). Similar results have been noted in patients with Parkinson's disease (Cadeddu et al. 2005; Albanese et al. 1997).

Recently, in a review of 7 studies including 189 patients, the median dose of Ona-A injected per procedure was 100 IU (range, 20–100 IU). Lateral injection was done in five trails and combined lateral and posterior injections in two trials. Three studies used endorectal ultrasonography-guided technique, one study used EMG-guided technique, whereas the remaining three studies used manual palpation with the index finger. The median percentage of patients who reported initial improvement of symptoms was 77.4% (range 37.5–86.7%), this percentage declined to a median of 46% (range 25–100%) at 4 months after injection of Ona-A. Rates of improvement evaluated by balloon expulsion test, EMG, and defecography ranged

Table 3 Published results of treatment of pelvic floor dyssynergia with BT

Author	Pts	Name of drug/dose (units)	Results	Complication
Hallan et al. (1988)	7	Abo-A – Nr	Maximum voluntary contraction from 70 to 28 cm H_2O. Anorectal angle from 96 to 124°. Symptomatic improvement in four patients	Incontinence in two patients
Joo et al. (1996)	4	Ona-A – 6–15 U	Symptomatic improvement in all treated patients. Two patients relapsed	0
Shafik and El-Sibai (1998)	15	Ona-A – 25 U	Symptomatic improvement in 13 patients, on average 4.8 months after the first treatment	0
Maria et al. (2000a)	4	Ona-A – 30 U	75% were improved at 8 weeks. Anal tone during straining from 96.2 to 42.5 mmHg at 4 weeks and to 63.2 mmHg at 8 weeks. Anorectal angle from 94 to 114°	0
Maria et al. (2001)	14 AR	Ona-A – 30 U	At 2-month evaluation, a symptomatic improvement was found in nine patients. At defecography, the rectocele depth was reduced from 4.3 ± 0.6 cm to 1.8 ± 0.5 ($P < 0.001$), and the rectocele area was reduced from 9.2 ± 1.2 to 2.8 ± 1.6 cm^2 ($P < 0.001$). The anorectal angle measured during straining increased from a mean of 98 ± 15° before treatment to a mean of 121 ± 19 ° ($P = 0.001$). At one-tear evaluation, there was no report of digitally rectal voiding, and rectocele was not found at physical examination	0
Ron et al. (2001)	25	Ona-A – 20 U	Symptomatic improvement in 75% of the patients	Perianal pain in three patients
Madalinski et al. (2002)	39	Ona-A – 25 U Abo-A – 150 U	Nr	Perianal pain in four patients
Albanese et al. (2003)	10 PD	Ona-A – 100 U	Following treatment, anal tone during straining was reduced from 97.4 ± 19.6 mmHg at baseline to 40.7 ± 11.5 mmHg 1 month after treatment ($P = 0.00001$); no further change was observed at 2-month evaluation (38.2 ± 10.4 mmHg; $P = 0.00001$ vs baseline values). The anorectal angle during straining (as measured with defecography) increased from a mean of 90° ± 7.9 before treatment to 122.2° ± 15	0

(continued)

Table 3 (continued)

