Review Article

Epidermal Growth Factor (EGF) and Botulinum Toxin (BTX); Can Paralysis Be A Bless?

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Abstract

Botulinum toxin (BTX) commercially known as Botox is produced by Clostridium Botulinum, it has many different subtypes. It is a relatively safe agent with very few local and systemic adverse effects, and is currently used in a wide range of medical, dental and cosmetic procedures. BTX has the potential for an expanding range of applications in the future. In this article we review the mechanism of action, and all the well documented applications of BTX with a specific focus on its usage in the treatment of hyper-salivation and drooling. We propose a combination treatment for the above mentioned salivary gland conditions, which consists of BTX and Epidermal Growth Factor (EGF); a well-known potent polypeptide that promotes healing and repair. EGF is secreted though many bodily fluids including saliva. This combination treatment aims to prevent the atrophy of salivary glands that accompanies treatment with BTX. We aim to provide answers to the question whether BTX induced paralysis is a burden or bless? Our proposed combination treatment (BTX + EGF) will hopefully obtain the best of both worlds; the therapeutic effect of BTX and the healing potential of EGF. This will maintain the salivary glands' integrity and will allow for long term treatment with BTX with minimal side effects.

Key words: Epidermal growth factor, Botulinum toxin, Clostridium, Salivary glands, Wound healing.

Botulinum toxin (BTX); types, uses and adverse effects

Currently, physicians use many types of dermal and subdermal fillers, which are classified according to their origin and average persistence in tissues. The properties of an ideal filler are to be safe, neither allergenic nor immunogenic, effective, injectable with reproducible technique and results, with high potential for use and low for abuse, non-carcinogenic, non-teratogenic, non-migratory, cost effective, physiologic, and permanent. None of the currently available materials satisfy all requirements [1].

Fillers can be divided into natural and synthetic materials. The natural fillers are safer to use, but temporary, and have to be used repeatedly to maintain the desired esthetics. Examples include bovine collagen, human-derived collagen, hyaluronic acid, poly-L-lactic acid, and calcium hydroxyapatite. The synthetic fillers may present with an increased risk of adverse reactions compared with the natural fillers. Examples include paraffin, silicone, polymethyl methacrylate, hydroxyethyl methacrylate, polyacrylamide, polyalkylimide, and polyvinylhydroxide [2]. Another classification is according to their source and average persistence in tissue into resorbable, non-resorbable, or temporary, semi-permanent, and permanent [3].

Botulinum Toxin A (BTX-A) also commercially known as Botox is one of the most potent toxins known. Estimated intravenous median lethal dose in humans is only 1 ng/kg or 70 ng/70 kg person [4]. One gram of toxin could kill more than one million people via inhalational route, making BTX a potential biological threat. Human botulism is caused mainly by types A, B, E, and rarely F. Types C and D cause toxicity only in animals [5].

Among the seven neurotoxins, types A and B have been introduced into clinical practice. After the initial demonstration in treating strabismus, the use of BTXs type A and B has proved effective and safe in a variety of conditions in, for example, adult and pediatric neurology, urology, dermatology, gastroenterology and plastic surgery [6].

The seven neurotoxins have different specific toxicities, different durations of persistence in nerve cells and different potencies. All BTX serotypes, ultimately inhibit acetylcholine release. Weakening of the surrounding muscles not injected may occur

as a local adverse effect because of toxin diffusion. Animal studies have demonstrated that BTX-A diffuses across facial planes to surrounding muscles [7].

The cosmetic use of BTX is the most common cosmetic procedure performed in the world today. Common adverse events seen in the aesthetic use of the BTX include swelling, localized bruising, headaches, injection site discomfort, excessive muscle weakness, and unintended paresis of adjacent muscles. Botulism is a neuro-paralytic disease with a low incidence, but fatal outcome in 5–10% of cases that shows as a systemic adverse effect of Botox treatment. Main features of botulism are the long term flaccid paralysis of skeletal muscles, and the impairment of gastrointestinal and autonomic nervous system functions. Symptoms of botulism usually appear within 12–36 hours following the exposure to toxin, but in some cases may occur with a delay of up to 8 days. Immediate treatment consists of early administration of antitoxin and intensive respiratory support [4].

