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The Use of Botulinum Toxin-A Injection in Medicine and Orthopaedic Surgery

Gartenberg A[1]*, Patel B[2] and Cho W[2]

[1]Department of Emergency Medicine, Montefiore and Jacobi Medical Center, USA
[2]Zucker School of Medicine at Hofstra, USA

***Corresponding author:** Ariella Gartenberg MD, Department of Emergnecy Medicine, Montefiore Medical Center/Jacobi Medical Center, USA, 41 Westgate Road, Apt A Teaneck NJ 07666, Tel: 201-787-1762; Email: aappleba@mail.einstein.yu.edu

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Abstract

Study Design: Literature Review
Background: Botulinum toxin A (BTX-A) targets specific muscle groups to block the release of acetylcholine at the neuromuscular junction and, therefore, reduce muscular activation. Through weaking of muscle activity, BTX-A injections have become widely used for cosmetic purposes, as well as the treatment of various neuromuscular disorders including strabismus, movement disorders, and overactive bladder syndrome.
Objective: To review the history of BTX-A injections, as well as discuss its current and future cosmetic, medical, and surgical applications.
Methods: A comprehensive literature review was performed on the development, application, and efficacy of BTX-A injections in the treatment of various neuromuscular and spinal disorders.
Results: Within the orthopaedic spine world, BTX-A injections have effectively been utilized for the treatment of spastic muscular disorders, including spinal cord injuries, cervical spine pain, lower back pain, and scoliosis. By reducing muscular tone, BTX-A injections have shown over 90% reduction in pain after repeated injections.
Conclusions: BTX-A is an essential neurotoxin that functions not only through cosmetic application, but also in the treatment of neuromuscular and spinal disorders. Further studies of greater sample size are needed to fully address potential limitations and assess long-term success of such treatment modalities.

Keywords: Botulism Toxin-A; Neuromuscular Disorders; Spinal Disorders; Spasticity

Introduction

Over the years, Botulinum Toxin injections have gained popularity in society for a variety of medical and cosmetic reasons. According to an article in the New York Times, the younger population has been increasingly interested in Botox treatments over the past few years as self-care has become a greater priority [1]. In fact, more patients began looking for Botox treatments after spending copious amounts of time seeing themselves on screens during the

pandemic [1]. These treatments serve for many people as a means to improve their self-esteem and image. However, this poses a social issue as Botox treatments only serve as a temporary treatment, and do not solve the root of the self-esteem insecurities people face.

The Clostridium botulinum bacteria strains produce a poisonous neurotoxin known as botulinum toxin [2]. While seven different serotypes (A-G) exist, botulinum neurotoxin type A (BTX-A) has been the most heavily studied and utilized in the treatment of movement disorders [3]. All seven botulinum neurotoxins have similar mechanisms of action involving vesicle fusion. A key difference among the neurotoxins is the duration of paralysis. In addition, the serotypes have distinct neurotoxin protein sizes, intracellular protein targets, and quantity of the toxin in the activated form [4,5].

The botulinum toxin functions to block the release of acetylcholine, a neurotransmitter of the neuromuscular junction. Botulinum toxin needs to be cleaved by either endogenous or exogenous proteases to be activated from its original inactive single-chain polypeptide form. The 150 kDa polypeptide is cleaved into an activated form of 100 kDa heavy chain and 50 kDa light chain that are linked together by a disulfide bond [6,7]. The heavy chain of botulinum toxin binds to high affinity receptors on cholinergic neuron membranes, which allows the toxin to enter the cell via endocytosis. The disulfide bond connecting the heavy and light chain of the toxin is cleaved to allow the toxin to enter the cytoplasm of the cell [7]. Here, the light chain interacts with proteins that function in neurotransmitter release. The SNARE protein complex allows vesicles that carry neurotransmitters to fuse with the synaptic membrane of the cell. BTX-A works to destabilize this SNARE complex by specifically cleaving SNAP-25, a protein component of the SNARE complex [6].