Author	Pts	Name of drug/dose (units)	Results	Complication
			($P = 0.0004$); nine patients evacuated the barium paste without the need for laxative or enemas	
Cadeddu et al. (2005)	18 PD	Ona-A – 100 U	At 2-month evaluation, inspection revealed a symptomatic improvement in ten patients. Anorectal manometry demonstrated decreased tone during straining from 96.2 ± 17.1 mmHg to 45.9 ± 16.2 mmHg at 1-month evaluation ($P < 0.00001$) and to 56.1 ± 10.7 mmHg at 2 months ($P < 0.00001$). Pressure during straining was lower than resting anal pressure at the same time in all patients. Defecography after the treatment showed improvement in anorectal angle during straining which increased from 99.1° ± 8.4 to 121.7° ± 12.7 at 2 months ($P < 0.00001$)	0
Maria et al. (2006)	24	Ona-A – 60 U	At 2-month evaluation, inspection revealed a symptomatic improvement in 19 patients. Anorectal manometry demonstrated decreased tone during straining from 98 ± 24 mmHg to 56 ± 20 mmHg at 1-month evaluation ($P < 0.01$) and 56 ± 29 mmHg at 2-month follow-up ($P < 0.01$). Defecography after the treatment showed improvement in anorectal angle during straining	0
Keshtgar et al. (2007)	42	Ona-A – 60 U	BT injection ($n = 21$) is equally effective and less invasive than M of IAS ($n = 21$) for chronic idiopathic constipation. At 3 months the median preoperative SS score improved from 34 to 20 in BT group ($P < 0.001$) and from 31 to 18 in the M group ($P < 0.002$). At 12 months the score was 19 and 14.5 in BT and M group, respectively ($P < 0.0001$)	0
Irani et al. (2008)	24	Ona-A – 20 U	Of 24 patients, 22 experienced significant improvement in their constipation lasting greater than 22 weeks. There was a statistically significant improvement from 2.1 to 6.5 bowel movement per week ($P < 0.001$). The benefit of the BTX-A persisted a variable period of time among the	5 fecal soiling

(continued)

Table 3 (continued)

Author	Pts	Name of drug/dose (units)	Results	Complication
			responders, with 12 patient (55%) demonstrating a response lasting 6 months or more	
Farid et al. (2009a)	48	Abo-A – 100 U	In BFB group ($n = 24$) initial improvement was recorded in 12 patients (50%), while long-term success was recorded in 6 patients (25%). In the BT group ($n = 24$), clinical improvement was recorded in 17 patients (70.8%), but the improvement persisted only in 8 patients (33.3%). There is a significant difference between BT group and BFB group regarding the initial success ($P = 0.008$), but this significant difference disappeared at the end of follow-up ($P = 0.23$)	Nr
Farid et al. (2009b)	30	Abo-A – 100 U	BT injection ($n = 15$) achieved initial success in 13 patients (86.7%). Long-term success persisted only in six patients (40%). PDPR ($n = 15$) achieved initial success in all patients (100%) with a long-term success in ten patients (66.6%). However this difference did not produce any significant value. Recurrence was observed in seven patients (53.8%) and five patients (33.4%) following BT injection and PDPR, respectively	0
Keshtgar et al. (2009)	16	Abo-A – 200 U	There were significant improvements in symptoms of constipation, soiling, painful defecation, general health and behavior, and fecal impaction of rectum ($P < 0.05$). Outcome was measured by a validated SS score questionnaire. At 3-month follow-up, the median SS score improved in all children after BT injection from 32.50 to 7.50 ($P < 0.0001$). At 12-month follow-up, the improvement of SS score in BT injection group was significantly more than the control group ($n = 31$) as follows: 4 vs 15, respectively ($P < 0.002$)	0
Farid et al. (2009c)	60	Abo-A – 100 U	The groups differed significantly regarding clinical improvement at 1 month [50% for BFB ($n = 20$), 75% BT injection ($n = 20$), and 95% for	Nr

(continued)

Table 3 (continued)

Author	Pts	Name of drug/dose (units)	Results	Complication
			PDPR ($n = 20$), $P = 0.006$], and differences persisted at 1 year (30% for BFB, 35% BT injection, and 70% for PDPR, $P = 0.02$). BT injection seems to be successful for temporary treatment, but PDPR is found to be effective with lower morbidity in contrast to its higher success rate	
Ahmadi et al. (2013)	88	Abo-A – 160 U	Defecation of painful stool existed in 88% of patients before BT injection, and it was reduced to 15% after BT injection ($P = 0.0001$). Stool was hard in 80% of patients before and was reduced to 28% after BT injection ($P = 0.0001$). Soiling existed in 62% of patients before and was reduced to 8% after BT injection ($P = 0.0001$). Defecation interval was 9.1 days and after BTX-A injection was reduced to 2.6 days ($P = 0.0001$)	Nr
Zhang et al. (2014)	31	Inco-A – 100 U	After treatment, the pressure of the anal canal during rest and defecation was significantly reduced from (93 ± 16.5) mmHg and (105 ± 28.3) mmHg to (63 ± 8.6.3) mmHg and (42 ± 8.9) mmHg, respectively. BT injection combined with pelvic floor biofeedback training achieved success in 24 patients with 23 maintaining persistent satisfaction during a mean period of 8.4 months	8 fecal incontinence