Botulinum toxin (BTX) and its medical applications:

In 1949, Burgen, Dickens and Zatman discovered that BTX blocks neuromuscular transmission. This discovery laid the foundation for the development of the toxin into a therapeutic tool. The cosmetic use of BTX was first reported in 1992, when 18 patients were treated for glabellar (frown) lines. It was reported that BTX “is more effective than soft tissue augmentation,” and that the intervention “is a simple, safe procedure” [8]. Moreover, in 2000 the FDA approved BTX-A and BTX-B as treatments for cervical dystonia and glabellar (frown) lines [9]. Purified BTX was the first bacterial toxin used as a medicine. Since its introduction into clinical use it has become a versatile drug in various fields of medicine. The clinical applications of BTX have been expanding and novel applications are developing [10].

BTX has revolutionized the field of cosmetic medicine. Its administration is by far the most common cosmetic procedure being performed in the United States. The rapid ascent in popularity of BTX with both clinicians and patients can be attributed to its remarkable efficacy, predictable and reproducible results, excellent safety record, the relative ease, comfort, and speed of administration [5]. To explain its mechanism of action, we need to understand that under normal circumstances, the acetylcholine-containing vesicles are located in the nerve endings. They bind to the cell membranes through SNARE protein complexes (N-ethylmaleimide-sensitive factor attachment protein receptor), which include VAMP (vesicle-associated membrane protein) where BTX-B exercises its main action, and SNAP-25 (synaptosome-associated protein of 25 kDa) where BTX-A has its action. They then release their content into the synaptic cleft through exocytosis. Acetylcholine crosses the synaptic space where it binds to nicotinic receptors found in muscle cells, producing muscle contraction [10].

Pharmacologic and morphologic studies suggest that the toxin enters the nerve endings via endocytosis and inhibits the release of the vesicle bound acetylcholine within the nerve terminal itself. The toxin is rapidly (within hours) and irreversibly bound to the presynaptic neuron at the neuromuscular junction. The BTX is internalized and then acts on a zinc-dependent endoprotease to disrupt some of the peptides necessary for acetylcholine release. This action may not be complete for 2 weeks and effectively destroys the affected neuromuscular junction, causing muscular paralysis. There is an ongoing turnover of neuromuscular junctions; however, it is enhanced by toxin exposure in a way that muscular function begins to return after approximately 3 months and is usually complete by 6 months [11].

Clinical effect of BTX occurs within approximately 3–7 days (typically seen after 1–3 days) after administration, followed by 1–2 weeks of maximum effect, which then levels off to a moderate plateau until full nerve recovery within 3–6 months [12]. The recovery phase is a multistage biologic event that attempts to overcome botulinum blockage of the neuro muscular junction (NMJ). Recovery may be a response to a growth factor secreted by the paralyzed muscle accessory terminals, which ‘‘sprout’’ from the poisoned presynaptic axon and stimulate the development of new NMJs. The primary nerve terminal recovers its full activity and re-establishes itself as the only functioning NMJ by 90 days after BTX administration. However, with repeated exposure to BTX, this process becomes progressively longer [13].

BTX has a wide array of cosmetic uses, including treatment of glabellar lines, chemical brow lift, forehead wrinkles, periorbital, and perioral lines [14]. Its mechanism of inhibiting acetylcholine release at neuromuscular junctions following local injection is unique for the treatment of facial wrinkles. Glabellar lines, also called frown lines, that occur naturally with facial expressions, as a result of the pulling of the skin by the underlying musculature, predominantly the procerus muscle and the corrugator supercilii. With aging and chronic

activity of the facial muscles, these lines become more prominent. BTX-A has been used to temporarily treat glabellar lines and other hyper-functional facial lines such as horizontal forehead lines, lateral canthal lines 'crow's feet', platysma bands and perioral lines [15].

In maxillofacial surgical practice, Niamtu (2000) [16] reported on the cosmetic use of BTX for facial rhytids and dynamic lines. During the mid- and late-1990s, BTX was used for lateral canthal lines (crow's feet), platysmal banding, orbicularis oris injection, masseter muscle injection and the treatment of temporomandibular disorders (TMDs). Later, there were many attempts to use BTX for different clinical situations in oral and maxillofacial surgery.