As botulinum toxin blocks acetylcholine release from carrying out its function at the neuromuscular junction, muscle activity decreases and weakens. Botulinum toxin can be prepared as Botox and administered intramuscularly. Botox involves the addition of BTX-A, albumin, and sodium chloride [7]. The effects of BTX-A can be seen within the first week of injection and last for three to six months [3].

Medical Applications of Botulinum Toxin-A Injections

BTX-A injections have been widely used across the medical field. BTX-A injections have been used in the treatment of spastic or dystonic muscular disorders, as BTX-A blocks acetylcholine release and decreases muscular activation [6].

Ophthalmology (Strabismus)

BTX-A injections were originally used to treat strabismus in the 1980s [8]. Scott studied BTX-A injections in 42 patients with strabismus. Injections were given in the horizontal muscles for patients with paralytic strabismus. Results showed success in preventing eye contracture and enabling relaxation of the extraocular eye muscles. The effects of these injections lasted for varying time periods of up to 411 days [8].

Neurology (Movement Disorders)

BTX-A injections are often used as adjunctive treatment for movement disorders, including all hypokinetic and hyperkinetic disorders [9]. Dystonia is a hyperkinetic movement disorder in which a patient has continued or sporadic muscle contractions that result in repetitive movements [10]. Cervical dystonia is the most common form of focal dystonia and primarily results in involuntary posturing of the head and neck [11]. Costa, et al. [11] verified the effectiveness of BTX-A as a treatment for cervical dystonia through thirteen BTX-A versus placebo trial studies. Most of the trials utilized a Tsui scale to measure the severity of postural deviance. BTX-A resulted in statistically significant improvements for cervical dystonia patients on all objective and subjective rating scales.

Another hyperkinetic movement disorder is essential tremor [9]. In a double-blind study by Mittal et al., BTX-A injections were given to treat essential hand tremor. 33 patients were given 80-120 units of BTX-A injection in 8-14 hand muscles through an individualized method. The results were compared by the Fahn Tolosa Marin tremor rating score at 4 and 8 weeks post-injection. Statistically significant improvement in the rating score at 4 and 8 weeks post-injection was demonstrated [12].

Rehabilitation (Spinal Cord Injuries)

The use of therapeutic BTX-A injections has also been applied to the treatment of spinal cord related injuries [13]. Spasticity is a very common feature in patients that have suffered spinal cord injuries. Around 78% of patients suffering a chronic spinal cord injury develop spasticity within one-year post injury. Specifically, of those with spinal cord injuries classified as ASIA A (American Spinal Injury Association), 93% of cervical spinal cord injury patients and 72% of thoracic spinal cord injury patients developed spasticity [14]. Spasticity occurs as the flow of signals controlling body movements from the spinal cord to the brain is disrupted through an injury to the spinal cord. Consequently, the signals revert to the motor neurons in the spinal cord and result in a reflex muscle spasm [15]. BTX-A injections are advantageous in helping to decrease

such spasticity, as BTX-A can localize its effect to a targeted muscle without affecting others [13]. In a study by Keren et al., BTX-A injections were given in four to eight points in the legs of five patients with severe spasticity from a spinal cord injury and no response to standard spasticity treatment. The aim was to block muscle-nerve synapses. The results showed improvement for all five patients with reduction of leg muscle tone in the area injected. Some patients also demonstrated reduced tone in more distal muscles [16].

Surgical Applications of Botulinum Toxin-A Injections

Plastic Surgery (Cosmetic Applications): BTX-A injections are also commonly used for cosmetic purposes. Clark and Berris conducted the first case report regarding the use of BTX-A injections for aesthetic purposes [17]. Clark, et al. [17] injected BTX-A into the contralateral functioning frontalis muscle to treat facial asymmetry. The patient had excessive wrinkling and frowning on the forehead due to frontalis, corrugators, and depressor supercilii muscle contractions. BTX-A injection resulted in a satisfactory improvement in wrinkling.