AR anterior rectocele, *BFB* biofeedback training, *BT* botulinum toxin, *M* myectomy, *Nr* non-reported, *PD* Parkinson's disease, *PDPR* partial division of puborectalis, *SS score* symptom severity score

between 37.5–80%, 54–86.7%, and 25–86.6%, respectively. Fourteen (7.4%) patients developed complications after injection of Ona-A. Complication rates across the studies ranged from 0 to 22.6%. Initial satisfactory improvement of symptoms after Ona-A injection remarkably deteriorated after 3 months of the procedure. However, repeated injection may provide better sustained results with no additional morbidities. Further analysis of more patients is necessary to conclude the safety of Ona-A for the treatment of anismus (Emile et al. 2016).

Rectoceles are commonly associated with outlet obstruction, such as pelvic floor dyssynergia. Therefore, decreasing anal sphincter tone during strain may decrease the size of the rectocele and improve symptoms of constipation. In a study of 14 patients with anterior rectocele, each patient received 30 Ona-A BT units into

3 sites, 2 on either side of the puborectalis muscle and the 1 in the anterior portion of the external anal sphincter, under ultrasonographic guidance (Maria et al. 2001). At 2 months, 9 of 14 patients had symptomatic improvement with a decrease in rectocele depth and area and decrease in tone during straining. At 1 year, no patient experienced incomplete or required digitally assisted rectal voiding.

Many questions still remain such as the dose of BT in the treatment of pelvic floor dyssynergia, location of injection, use of ultrasound or electromyography, number of treatments, and combination with biofeedback. These questions need further study using placebo-controlled trials and larger sample sizes.

4.2 Chronic Idiopathic Anal Pain

Chronic idiopathic anal pain is part of a rather ill-defined group of disorders termed chronic idiopathic perineal pain, which also includes proctalgia fugax and coccygodynia (Christiansen et al. 2001). The main feature of these syndromes is that no objective abnormalities are found on clinical examination, and the distinction between the different groups of perineal pain is based solely on the patient's description of the pain and location of tenderness by palpation. In the majority of patients, the pain is present constantly, usually intense, sometimes burning, often with some irradiation; it was usually aggravated by sitting, whereas defecation had no constant effect and is relieved by lying down. The pathogenesis of the syndromes is unknown. There is no satisfactory treatment for chronic anal pain; nonetheless, anal stretch and lateral internal sphincterotomy (LIS) are still used in some patients on the assumption that the pain might be caused by a hypertonic IAS, because no objective changes can be demonstrated. Eighteen patients who met the criteria for chronic idiopathic anal pain were studied. Treatment consisted of analgesics only in four patients, 0.2% nitroglycerin ointment in four, and ultrasound BT injection into the intersphincteric space in nine. Four patients were managed satisfactorily on analgesic treatment under the guidance of the hospital's pain clinic. Nitroglycerin ointment resulted in temporary pain relief in one of four patients. BT injection resulted in a permanent improvement in four patients, a temporary improvement in one patient, and no effect in four patients. Two patients had a colostomy, resulting in complete pain relief (Christiansen et al. 2001). As in other syndromes based on muscular dystonia, some patients may benefit from BT injection.