The potential applications of BTX extend beyond facial cosmetic surgery. BTX therapy is a superior treatment modality for a number of conditions when compared to pharmacotherapy or surgical intervention in terms of morbidity and mortality [13]. Therapeutic use of BTX-A has expanded to cover different painful disorders. Initially it was reported that BTX-A relieves pain associated with spasticity and cervical dystonia. Based on the discovery that BTX-A may reduce the frequency of chronic migraine attacks and associated pain, its efficacy has been clinically investigated in chronic migraine treatment [17].

BTX is clinically used in various neuromuscular and autonomous disorders. The idea of using small doses of BTX for therapeutic purposes was proposed for the first time by Kerner in 1822. Clostridium Botulinum bacteria that produces BTX was first characterized in 1897, and different BTX serotypes were identified and purified in the 20th century [18]. In the late 1960s and 1970s, based on preclinical experiments with monkeys, injections of small doses of purified BTX-A into the lateral or medial rectus muscle have been initially used in the treatment of strabismus. BTX-A has been approved for the use in strabismus in 1989, and later in other types of muscular hyperactivity disorders like hemifacial spasm, focal dystonia and upper limb spasticity, vocal tic, stuttering, cricopharyngeal achalasia, various manifestations of tremor, temporomandibular joint dysfunction, bruxism, masticatory myalgias, sialorrhea, and hyperhidrosis [19]. Intramuscular injections of BTX-A have been shown to effectively treat spasticity in multiple sclerosis patients, especially when associated with early mobilization and physical therapies [20].
Apart from movement disorders, BTX-A has been also used for treatment of autonomic system disorders and in non-muscular pain conditions [21].

Botulinum toxin (BTX) and dentistry:

In addition to the above mentioned applications of BTX in medical and cosmetic procedures, BTX can be used in the management of a number of dental disorders including; temporomandibular disorders (TMDs), dental implants and surgery, prominent gums (gummy smile), masticatory muscles hypertrophy, myofacial pain and neck pain as well as salivary glands disorders.

Tempromandibular disorders

Temporomandibular disorders (TMD) is an umbrella term used to describe a number of diseases affecting masticatory function, which may include true pathology of the temporomandibular joint as well as masticatory muscles dysfunction. TMD manifests with facial pain, clicking, headache, peri-auricular pain, neck pain, and/or decreased joint excursions. Muscular spasticity secondary to bruxism, external stresses, oro-mandibular dystonia, and psychomotor behaviors are common etiologic factors of TMD [22].

In untreated cases of excessive pathologic clenching or TMD, tooth decay is more prevalent because excessive forces can cause micro-fractures and abfracturing of enamel, especially around the existing restorations and may also be followed by gingival recession [23]. Several studies have conducted trials on patients suffering from TMD and bruxism and found that injections of BTX into the temporalis and masseter muscles significantly decreased pain and tenderness and improved function and mouth opening [24].

An earlier study investigated the effect of BTX-A injection in the lateral pterygoid muscle on temporomandibular joint (TMJ) clicking. BTX-A was injected in the ipsilateral lateral pterygoid muscle with electromyogram (EMG) guidance and the subjects were assessed for 4 months. It was concluded that BTX injection in the lateral pterygoid muscle resulted in disappearance of joint clicking clinically and a significant improvement in disc position as shown on MRI [25]. More recently, a case of a child presenting with recurring TMJ dislocation secondary to muscle hyperactivity that was managed with injections of BTX type A into the inferior lateral pterygoid muscles has been described and it was reported that the use of BTX is a reasonable, safe, and conservative, palliative treatment option for pediatric patients suffering from chronic recurring TMJ dislocation [26].

Dental implants

Overloading of the muscles of mastication can prevent or impede osseointegration of implants and/or fracture callus formation. The muscular relaxation achieved with BTX-A injections to the masticatory muscles can be therapeutically beneficial by allowing implants a better osseointegration and fracture healing in a more stable environment [27]. The muscular relaxation achieved with prophylactic use of BTX injections to the masticatory muscles before implant placement can be beneficial by allowing implant structures better osseointegrated, especially when immediate loading is needed [28].

Treatment of gingival smile (prominent gums or gummy smile) with BTX-A

The display of excessive gingival tissue in the maxilla upon smiling, or “gummy smile,” is both an oral hygiene and cosmetic issue with no simple remedy. Excessive gum exposure is frequently attributable to over-contraction of the upper lip muscles. The upper lip should symmetrically expose up to 3 mm of the gum and the gum line must follow the contour of the upper lip [29]. Various correction methods are proposed, including gingivoplasty, orthodontic treatment, orthognathic surgery, and bone resection. As they are highly complex procedures involving moderate to severe morbidity, high cost, and considerable time, they have become less frequently recommended. By contrast, the use of BTX injections into the upper lip muscle represents a simple, fast, and effective method for the aesthetic correction of gummy smile as it represents a non-surgical minimally invasive treatment option [30].

