Botulinum Neurotoxin as a Therapeutic Modality in Orthopaedic Surgery: More Than Twenty Years of Experience

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Botulinum Neurotoxin as a Therapeutic Modality in Orthopaedic Surgery: More Than Twenty Years of Experience

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Introduction

Botulinum neurotoxins are among the most potent toxins found in nature, and are produced by Clostridium botulinum, an anaerobic, gram-positive, spore-forming rod-shaped bacterium. There are seven known serotypes of botulinum neurotoxins (termed A, B, C1, D, E, F, G) that cleave soluble N-ethyl-maleimide-sensitive factor attachment receptor (SNARE) proteins, preventing effective release of neurotransmitters across specialized synaptic junctions. Blocking SNARE protein function within neuromuscular junctions produces flaccid paralysis, results in anhidrosis within sweat glands, and increases nutritional blood flow in vascular beds. On the basis of these findings, it was hypothesized that controlled injections of botulinum neurotoxins could be used to treat neuromuscular disorders. The benefits of botulinum neurotoxin injections in the treatment of various neurological disorders have captured the attention of physicians from multiple specialties and have contributed to the widespread use of botulinum neurotoxins in modern medicine.

Currently, only botulinum neurotoxin type-A (BoNT-A) and B (BoNT-B) serotypes are approved by the U.S. Food and Drug Administration. The mandated labeling includes the following therapeutic and anesthetic indications: (1) treatment of cervical dystonia in adults; (2) treatment of strabismus and blepharospasm associated with dystonia, including benign essential blepharospasm or seventh cranial nerve disorders in patients who are twelve years of age or older; (3) treatment of severe primary axillary hyperhidrosis; and (4) treatment of severe glabellar lines associated with corrugator and/or procerus muscle activity in patients who are sixty-five years of age or younger.

This article outlines the role of botulinum toxins, particularly type A, as a therapeutic modality in musculoskeletal conditions on the basis of the peer-reviewed literature and the personal experience of the authors. Some of the information presented in this article describes off-label indications for drugs as defined by the Food and Drug Administration. The doses, side effects, techniques, and information reflect the opinions of the authors and the cited literature.

Mechanism of Action

Regulated exocytosis of neurotransmitters, in which synaptic or secretory vesicles fuse with the plasma membrane to release their contents in response to a Ca²⁺ trigger, underlies neurotransmission and hormone secretion. Considerable advances have resulted in the identification of SNARE proteins (synaptobrevin, syntaxin, and synaptosomal-associated protein-25 [SNAP-25]), which are essential for synaptic or secretory vesicle fusion to the plasma membrane and neurotransmitter exocytosis (Figs. 1-A and 1-B). Much of our understanding of the critical role of these proteins is related to the finding that the application of clostridial neurotoxins (botulinum toxins A through G and tetanus toxin) blocks Ca²⁺-triggered neurotransmitter release by cleavage of these proteins.