4.3 Anal Fissure

Anal fissures are tears in the anoderm that start at the anal verge and can extend to the dentate line (Lund and Scholefield 1996; Madoff and Fleshman 2003; Shawki and Costedio 2013). They can manifest into painful defecation and rectal bleeding. These fissures, which most commonly arise in the mid-posterior position of the anus, are thought to occur secondary to ischemia as a result of increased anal sphincter pressures and decreased blood flow (Lindsey et al. 2004a). Once chronic fissures

develop, treatment options are aimed at interrupting this cycle by reducing sphincter tone using topical nitroglycerin, BT injection, oral nifedipine, or LIS performed surgically (Lindsey et al. 2004a). There are many reports on the efficacy of BT for this condition (Table 4).

These studies include several controlled trials comparing the toxin to either placebo or other modalities (Gandomkar et al. 2015; Maria et al. 1998a, b). Clinical benefit is seen in the vast majority of patients, typically accompanied by reduction in resting anal sphincter pressure (Brisinda et al. 1999; Maria et al. 2000b).

The exact site and dose of injection remain somewhat unsettled. Most of the trials to this point have evaluated BT administration at the point of the fissure, primarily, the posterior midline area of the anal verge. However, there is evidence that IAS fibrosis exists at the base of the fissure and is more prominent in this zone than other sites in the smooth muscle. This fibrosis may decrease the effects of BT on sphincter relaxation, thus delaying fissure healing. A study to evaluate this theory was conducted on 50 patients with posterior anal fissures who were either given 20 Ona-A BT units lateral to the posterior fissure or 20 Ona-A BT units on each side of the anterior midline (Brisinda et al. 1999). After 2 months, a healing scar was observed in 15 patients (60%) of the posterior midline group and in 22 patients (88%) of the anterior midline group ($P = 0.025$). Resting anal pressure was significantly different from the baseline values at 1 and 2 months in both groups, but the values were significantly lower in patients of the anterior midline group.

Another study evaluated 150 patients with posterior anal fissures who were treated with BT injected in the IAS on each side of the anterior midline. Patients were randomized to receive either 20 Ona-A BT units and, if the fissure persisted, were retreated with 30 units or 30 units and retreated with 50 units, if the fissure persisted (Maria et al. 2000b). One month after the injection, examinations revealed complete healing in 55 patients (73%) in the group receiving the lower dose and 65 patients (87%) in the group receiving the higher dose ($P = 0.04$). Five patients from the second group reported a mild incontinence of flatus that lasted 2 weeks after the treatment and disappeared spontaneously. The values of the resting anal pressure ($P = 0.3$) and the maximum voluntary pressure ($P = 0.2$) did not differ between the two groups. However, after 2 months, healing rates were similar between the two groups (89% and 96%). The authors concluded that the higher dose was more effective, but the improved effectiveness was not seen at 2 months (Maria et al. 2000b).

The gold standard for treatment for anal fissures is surgery, primarily LIS. However, surgical intervention is associated with a low complication rate resulting in fecal incontinence, hematoma, and wound infection. A study compared BT injection (20–30 Ona-A units) and LIS (Brisinda et al. 2002). Overall healing rates were similar in both groups at 6 months with 10 of 61 patients requiring a second BT injection at 2 months. However, the response rate was higher at 1 and 2 months in the sphincterotomy group, 82% (41/50) at day 28 and 98% (49/50) at the second month ($P = 0.023$ and $P < 0.0001$, respectively, compared with the BT group). The response to BT was not as durable as surgery at 12 months falling to a success rate 75.4% (46/61) with seven recurrences in the BT group, whereas it remained

Table 4 Comparison of published results on the treatment of patients with chronic anal fissure