Botox is indicated when the gummy smile is due to hyper functional upper lip elevator muscles. The duration of effect ranged from 3 to 6 months, and no adverse effects were reported or observed. However, the improvement is temporary and must be repeated every six months to one year [31].

Masticatory Muscles hypertrophy

In humans, BTX injections are used in masticatory muscles (masseter, temporalis, lateral pterygoid and rarely medial pterygoid) for several indications such as trismus, bruxism, masticatory myalgia, temporomandibular joint disorders or masseter hypertrophy [32]. Paralysis of the masticatory muscles using BTX is a common treatment for cosmetic reduction of the masseters as well as for conditions involving muscle spasm and pain [33].

Masseteric hypertrophy is a rare disorder that may present as either a unilateral or bilateral swelling in the region of the angle and the ramus of the mandible. Patient complaints are usually aesthetic in nature, but there may also be pain in the region and limitation of mouth opening. The surgical treatment of this anomaly involves resection of a portion of the masseter muscle. However, there are several complications associated with surgery. These complications include severe bleeding, hematoma, prolonged edema, facial nerve injury, trismus, and bad scarring. BTXA injection intramuscularly is an alternative, relatively non-invasive, and effective treatment for masseter muscle hypertrophy [34]. Temporalis muscle hypertrophy is less common but has been managed successfully using BTX injection [35].

Myofacial pain and neck pain

Myofacial pain syndrome (MPS) is a regional pain disorder caused by taut bands of muscle fibers in skeletal muscles called myofascial trigger points. MPS is a common disorder, often diagnosed and treated by physiatrists. Treatment strategies for MPS include exercises, patient education, and trigger point injection. Pharmacologic interventions are also common, and a variety of analgesics, anti-inflammatory medications, antidepressants, and other medications are used in clinical practice. The etiology of myofacial pain syndrome is believed to be a result of either an acute episode of muscle overload or from chronic and/or repetitive muscle overload. Active myofacial trigger points, which cause pain, exhibit marked localized tenderness and often refer pain to distant sites and disturb motor function. Injection of muscles with BTX has been reported to be effective for myofacial pain caused by trigger points [36].

Salivary glands disorders

Salivary secretory diseases constitute a true challenge to the treating surgeon. These disorders may result from complications following major salivary gland surgery, oropharyngeal cancer surgery [37], or post-traumatic/iatrogenic salivary sialoceles [38]. These diseases also include neurologic drooling or sialorrhea, which are caused by either impaired swallowing after head and neck oncological surgery or radiation [39].

Sialorrhea or drooling refers to the unintentional spillage of saliva from the oral cavity. It is very common during infancy and early childhood and improves gradually as oral motor control and sensory input mature. Although drooling is considered pathologic after the age of 4 years, it

can be present until the age of 6 years in children with developmental delay [40]. The major salivary glands (the paired parotid, submandibular, and sublingual) are responsible for 95% of the 1.5 liter of saliva secreted daily. BTXA intraglandular application has been shown to significantly decrease saliva production and is considered a safe treatment for hypersalivation [41].

Xerostomia is one of the first manifestations of botulism, which led to investigations of its application for sialorrhea and drooling. Topical injection of BTX-A as a minimally invasive option for the treatment of drooling has been used for many years in neurological diseases [42]. Its greatest limitation in this indication is its transient effectiveness (3–4 months), requiring multiple and expensive administrations. BTX injection into the salivary glands has been proven effective and safe in the treatment of drooling. Efficacy rates as high as 89% to 95% have been reported when injected in the submandibular glands and parotid glands [43].

BTX injection in the salivary glands can be performed under either local or general anesthesia. BTXA is currently the most commonly used agent in the treatment of drooling in children [40]. Several studies used BTX injection into the submandibular gland of patients with cerebral palsy to treat hypersalivation associated with this disease. These studies showed that after 4 weeks marked clinical improvement in the severity of hypersalivation was recorded [43].