Research has shown that when botulinum neurotoxins find their primary targets, i.e., neuromuscular junctions, they interfere with the acetylcholine release process, but not with acetylcholine storage or Ca²⁺ influx, leading to a blockade of neurotransmitter release and muscular paralysis. All botulinum neurotoxins employ a similar mechanism of action, which may be divided into three main steps: binding, internalization, and intracellular action. Prior to binding, botulinum neurotoxins are synthesized as single polypeptide chains of approximately 150 kDa. This single chain is posttranslationally cleaved into a 50-kDa light chain and a 100-kDa heavy chain. On cleavage, the light chain and heavy chain of botulinum neurotoxins remain covalently and reversibly linked by a disulfide bond. The heavy chain of botulinum neurotoxins acts as the binding and translocation domain of the other chain. The light chain contains the enzymatic domain of the neurotoxin, and is responsible for inhibiting NSF (N-ethyl-maleimide-sensitive factor) fusion activity, thereby preventing the release of neurotransmitter.
The heavy chain of the BoNT-A targets the toxin to specific types of axon terminals due to their high affinity for external ectoreceptors. After the heavy chain attaches to proteins on the surface of axon terminals, the toxin is taken into neurons by endocytosis. The light chain leaves the endocytotic vesicles and reaches the cytoplasm. The light chain of the toxin has protease activity and prevents the formation of the SNARE complex. (Reprinted, with permission, from: Koman LA. Wake Forest University Orthopaedics Handbook. Winston-Salem, North Carolina: Wake Forest University Orthopaedic Press; 2004. p 2.)
domain, facilitating endocytosis into cholinergic nerve terminals. Within the nerve terminal, the light chain of botulinum neurotoxin, a zinc-dependent endopeptidase, is activated by the acidic environment and acts as the catalytic domain, cleaving SNARE proteins. This proteolytic attack prevents formation and fusion of the synaptic fusion complex necessary for release of intracellular neurotransmitters, such as acetylcholine. SNARE proteins are involved in the release of various neurotransmitters other than acetylcholine, which explains in part the diverse effects of botulinum neurotoxins. These autonomic and noncholinergic effects of botulinum neurotoxin introduced into noncholinergic nerve terminals formed the rationale for the clinical application of botulinum neurotoxin in hypersecretory and pain conditions. For example, exocytosis is necessary for SNARE-protein mediated release of pain mediators such as substance P, calcitonin-gene-related peptide, and/or glutamate. Thus, blockade of the exocytosis of these substances decreases painful stimuli.

**Rationale for the Use of Botulinum Toxins in Musculoskeletal Conditions**

For patients with musculoskeletal disorders, botulinum neurotoxin injections produce safe, predictable, and reversible motor weakness as demonstrated in both clinical and basic research. The use of botulinum neurotoxins, namely BoNT-A, to modulate musculoskeletal disorders has evolved as a result of the initial experiences with spasticity associated with cerebral palsy, stroke, head injury, spinal cord injury, and multiple sclerosis. To date, many other potential indications have been identified (Table 1). However, it is important to remember that the Food and Drug Administration-approved indications for orthopaedic applications are limited and that most of the usage is considered to be off-label.

**Botulinum Toxin Preparations and Potency**

Although there are seven known serotypes of botulinum neurotoxins, only BoNT-A and BoNT-B preparations are commercially available. There are three preparations of BoNT-A: Botox (Allergan, Irvine, California), Dysport (Ipsen, Slough Berkshire, United Kingdom), and Xeomin (Merz, Frankfurt, Germany). There is only one form of BoNT-B, and that is Myobloc (Elan Pharmaceuticals, South San Francisco, California). In Europe, Myobloc is distributed under a different trade name, Neurobloc. As of May 2008, only Botox and Myobloc were approved by the Food and Drug Administration for clinical use in the United States.

The formulations of the three available BoNT-A preparations are different. Botox is supplied in vials containing 100 units (U) of BoNT-A, 0.5 mg of human albumin, and 0.9 mg of sodium chloride. Similar to Botox, Xeomin is available in 100-U vials also containing human albumin, and 20% sucrose. Dysport is available in vials containing 500 U of BoNT-A, 125 μg of human albumin, and 2.5 mg of lactose. All three preparations contain BoNT-A in a lyophilized form requiring reconstitution with normal saline solution. Botulinum neurotoxin-B differs from BoNT-A not only by serotype but also by method of production and toxin activity. Unlike BoNT-A preparations, Myobloc (BoNT-B) is supplied as a solution in vials containing 5000 U/mL of BoNT-B, 0.05% albumin (human), 0.01 M sodium succinate, and 0.1 M sodium chloride buffer at a pH of 5.6.

Within BoNT-A formulations, there are differences in potency among Botox, Xeomin, and Dysport and caution is
required when extrapolating dosage from one product to another. The standard unit used to measure botulinum neurotoxin potency is derived from the mouse lethality assay, in which one mouse unit is defined as the amount of botulinum neurotoxin injected intraperitoneally that kills 50% of female Swiss-Webster mice that weigh 18 to 22 g each (i.e., Lethal Dose-50). However, the assay methodology varies among manufacturers, making dose comparisons difficult.