The use of BTX-A injections for facial wrinkles is the most frequent type of cosmetic treatment in the United States [18]. A major area of interest in the cosmetic field involves the use of BTX-A injections to smoothen glabellar frown lines. Rzany, et al. [19] evaluated the efficacy and safety of BTX-A injections in the treatment of glabellar and central forehead wrinkles [19]. A double-blind, randomized control trial was conducted involving 221 patients with glabellar wrinkles. Either three or five BTX-A injections were given in the procerus and corrugator muscles. The severity of the wrinkles was graded on a scale of 0 to 3, with 3 being severe wrinkles. A statistically significant decrease in wrinkle severity was observed in the group receiving BTX-A injections. No adverse effects were reported [19]. Similarly, Satriyasa evaluated the efficacy of BTX-A injections in reduction of facial wrinkles. The optimal dose of cosmetic Botox was demonstrated to be 20 units and did not result in any adverse side effects [20]. Furthermore, a study by Small demonstrates better outcomes in BTX-A injections given for dynamic wrinkles as compared to static wrinkles. Dynamic wrinkles are seen during muscle contraction and static wrinkles are seen at rest [18].

BTX-A injections have also shown positive effects in wound healing of hypertrophic scars involving the face and neck [21]. The effects of BTX-A injections was assessed through measurement of scar width, visual analysis score (VAS), and patient satisfaction. The patients treated with BTX-A had significantly narrower scars ($p=0.006$) and higher VAS compared to patients who only received saline [21]. However, only nine studies were analyzed for these results, of which only three were completely unbiased. Further research is needed to assess the efficacy of BTX-A injections in wound healing.

Urology (Overactive Bladder Syndrome): BTX-A injections have been studied as a potential treatment for overactive bladder syndrome. Chapple et al. evaluated patients given 100U BTX-A injections as compared to placebo for management of overactive bladder syndrome. At 12 weeks post-injection, a significant decrease in daily urinary incontinence episodes ($p<0.0001$) was demonstrated in patients receiving BTX-A. Additionally, a significantly higher quality of life after BTX-A injections was observed utilizing the King's Health Questionnaire ($p<0.001$) [22]. Duthie, et al. [23] reports better outcomes in incontinence episodes, bladder capacity, and quality of life in patients receiving BTX-A injections relative to placebo [23]. Similarly, Anger et al. demonstrates an average of 3.88 less daily incontinence urinary episodes in BTX-A treated patients. There was also a significant improvement in the quality of life following BTX-A injections [24].

Orthopaedic Surgery

BTX-A injections were first utilized in the orthopaedic field in 1993 for controlling spasticity in pediatric cerebral palsy (CP) patients. Koman, et al. [25] administered intramuscular BTX-A to 27 pediatric patients to control muscular imbalances from cerebral palsy. The effects of BTX-A injections became apparent within 12-72 hours of injection and lasted 3-6 months. With limited side effects noted, BTX-A was considered an adjunctive measure to delay surgery in pediatric patients with CP [25].

Hoare et. al found high-level evidence supporting the use of BTX-A in combination with occupational therapy for children will upper limb spastic CP [26]. Similarly, Kanellopoulos, et al. [27] describes 20 children with upper limb spastic CP that were treated with BTX-A injections, followed by static night splint in half of the patients. Upper limb function was assessed at baseline, at 2 months, and at 6 months following injection. No complications relating to BTX-A injections were observed. Statistically significant improvement ($p=0.000$) was observed in all patients, with a greater rise from baseline (15.9% vs. 4.2%) in patients that received BTX-A injections followed by static night splinting [27].

Additionally, Satila, et al. [28] conducted a prospective longitudinal study across 2 years to assess BTX-A injection use on upper limb function for 6 children with cerebral palsy. Some of the measurements taken included spasticity, active and passive range of movement, ability to grip, and self-

care capability. These factors were assessed at baseline, 1, 3, and 6, 12, 18, and 24 months follow-up after each BTX-A injection. The results showed that all children had muscle tone reduction and increased range of motion with BTX-A treatment. While the spasticity returned within 6 months for the children, improved range of motion was noted for four children. Across the 2 year period, an improvement in cosmetic appearance was also observed [28].