Author	Cases (*n*)	Units/ injection's site	Healing rate (%)		Reinjection (%)/ dose	Complete healing rate (%)	Temporary incontinence (%)	Recurrence (%)
			1 m	2 m				
Gui et al. (1994)	10	15 B/IAS	60	70	40/20 B	90	10	10
Jost and Schimrigk (1994)	12	5 B/EAS	Nr	83.3	–	83.3	0	8.3
Jost and Schimrigk (1995)	54	5 B/EAS	Nr	78	–	78	6	6
Mason et al. (1996)	5	NR D/IAS	Nr	60	–	60	0	NR
Jost (1997)	100	2.5–5 B/EAS	Nr	82	–	82	7	8
Maria et al. (1998a)	15 15	20 B/IAS Saline	53.3 13.3	73.3 13.3	26.6/25 B	100	4	6.7
Maria et al. (1998b)	23 34	15 B/IAS 20 B/IAS	21.7 50	43.5 67.6	8.7/20 B 20.6/25 B	100 100	0	0
Minguez et al. (1999)	23 27 19	10 B/IAS 15 B/IAS 21 B/IAS	48 74 100	Nr	52 30 37	83 78 90	0	37–52
Jost and Schrank (1999)	25 25	20 D/EAS 40 D/EAS	Nr	76 80	–	76 80	4 12	4 8
Brisinda et al. (1999)	25 25	20 B/IAS 0.2% GTN	88 40	96 60	–	96 60	0	0
Fernandez Lopez et al. (1999)	76	40 B/IAS	56	67	45.2/40 B	67	3	0
Madalinski et al. (1999)	13	20 B/EAS	84.6	Nr	–	–	NR	15.4
Maria et al. (2000b)	25 25	20 B/IAS PI 20 B/IAS AI	48 88	60 88	24/25 B 12/25 B	80 100	0	0
Lysy et al. (2001)	15 15	20 B + ID/IAS 20 B/IAS	66 20	73 60	–	73 60	0	0

(continued)

Table 4 (continued)

Author	Cases (*n*)	Units/ injection's site	Healing rate (%)		Reinjection (%)/ dose	Complete healing rate (%)	Temporary incontinence (%)	Recurrence (%)
			1 m	2 m				
Madalinski et al. (2001)	14	25–50 B/EAS	Nr	54	–	54	0	8
Tilney et al. (2001)	10	Nr D/IAS	Nr	Nr			NR	NR
Jost (2001)	10	200 NB/EAS	Nr	70	Nr	0	NR	NR
Brisinda et al. (2002)	75 75	20 B/IAS 30 B/IAS	73 87	89 96	10.7/30 B 4/50 B	100 100	0 3	0 4
Brisinda et al. (2003b)	6	150 D/IAS	100	Nr	–	100	0	0
Mentes et al. (2003)	61 50	20–30 B/IAS LIS	62.3 82	73.8 98	–	86.9 98	0 16	11.4 0
Siproudhis et al. (2003)	22 22	100 D/IAS Saline	50 45	32 32	Nr	NR	NR	NR
Brisinda et al. (2004a)	50 50	50 B/IAS 150 D/IAS	82 84	92 94	– 6/150 D	92 94	22 16	0
Giral et al. (2004)	10 11	20 B/IAS LIS	Nr	70 82	–	70 82	0	0
Simms et al. (2004)	47	30 B/IAS	Nr	Nr	17/Nr	78.7	0	27
Lindsey et al. (2004b)	30	25 B/IAS + FIS	Nr	Nr	–	93	7	0
Arroyo et al. (2005a)	40 40	25 B/IAS LIS	Nr	85 97.5	–	45 92.5	5 7.5	55 7.5
Arroyo et al. (2005b)	100	25 B/IAS	–	88	–	47	6	53
De Nardi et al. (2006)	15 15	20 B/IAS 0.2% GTN	33.3 13.3	53.3 66.7	–	33.3 40	0	33 33