Dosing and Injection Technique

Historically, the reported dosage of BoNT-A used in studies has varied (see Appendix). While some studies used dosages of 100 or 200 U regardless of patient weight, many early reports were consistent with recommendations that determined the units of toxin per kilogram of body weight, with the maximum total dose being based on body weight. Although these early recommendations proved to be safe, they did not address differences in the mass of the specific muscles being injected. A more specific approach has been developed on the basis of the number of neuromuscular junctions and associated SNARE-containing organelles that need to be blocked. This recommended approach is based on three primary concepts: (1) the optimal dosage for a 110-g lateral gastrocnemius muscle is 100 U, (2) higher dose volumes are more effective, but volume should not exceed 30% of the mass of muscle to be injected, and (3) blockade of each neuromuscular junction requires the same amount of toxin. After adjusting the ideal gastrocnemius muscle dose for the muscle weight (e.g., a 55-g muscle would require only 50 U), the required dose for a specific muscle is determined by multiplying the calculated gastrocnemius muscle dose by a predetermined factor (see Appendix).

The decision about which muscles to inject with BoNT-A is based on localization of the tightness and severity of spasm in each individual patient. Additionally, a clinical examination is required to determine the localization of the muscle tightness as well as patient history and range-of-motion measurements. The clinical examination consists of standard range-of-motion assessments for the involved joint(s) as well as palpation of the associated muscle(s) under stretch. While palpation and the use of osseous landmarks can be used to determine optimal injection sites for large, superficial muscles (Fig. 2), electromyographic control and/or ultrasound guidance is recommended for technically demanding muscles that require precise needle placement to optimize results (Fig. 3) (see Appendix). Our injection algorithm is based on two fundamental concepts: (1) the ideal injection site(s) is determined by the spatial distribution of the neuromuscular junctions, and (2) the number of injection sites reflects the anatomy of the target muscle and assumes a toxin diffusion of 25 to 35 mm. On the basis of this estimated diffusion radius, there needs to be ap-
proximately one injection for every 50 to 70 mm of measured muscle-belly length.

After identifying the appropriate injection sites, a needle size (ranging between 23 and 27 gauge) should be selected on the basis of muscle depth, the amount of difficulty encountered in palpating the muscle, and whether electromyograms will be utilized. If a long needle is required or the muscle is difficult to palpate under stretch, a larger-bore needle should be selected. The larger bore helps facilitate the sense of fascial penetration on the part of the practitioner and provides an appreciation of the relative resistance of a muscle belly compared with that of fat. Injections that require the use of electromyography should be performed with a needle that permits the simultaneous injection of BoNT-A.

In general, BoNT-A injections may be safely performed without sedation. Over the past fifteen years, more than 95% of our patients (more than 20,000 injections) have tolerated injections either with no anesthesia or with analgesia with topical spray techniques (e.g., dichlorodifluoromethane 15%, trichloromonofluoromethane 85% spray; Fluori-Methane Spray and Stretch; Gebauer, Cleveland, Ohio). Recently, it has been reported that cooling by spray solutions or ice can be used to reduce anxiety and pain during injection. Although general anesthesia is typically not required, it can be used for patients who experience severe apprehension or who require multiple injections, iliopsoas injections, and/or injection in muscles that are difficult to localize (Fig. 4).