Salivary gland secretion is controlled by the autonomic nervous system, mediated by adrenergic and cholinergic nerve endings, but primarily under parasympathetic cholinergic control. Neurotransmitter stimulation of plasma membrane receptors stimulates salivary gland fluid secretion via a complex process that is determined by coordinated temporal and spatial regulation of several Ca^{2+}signaling processes as well as ion flux systems [44]. The BTXs work by inhibiting the release of the neurotransmitter, acetylcholine, at the neuromuscular junction thus causing muscle relaxation. Acetylcholine is also the neurotransmitter in postganglionic fibres of the parasympathetic division of the autonomic nervous system. These fibres innervate various glands, such as the salivary glands [45]. By inhibiting the release of acetylcholine at the neuro-glandular junction, a temporary salivary flow rate reduction can be achieved [41, 46]. Furthermore, researchers tested the efficacy of using Botox in neurologically impaired children. A controlled clinical trial with single injections of BTXA into the submandibular salivary glands was conducted and compared with scopolamine treatment in school-aged children diagnosed with cerebral palsy. The injections were performed under general anaesthesia with ultrasound guidance and dosages were based on the child's weight. The mean decrease in salivary flow was 25% during scopolamine and 42% following the Botox injection. In addition, fewer and less serious side effects were noted with the BTX injection [46].

Epidermal growth factor (EGF) and Botulinum toxin (BTX):

EGF is a single-chain polypeptide consisting of 53 amino acids that is derived from the cleavage of a larger precursor. EGF is now known as the prototype of the group I EGF family that also includes transforming growth factor-α (TGF-α), heparin-binding EGF (HB-EGF), amphiregulin, betacellulin, epiregulin and epigen. Functionally, these growth factors share the ability to bind the same receptor, the EGF receptor (EGFR), activate its intrinsic tyrosine kinase activity, and couple the receptor to downstream signaling pathways controlling cell proliferation, differentiation, survival, or motility [47].

In humans, the major sources of EGF are the parotid glands and kidneys. Moreover, EGF has been detected in a variety of body fluids, such as breast milk, saliva, urine, plasma, intestinal fluid, amniotic fluid. This means it is locally produced and secreted by the lactating breast, submandibular gland, kidney, Brunner's glands of the duodenum, and placenta, respectively [48]. EGF facilitates epidermal cell regeneration and plays an essential role in the process of dermal wound healing through stimulation of proliferation and migration of keratinocytes. It also promotes formation of granulation tissue and stimulates fibroblast motility. It initiates a signal transduction that results in DNA synthesis and cell proliferation [48].

A higher dose of EGF has been shown to achieve higher healing rates and shorter time to heal than a lower dose. This brings up safety concerns, as repeated application of EGF can induce hyperplasia and hypertrophy of skin keratinocytes and fibroblasts, as well as promote angiogenesis, which may predispose to cancer development, especially in patients who are immune-incompetent. However, the clinical data so far have shown that EGF treatments have been well tolerated, and no significant adverse reactions have been observed [49]. EGF receptor is expressed on most human cell types including those which play critical roles for wound repair such as fibroblasts, endothelial cells

and keratinocytes (hair follicles, sweat ducts and sebaceous glands). The EGF-induced mitogenic, motogenic and cytoprotective actions are instrumental for healing events that at the gross expression may be summarized as: (i) stimulation of productive cells migration toward and homing within the injured area, (ii) stimulation of granulation tissue outgrowth–including extracellular matrix accumulation, maturation and de novo angiogenesis, (iii) stimulation of wound contraction by stimulating myofibroblast activation and proliferation and (iv) stimulation of the damaged area resurfacing by epithelial cells migration and proliferation [50]. With regards to tissue regeneration, considerable progress has been made in identification of micro-environmental factors favoring the growth and expansion of the stem cell pool. Among them, EGF has emerged as a powerful regulator of stem cells in different tissues, such as neural stem/progenitor cells and, neural crest stem cells, germ line stem cells, cardiac stem cells, bone marrow multi-potential stromal cells (MSCs), brain tumor stem cells, mouse embryonic stem cells, gut stem cells, keratinocyte stem cells, and multipotent stromal cells in the heart [51].