Lukban, et al. [29] describes the effectiveness of BTX-A injections in upper and lower limb spasticity for children with CP [29]. Regarding upper limb spasticity, five out of six randomized controlled trials showed a decrease in muscle tone, most commonly at the wrist, and improved hand function. Regarding lower limb spasticity, six Class I randomized control trials were assessed. Of those studies, three listed an improvement in gait pattern with gastrocnemius spasticity and one study found a significant decrease in hip adductor muscle tone [29].

Multani, et al. [28] examined the literature associated with the adverse muscular effects of BTX-A injections. It was found that injections cause a denervation in the skeletal muscle, with resultant muscle atrophy. Muscle atrophy is when muscle fibers are replaced by fat and connective tissue. Even once the BTX-A effects start to diminish, the recovery of muscular function and morphology is still incomplete 12 months following injection [28]. Therefore Multani, et al. [28] suggests a reduction in the frequency of BTX-A injection, as well as measurement of muscle volume before and regularly after treatment to detect possible muscle atrophy.

Cervical Spine Pain

BTX-A injections have also been used for postoperative pain management following cervical spine surgery for cervical spondylotic myelopathy. In a study done by Finiels and Batifol, 215 patients underwent cervical spine surgery and 38 patients expressed postoperative neck pain [30]. One group consisted of 19 patients who were given BTX-A injections in the trapezius, supraspinalis, splenius capitis, and rhomboids. The second group consisted of 19 patients who were treated conservatively with physical rehabilitation. The results showed promising benefits of BTX-A as a treatment for postoperative cervical spine pain. Patients that received BTX-A injections reported a decreased level of pain based on a 4.6 point decrease in the VAS scale after 1.5 months of treatment, as compared to a 0.6 point decrease in the control group.

Langevin et al. found that BTX-A injections do not have a statistically significant positive effect on chronic neck pain. This study systematically reviewed nine trials, with a total of 503 participants who experienced neck pain with or without associated cervicogenic headaches, but excluding cervical radiculopathy and whiplash associated disorder. The results showed no difference in pain levels for patients given BTX-A injections compared to those given saline injections (SMD pooled -0.07 (95% confidence intervals (CI) -0.36 to 0.21) [31].

Cervical injury and muscle spasms have been associated with whiplash-associated disorder (WAD). WAD results from trauma, most often due to motor vehicle accidents and sports injuries. The cervical injury ensues because of rapid extension followed by neck flexion. Patients with chronic WAD experience continual cervical pain and decrease in range of motion [32]. Freund and Schwartz studied the efficacy of BTX-A injections as therapy in 26 patients with chronic neck pain resulting from WAD post motor vehicle accident. BTX-A injections were given at five injection sites chosen by palpation, including the splenius capitis, rectus capitis, semispinalis capitis, and trapezius. The group receiving BTX-A had a significant improvement in range of motion and pain reduction ($p<0.01$) 4 weeks post-injection as compared to placebo [33].

Lower Back Pain

Studies have shown the benefits of BTX-A injections in lower back pain. Lower back pain is an extremely prevalent condition and is the second most common illness among patients in the United States [34]. According to the Health Policy Institute at Georgetown University, around 65 million people from the United States currently suffer from lower back pain [35]. In a double-blind, placebo-controlled study, patients with chronic, refractory lower back pain were given BTX-A injections in the paraspinal muscles. The injections were administered at each lumbar level. The results of this study demonstrated that 91% of patients continued to have less pain after repeat injections [36]. The results of the study recommend the use of BTX-A injections to treat refractory lower back pain. Additionally, Foster et al. studies 15 patients with chronic lower back pain who were given BTX-A injections at five lumbar paravertebral levels ipsilateral to the patient's reported greatest discomfort. The results of the study showed that at 3-weeks post-treatment, 11 out of the 15 patients with the injection treatment had more than 50% pain relief compared to pain relief in only 2 out of 16 patients with placebo saline treatment [37]. Improvement in pain relief was measured according to the visual analog scale and demonstrated a statistically significant rise.