Orthopaedic Indications for the Use of Botulinum Neurotoxin-A

Cerebral Palsy

Cerebral palsy is a nonprogressive group of syndromes of posture and motor impairment that affects >500,000 individuals in the United States. These syndromes are characterized by fixed contractures, torsional deformities of long bones, and joint instability resulting from muscle hypertonia during growth and development (Fig. 5). Patients commonly present with muscle spasticity as well as weakness, pain, joint deformity, osseous deformity, and/or rigidity. Traditional treatment has been physical therapy and bracing. Unfortunately, some problems are recalcitrant to these conventional interventions. Although physical therapy combined with appropriate splinting has been shown to improve health-related quality of life and to decrease disability, the lack of supporting randomized prospective studies makes the long-term efficacy of these interventions unclear. A recent randomized controlled study reported that physical therapy, five times per week, provided improved motor function in the short term; however, the results were not sustained. Similarly, another randomized controlled trial indicated that there was no evidence that addi-
The efficacy of BoNT-A for the treatment of spastic-type cerebral palsy has progressed over the last fifteen years. On the basis of the reported efficacy of the use of BoNT-A for other spastic disorders, such as torticollis, the senior author (L.A.K.) recognized the potential benefit of BoNT-A injections for the management of spasticity in patients with cerebral palsy and, in January 1987, initiated the first clinical trial in the United States for the purpose of studying this modality. That study assessed twenty-seven pediatric patients who had dynamic deformities that were unresponsive to other nonoperative treatment modalities and for whom surgery was the only other realistic alternative. Following BoNT-A injections, all patients showed improvement in clinical assessment (Table II). There were no major adverse outcomes in this initial cohort. The only side effects reported were soreness at the injection site, generalized fatigue, and weakness of the injected muscle. These symptoms were transient, with complete resolution at the time of the final follow-up visit. In addition, a placebo-controlled, randomized double-blind study assessing BoNT-A in the management of patients with cerebral palsy was also undertaken to evaluate the efficacy of toxin injections in the management of dynamic equinus deformities. Five of six patients receiving BoNT-A showed improvement as compared with two of six patients in the placebo cohort.

On the basis of the success of these initial trials, a larger, prospective, double-blind randomized clinical trial involving 114 children with cerebral palsy and dynamic equinus foot deformities was initiated to evaluate the safety and short-term efficacy of BoNT-A. Patients were seen at five scheduled follow-up visits. The Physician Rating Scale composite score responder rate was significantly greater in the BoNT-A group compared with the placebo group at all follow-up visits. By week eight, thirty-one (61%) of fifty-one patients in the BoNT-A group responded as compared with only fourteen (25%) of fifty-five in the placebo group. Similar to previous study cohorts, there were no serious adverse events reported in the BoNT-A group.

The most recent assessment at Wake Forest University School of Medicine included 172 children who received injections of BoNT-A for the treatment of spastic-type cerebral palsy. A mixed modeling procedure was used to identify changes both in physical functioning outcomes (Functional Independence Measure for Children) as well as in quality of life of the parent caregiver (Stein and Riessman Impact on the Family Scale). It was reported that, in comparison with baseline, the administration of each additional BoNT-A injection was associated with a 2.3% improvement in the functional outcomes and a 2.5% improvement in the parent’s overall perception of the severity of the child’s condition.

Following the release of the initial report in 1993, other research centers also began to assess the possible benefit of BoNT-A in the treatment of cerebral palsy patients. The interest in this treatment option is reflected in the more than doubling of publications concerning “cerebral palsy and botulinum” in the most recent five-year publication period (2003 to 2007, n = 250) as compared with the preceding five-year period (1998 to 2002, n = 123). The recent studies (2003 to 2007) represent nearly 62% of the published cerebral palsy-related botulinum reports to date; during the first five-year period, relatively few studies (n = 32) were published. This interest served as one of the justifications for this current study, in which we attempted to understand how the treatment of cerebral palsy has progressed over the last fifteen years.

In order to assess the reported efficacy of BoNT-A in the treatment of cerebral palsy at other institutions, a systematic review was conducted of the literature found on the MEDLINE and EMBASE bibliographic databases. The initial search parameters used to identify potentially relevant articles were cerebral palsy and botulinum. Bibliographies of review articles were then searched for any additional relevant studies. Two of the authors (D.R.M. and T.M.S.) screened all articles according to a previously defined protocol. The review was limited to Level-I or Level-II studies that reported clinical outcomes following BoNT-A injections in patients with cerebral palsy. There were thirty-three studies that were reviewed, with a total of 1267 patients treated in these studies. Twenty-six of the studies assessed lower-extremity treatments. Overall, the conclusions from these studies were: (1) BoNT-A improved clinical outcomes as compared with the outcomes in placebo cohorts, (2) BoNT-A combined with casting and/or therapy is more effective than BoNT-A alone (maintenance and increases in muscle-fiber length are enhanced by active and passive range-of-motion exercises, splinting, and strengthening programs), and (3) relatively few adverse events have been reported at the dosages used (see Appendix). We found only seven randomized prospective studies that assessed the use of BoNT-A for the treatment of upper-extremity spasticity in patients with cerebral palsy, which implies that the absolute ben-
The outcomes seen by us and the outcomes reported in other studies suggest that the efficacy of the botulinum toxin is variable. The outcome may be affected by the dosage and toxin formulation, the location of the injection site within the muscle, the type of muscle motor units that are injected, the variability of the distribution of neuromuscular junctions among muscle groups, and the variability in patient responses to the injections. Additional research will be required to evaluate these variables.