Brisinda et al. (2007a)	50 50	30B/90D/IAS 0.2% GTN	82 58	92 70	–	92 46	0 0	0 34
Scholz et al. (2007)	40	10 B/IAS + FIS	95	Nr	5/Nr	79	2.5	10
Witte and Klaase (2007)	100	40–60 D/IAS	Nr	Nr	22/40–100 D	66	1	14
Festen et al. (2009)	37 36	20B/IAS + Poin 1%ISDN+Pinj	Nr	18.9 44.4	21.6/20 B	37.8 58.3	17.8	13.5 25
Nasr et al. (2010)	40 40	20 B/IAS LIS	55 80	62.5 90	–	62.5 90	0 10	40 12.5
Samim et al. (2012)	60 74	20 B/IAS 2% Dz	25 14	43 43	–	32 26	5.5	11.7 17.6
Valizadeh et al. (2012)	25 25	50 B/IAS LIS	28 40	44 88	Nr	48 92	12 48	50 8
Berkel et al. (2014)	27 33	60 D/IAS 1% ID	Nr	66.6 33.3	3.7/Nr	66.6 33.3	18.5 12	28 50
Halahakoon and Pitt (2014)	30	40 B/IAS + AF	86.7	Nr	–	60	3.3	NR
Farouk (2014)	141	100 B/IAS + FIS	Nr	Nr	14/Nr	76	8	18
Gandomkar et al. (2015)	49 50	150D/ IAS + 2%Dz LIS	46.9 74	67.3 92	–	65.3 94	2 7	10.2 0

AI injection in anterior midline, *AF* advancement flap, *B* Ona-A (Botox), *D* Abo-A (Dysport), *DZ* diltiazem, *EAS* external anal sphincter, *FIS* fissurectomy, *GTN* glyceryl trinitrate, *IAS* internal anal sphincter, *ID* isosorbide dinitrate, *LIS* lateral internal sphincterotomy, *NB* neuroblock (trade name of the type b preparation manufactured by Elan Pharma International Ltd, Ireland), *NR* not reported, *PI* injection in posterior midline, *PINJ* placebo injection, *POIN* placebo ointment

stable in the LIS group (94%, $P = 0.008$). Sphincterotomy was associated with a significantly higher complication rate, eight cases of anal incontinence versus none in the BT group ($P < 0.001$) (Brisinda et al. 2002). Thus, it appears that surgery is still the more durable treatment option but associated with more complications. These results have been supported in a more recent study. Some investigators have recommended surgery in younger patients and those with high resting anal pressures, as this is a risk factor for recurrence. Older patients may benefit from BT injection as they may be at higher risk of fecal incontinence.

A recent meta-analysis showed that even though LIS is associated with a better healing rate and recurrence rate, BT treatment is superior to LIS in overall complication rates and incontinence rates (Mentes et al. 2003). Thus, some advantages BT offers to patients with anal fissure include a good tolerance of the procedure, an outpatient setting, and a low risk of incontinence. The results of the meta-analysis are in line with previous research (Chen et al. 2014). Furthermore, in a recent study, BT injection was used not only as a therapeutic tool but also as a diagnostic test to identify patients who would not be suitable for further surgical LIS if they developed temporary incontinence after BT injection (Sajid et al. 2008). Combination therapy such as nitroglycerine and BT has also been evaluated; it appears that this only results in a modest increase in the rate of healing (Brisinda et al. 2008; Asim et al. 2014).

BT injection is efficacious in the treatment of chronic anal fissures. With greater than 60% response rates noted at 2 months with further response to re-treatment, BT can be considered a viable treatment option when more conservative treatment fails. In elderly patients, in whom rates of fecal incontinence after surgery may be increased, BT can be considered first-line treatment. Surgery is still the most durable treatment option, but the risks of fecal incontinence must be weighed carefully against the benefits of the procedure.

Thus, according to many authors, we recommend a safety-first approach and treat all patients medically in the first instance. We believe that specific indications for surgical intervention in patients with anal fissure include persistence/recurrence and noncompliance or intolerance to the medical treatment. Patients at higher incontinence risk can be evaluated by anorectal manometric and endoanal sonography test, or, at best, the patient should be offered a sphincter-sparing procedure. The need for further investigations imposes a cost increase. Furthermore, it is difficult to calculate the increased cost in the event of complications. Some of these patients may wish to avoid LIS and persist with an alternative medical therapy.