Cogne, et al. conducted a randomized double-blinded trial study with 19 patients suffering chronic low-back pain. Low back pain intensity level was measured according to a visual pain scale as well as functional disability by the Quebec Back Pain Disability Scale. 200 units of BTX-A injection was

given in the paravertebral muscles to one group and placebo was given to the other group. No statistically significant difference was found in the low back pain between the two groups 30 days after treatment (p=0.97) [38]. Limitations of this study included a lower dose of BTX-A injection given and small sample size.

According to a study by Joumaa et al., BTX-A injections in the paraspinal muscles of rabbits were found to result in a decrease of active force and shortening velocity in fast fibers, but not in slow fibers [39]. These results are significant as it was shown that BTX-A injections can lead to muscle atrophy and fat infiltration. Therefore, when patients are given Botox injections for back pain, side effects are important to consider such as a loss of muscle mass and contraction affecting joint health and function.

Neuromuscular Scoliosis

BTX-A injections are also being studied as a potential treatment modality for neuromuscular scoliosis. Neuromuscular scoliosis is the second most common spinal deformity and is most often caused by CP [40]. CP consists of a group of non-progressive developmental and postural disorders that occur in the developing fetal or infantile brain. The most common form of CP includes the spastic motor type. While there are no definitive treatments, therapeutic options include splinting, casting, passive stretching, and medication and surgery to reduce spasticity. BTX-A injections have been used as an adjunctive therapy to such techniques to reduce spasticity and improve range of motion and function [41]. In a study by Wong et al., 16 patients with CP-associated scoliosis were given BTX-A injections into the spinal musculature using ultrasonic-guidance [42]. The radiographic and clinical examinations before and six weeks after the injection were recorded. According to the Wilcoxon matched pair signed-rank test, there were no significant differences in the radiographic or clinical examinations between patients receiving BTX-A injections and placebo (NaCl injections) [42]. However, a larger population size is needed to assess for potential differences involving such patients.

Conclusion

BTX-A is an essential neurotoxin that serves as a treatment option for a variety of disorders and cosmetic applications. It is most effective in the treatment of spastic or dystonic muscular disorders due to reduction in muscular tone. Consequently, the application of BTX-A injections can be expanded to include illnesses that have chronic or significant spasticity. The application of BTX-A injections is thus promising in the orthopaedic spine field. Further trials involving BTX-A injections in spinal disorders involving a larger sample size are needed to assess for treatment success. The efficacy of BTX-A injections should also be investigated in postoperative spinal surgery and neuromuscular scoliosis. Overall, BTX-A is a very effective neurotoxin that serves a wide variety of purposes and continues to help in patient recovery.

Authors Preferred Treatment

Plastic Surgery (Cosmetic Applications): Botulism Toxin A injections can be utilized successfully in the treatment of excessive facial wrinkling with no reported adverse outcomes. BTX-A injections have also been utilized for wound healing of facial hypertrophic scars, however further data is needed.
Urologic Applications: BTX-A injections have improved quality of life in patients suffering from overactive bladder syndrome.
Cerebral Palsy (Pediatrics): BTX-A injections have shown success in delaying surgical interventions for the pediatric population suffering from cerebral palsy induced upper and lower limb muscle spasticity.
Cervical Spine Pain: BTX-A injections have been used successfully in the treatment of postoperative pain following cervical spine surgery, as well as chronic neck pain related to whiplash-associated disorder. Significant improvement in range of motion and pain reduction has been reported.
Lower Back Pain: BTX-A injections have shown promising benefit in the use of refractory chronic lower back pain; however various side effects have been reported, including loss of muscle mass and contraction, when BTX-A is injected within the paraspinal muscles.

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