**Lateral Epicondylitis**

Lateral epicondylitis affects 1% to 2% of the general population each year\(^1\). Men and women are affected equally, with symptoms more commonly seen in the dominant arm. Although the term *lateral epicondylitis* suggests an inflammatory process, it is often a self-limiting disease; approximately 80% of newly diagnosed patients report symptomatic improvement at one year\(^{19,20}\). The majority of cases are idiopathic and are often related to repetitive activity, such as playing tennis. The origin of the extensor carpi radialis brevis muscle is thought to play a major role in the etiology because of its unfavorable anatomic situation. Scars within any of the wrist extensor origins, as well as irritation of the posterior interosseous nerve and intra-articular involvement of the elbow, may also contribute to the disease. The resulting pain and wrist extensor dysfunction can be extremely debilitating, leading to an interference with work and a negative impact on health-related quality of life\(^2\). Given the high prevalence of lateral epicondylitis (reported in one study to be 1.3% of the population between the ages of thirty and sixty-four years\(^{21}\)) and its impact on health-related quality of life, early initiation of nonoperative treatment modalities is indicated. On the basis of our experience, BoNT-A injection appears to be a viable option for the treatment of lateral epicondylitis when initial nonoperative treatment (rest, anti-inflammatory medications, physical therapy, counterforce bracing, and corticosteroid in-
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Tendons Repair
Research on tendon repair techniques has been directed primarily at increasing the strength of the repair site in order to prevent tendon gapping and/or rupture during rehabilitation. Rupture of the tendon repair site is a devastating complication frequently caused by the excessive force generated by active muscle contraction, co-contraction of antagonist muscles, and friction between the tendon and the surrounding tissues. Following tendon repair, motion at the repair site is essential to minimize adhesion formation and facilitate healing. However, disproportionate contraction of muscles may result in forces strong enough to cause the repair to rupture. Therefore, pharmacologically mediated aid (bioprotection) with the use of BoNT-A may represent an important role in securing the tendon repair site while achieving effective active mobilization. Due to the reversible nature of the toxin-caused muscle weakness, the effects of the toxin are gone by the time that the repaired tendon has healed.

The Orthopaedic Research Laboratory at the Wake Forest University School of Medicine developed an animal model to evaluate the temporary and controlled reduction of muscle force as a result of injection with BoNT-A, especially with regard to protecting the integrity of the tendon repair site, permitting safe postoperative active and passive range of motion, and reducing the prevalence of postoperative complications. The protective effects of BoNT-A injections on the tendon repair site were evaluated by measuring gap size, rupture rate, electrophysiology (twitch, tetanus), and mechanical strength and through histologic examination of the repaired tendon. Botulinum neurotoxin-A treatment prevented gap formation and rupture when compared with saline-solution injections. Moreover, the mechanical force that was required to mechanically rupture the tendon was significantly higher in the BoNT-A group than in the saline-solution group at early time points (less than four weeks) following tendon repair (p < 0.007 and p = 0.0285). With regard to muscle force generation, intramuscular BoNT-A injections resulted in a significant decrease (p < 0.007) in the force of twitch contractions (Fig. 6) and tetanic contractions (Fig. 7). At all time points prior to eight weeks, twitch and tetanic contractions were significantly decreased in the BoNT-A injected group as compared with the saline-solution-injected group (p < 0.007).