The recommendations are that simple and readily available therapy associated with fewer complications and requiring no hospitalization should be offered as first line of care. Rational thinking suggests conservative measures as the first-line therapy given that they are simple and have good safety records. Local application of NO donors is readily available, and many reports support these agents as the starting point in the management of these patients. Nevertheless, drawbacks of these drugs are headaches, orthostatic hypotension, and tachyphylaxis, which usually limit their benefits and call for second-line therapy, such as BT. BT injection has an excellent healing rate, can be repeated if necessary, and obviates the patients'

compliance. BT potential side effects should be kept in mind, however, including patient aversion to injection.

Recently, Mishra et al. concluded that both treatments (NO donors and BT) may be considered as first-line treatment even if less effective than surgery (Tranqui et al. 2006). However, this view has been challenged by other observations based on smaller series, providing inferior evidence of efficacy. The results of some studies are so disappointing that it led Nelson and coworkers to conclude a Cochrane review stating that "...medical therapy for chronic anal fissure... may be applied with a chance of cure that is only marginally better than placebo..." (Mishra et al. 2005). We think that such conclusion is too pessimistic and welcome further multicenter trials with appropriate methodology (intention-to-treat based selection of patients, doses, and injection technique) and adequate follow-up, to ascertain the safety and efficacy of the therapy. Moreover, the addition of multiple treatment modalities prolonged time to healing from initial evaluation but allowed up to 75% of patients to avoid the need for permanent sphincter division while maintaining the highest rate of healing.

The introduction of these therapies has made the treatment of anal fissure easier, in the outpatient setting, at a lower cost, and without permanent complications. Any conservative treatment used has lower costs than surgery (Nelson et al. 2012). Considering the three hypothetical scenarios reported in a recent paper, we found that the BT approach is more cost-effective than the ointment approach. In addition to cost reduction (on average 62% lower than the association NO donors plus surgery and on average 50% lower than the association CCA plus surgery), BT reduces the number of patients who need further surgery.

4.4 Other Anorectal Conditions

BT into the IAS has been applied both diagnostically and therapeutically after pull-through surgery for Hirschsprung's disease in which it is postulated that IAS spasm can result in persistent obstructive symptoms. Minkes and Langer prospectively evaluated 18 such children who underwent BT injection (total dose 15–60 Ona-A units) into 4 quadrants of the sphincter (Brisinda et al. 2014). Twelve patients (67%) improved for at least 1 month; improvement was sustained beyond 6 months in five patients. These investigators advocated BT, not only as an alternative to myectomy in such cases but also as a diagnostic trial, with persistent symptoms after injection, despite a decrease in sphincter pressure, suggesting another etiology for the constipation.

A total of 33 children with surgically treated Hirschsprung's disease treated with intrasphincteric BT injection for obstructive symptoms were analyzed in a recent study (Minkes and Langer 2000). The median time of follow-up was 7.3 years. A median of two injections was given. Initial improvement was achieved in 76%, with a median duration of 4.1 months. Proportion of children hospitalized for enterocolitis decreased after treatment from 19 to 7. A good long-term response was found in 49%. Basson and coworkers have studied 43 patients with idiopathic constipation,

Hirschsprung's disease, anorectal malformation, and GIT dysmotility (Han-Geurts et al. 2014). A total dose of 200 Ona-A BT units has been injected. Successful outcomes occurred in 72% patients after the first BT treatment, and 25% required further surgical management of their symptoms.

Pain after hemorrhoidectomy appears to be multifactorial and dependent on individual pain tolerance, mode of anesthesia, postoperative analgesia, and surgical technique. IAS spasm is believed to play an important role (Basson et al. 2014). The BT role in reducing pain after hemorrhoidectomy has been assessed in a double-blind study on 50 consecutive patients undergoing Morgan hemorrhoidectomy and assigned to an IAS injection of 0.4 mL of solution containing either 20 Ona-A BT units or normal saline (Patti et al. 2006). Those patients who had BT had significantly less pain toward the end of the 1st week after surgery. Reduction in IAS spasm is the presumed mechanism of action.

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