A number of studies have investigated the role of EGF on the salivary gland and its effect on stem cells. EGF has shown to impose synergistic effects on stem cell expansion with other growth factors in combined therapy or through EGF-initiated upregulation of other growth factors [52]. It has been reported that EGF acts synergistically with insulin-like growth factor- I (IGF-I) I, another growth factor present in wound fluid, in stimulating keratinocyte proliferation in vitro. IGF-I contributes to the maintenance of the number of salivary gland cells as well as their para-cellular barrier function via the expression and distribution of tight junction proteins [53]. In addition to the above, the therapeutic potential of stem cells on salivary gland regeneration both in vitro and in vivo has been studied. After 3 weeks of culture, about half of the stem cells had differentiated into acinar-like cells, demonstrating stem cells' differentiation capacity in vitro. Both stem cells and differentiated acinar-like cells significantly increased saliva production, salivary gland weight, and body weight when transplanted into radiation-treated mice; these systemic and local effects indicate salivary gland regeneration [54]. Currently our research team is investigating the effect of EGF on reversing the effect of a single BTX injection on the submandibular salivary glands of rats. Submandibular salivary glands will be examined histologically, immunohistochemically through localization of cytokeratin, myosin and E-cadherin, as well as detection of ultrastructural changes using transmission electron microscopy. From the above mentioned extensive literature related to the effects of BTX and the healing potential of EGF, we hypothesize that EGF is capable of restoring the normal structural integrity of submandibular salivary glands without affecting the desirable paralyzing effect of BTX.

Paralysis a burden or bless?

Despite the simplicity and reliability of BTX office-based procedures, complications can occur even with an astute and experienced injector. The goal of any procedure is to perform it properly and safely; thus, early recognition of complications when they do occur is paramount in dictating prevention of long-term sequelae [55]. Regarding this, the most reported complications in oral or facial injections are granuloma formation, asymmetry, migration, extrusion and, more rarely, allergic reactions, infection, and haematomas [56].

The most important side effects reported for cosmetic use of BTX include immunogenicity, allergy and local complications. Neutralizing antibodies to BTX-A toxins can lead to loss of treatment effect. Clinical resistance to BTX-A has been estimated as high as 7%, and BTX-B is being investigated as an alternative therapeutic agent. In theory, because human albumin is used in the preparation of Botox, a patient could exhibit an allergic reaction, but no case has been reported. Adverse effects such as pain, oedema, erythema, ecchymosis and short-term hypoesthesia may occur after injection of BTX-A. Other reported adverse events are headache, blepharoptosis and perioral muscular palsy [57]. In therapeutic applications, complications are mostly local and relatively mild, such as pain, erythema, ecchymosis of the region injected, dry eyes, mouth droop, ptosis and lid edema, facial muscle weakness, asymmetry of facial expression during dynamic facial movements, xerostomia, transient dysphagia, restricted mouth opening, nasal regurgitation and nasal speech, headache, blurred vision, dizziness, upset stomach, infection, neck weakness, voice changes, difficulties in chewing and breathing risk of aspiration, recurrent jaw dislocation, dysarthria, salivary duct calculi and local injuries of the carotid arteries or branches of the facial nerve [11].

Systemic side effects are rarely reported, generally not dose related, and can include transient weakness, fatigue, nausea and pruritis. Flu-like syndromes have been reported, but they are generally of brief duration [58]. Perioral complications can also arise from chin, oral

commisure, and perioral injections. Correction of chin dimpling or peau d'orange skin can be achieved by medial mentalis muscle injections. Overly lateral placement of injections can paralyze the depressor labii muscles which results in a lower lip droop and weakness. Injections that are aimed at achieving subtle elevation of the oral commisure can be accomplished by injecting the depressor anguliaris muscle located laterally over the mandible. This muscle is best palpated while the patient is clenching their teeth. A lower lip dysfunction can occur if the injections are carried too medially into the depressor labii muscles. Lip weakness can also occur from perioral injections that are aimed at softening of radial perioral lines [59].

CONCLUSION

In this article we highlight the increasing importance and usage of BTX in different medical, cosmetic and dental procedures. We illustrate its types, mechanism of action and side effects. We also shed some light on the well documented healing and reparative mechanisms of EGF. Finally we propose a treatment protocol that is currently in trial, which combines the use of BTX and EGF on submandibular salivary glands of rats. This combined treatment will open the horizons for using BTX safely while maintaining the structural integrity of tissues, especially over long term treatment protocols. If successful, BTX induced muscle paralysis can then be considered blessful with no long term complications or changes to tissues.

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