Tüzün et al. reported on the results of BoNT-A injections as adjunctive therapy in zone-II flexor tendon repair in seven children who were younger than six years. Sufficient relaxation of muscle tone was noted forty-eight to seventy-two hours after BoNT-A injection, and it continued for about six weeks (range, three to ten weeks). Surgically, there were two good and five excellent results according to the Strickland criteria. Botulinum neurotoxin-A injections appeared to be well-tolerated, safe, and effective at the injected dose (2.5 to 7 U/kg of body weight).

Contractures Following Total Joint Arthroplasty
Flexion and extension contractures may develop following total knee arthroplasty and total hip arthroplasty despite the use of aggressive rehabilitation protocols. Because of its ability to...
provide temporary muscle paralysis and reduce musculoskeletal pain by inhibiting release of pain mediators and decreasing muscle spasm, we evaluated BoNT-A as a potential treatment for flexion contractures that occurred after total joint arthroplasty and were recalcitrant to standard nonoperative treatment methods. Our initial case series consisted of ten patients (eleven knees; nine primary total knee arthroplasties, two revision total knee arthroplasties) with a flexion contracture following total knee arthroplasty. The preoperative mean range of motion, extension lag, and flexion contracture were 75° (range, 40° to 120°), 13° (range, 0° to 30°), and 6° (range, 0° to 20°), respectively. The mean time from the index surgery to treatment with BoNT-A injections was twenty-eight months (range, three to eighty-one months). The medial hamstring muscles were injected in nine patients, and both the medial and lateral hamstring muscles were injected in one patient. Two patients also received injections to both heads of the gastrocnemius muscle in addition to the medial hamstring. All patients were followed for a minimum of two years after the BoNT-A injection. Clinical improvement was seen in all nine primary total knee arthroplasties. The injections were less effective in the two patients who had flexion contractures following revision knee arthroplasty. In summary, BoNT-A injections used following primary total knee arthroplasty resulted in sustained improvement and desirable outcomes at the time of the two-year follow-up. These results suggest that BoNT-A therapy is an appropriate treatment modality for patients who have a flexion contracture following primary total knee arthroplasty. The outcomes suggest that patients with any history of infection or component revision may not be appropriate candidates.

Following the encouraging results of our total knee arthroplasty cohort, additional patients were treated for flexion contracture of the knee (n = 20), extension contracture of the knee (n = 7), adductor contracture of the hip (n = 5), abductor contracture of the hip (n = 7), and flexion contracture of the hip (n = 4). These patients are part of an ongoing study. Longer-term follow-up will be conducted, but the preliminary results have shown excellent clinical outcomes in the majority of patients. Overall, including the initial cohort of total knee arthroplasty patients, twenty-six or 87% of knees achieved extension to within 10° of a neutral position and had improvement in gait parameters and Knee Society scores following BoNT-A treatment. Similar results were seen in the patients with extension contractures of the knee, with six or 86% of knees showing no residual limit in flexion. All five patients who underwent BoNT-A injection for the treatment of adductor contractures following total hip arthroplasty had excellent clinical outcomes on the basis of a final Harris hip score of 280. Table III depicts the percent correction following BoNT-A injections.

To the best of our knowledge, there are only two other case reports in the literature that investigate the effect of BoNT-A treatment following total joint arthroplasty. Shah et al. reported on the use of BoNT-A treatment for flexion contracture after total knee arthroplasty in a patient with Parkinson disease. At one month postoperatively, their patient showed little improvement and had a range of motion from 30° to 100° of flexion. The patient was injected with 200 U of BoNT-A into the long head of the biceps femoris and the semitendinosus muscles at six weeks after surgery and also received an injection in the gastrocnemius muscle at four months after surgery. At the time of final follow-up of 6.5 months, the patient demonstrated improvement, with a range of motion from 8° to 125° of flexion. Fish and Chang reported on the use of BoNT-A for the treatment of tendinitis of the iliopsoas after a left total hip arthroplasty. A seventy-one-year-old woman reported pain that worsened over four months and interfered with daily activities such as walking and climbing stairs. She showed no signs of periprosthetic infection or malpositioning of the prosthesis. Following injection of 100 U of BoNT-A, she experienced an improvement in function and a decrease in pain. In addition, the Oswestry Disability Index functional score improved from 26% to 18% and the pain intensity numerical rating decreased from 7 to 1 on a 10-point scale (for which 10 indicated the worst pain imaginable).

**Table III Percent Correction of Contractures for Total Joint Arthroplasty Patients Following BoNT-A Injections**

<table>
<thead>
<tr>
<th>Joints</th>
<th>Knee Flexion (%)</th>
<th>Knee Extension (%)</th>
<th>Hip Adductor (%)</th>
<th>Hip Abductor (%)</th>
<th>Hip Flexion (%)</th>
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<tbody>
<tr>
<td>Maximum</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>90</td>
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<tr>
<td>Mean</td>
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<td>74</td>
<td>84</td>
<td>65</td>
<td>72</td>
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<tr>
<td>Minimum</td>
<td>–67</td>
<td>–10</td>
<td>50</td>
<td>0</td>
<td>43</td>
</tr>
</tbody>
</table>

**Talipes Equinovarus (Clubfoot)**

Idiopathic talipes equinovarus has a prevalence of approximately one in 1000 live births in the United States. In children with this disorder, the pathology includes contracture of muscle-tendon units in addition to abnormalities of the tarsal bones and joint capsules. Correction of this deformity requires stretching of the musculotendinous structures, including the Achilles, the flexor digitorum communis, the posterior tibial, and the flexor hallucis longus tendons. Lengthening of the Achilles tendon is critical for the success of the various surgical techniques as well as nonoperative interventions, such as weekly manipulations and casting. Botulinum neurotoxin-A has been utilized to facilitate nonoperative techniques (stretching and application of a cast), to augment surgical release, and to serve as an alternative to Achilles tendon-lengthening (see Appendix).
est University School of Medicine experience with use of BoNT-A injections and casting parallels the report of Alvarez et al., who evaluated the effectiveness of BoNT-A in attenuating the function of the triceps surae muscle complex as an alternative to Achilles tenotomy. There were fifty-one patients (seventy-three idiopathic clubfeet) who were divided into two age groups (less than thirty days old and greater than thirty days old). They reported that, following BoNT-A injections, ankle dorsiflexion with the knee flexed and with it extended remained above 20° and 15°, respectively. Other studies have reported on the treatment of patients with injections during percutaneous tenotomy, during extensive posterior medial release, and as an alternative to surgery for recurrence after surgery. There have been no complications observed to date, and BoNT-A appears to be a safe and effective alternative to selected surgical interventions in the treatment of idiopathic talipes equinovarus.

**Idiopathic Toe-Walking**

It is not unusual for children to display intermittent tip-toe gait when they first begin to walk; however, a more mature heel-to-toe gait pattern should become consistent during independent (unsupported) walking. Older children with persistent tip-toe gait are often referred to as idiopathic toe-walkers. In 1967, Hall et al. first described this entity as “congenital short tendon calcaneus.” Although the majority of cases occur in normal children, toe-walking has been associated with neurological disorders, including autism and cerebral palsy. Treatment recommendations for idiopathic toe-walking range from conservative modalities, such as stretching, behavior modification, night-splinting, and serial casting, to surgical release and Achilles tendon-lengthening. The management of this entity and its associated impairments (the development of progressive Achilles tendon contractures) may be frustrating for parents and health-care providers. The use of BoNT-A has markedly changed the management of idiopathic toe-walking. In our experience, 100 U of BoNT-A, per extremity, diluted in 2 to 6 mL of saline solution can be used alone for patients with mild cases of tip-toe gait or in conjunction with night bracing for patients with moderate cases of tip-toe gait. In a recent review of this experience, we reported on the injection of ten idiopathic toe-walking patients who were between the ages of two and seventeen years. In all patients, previous treatment, including physical therapy, bracing, and/or casting, had failed. Following BoNT-A injections, one to three weeks of subsequent bracing and physical therapy was provided. Nine out of the ten patients had resolution of toe-walking by three months. One patient required repeat injections at three months and another patient at one year. Later follow-up (not previously reported) documented the need for surgery in one patient. Similarly, Brunt et al. assessed the effects of BoNT-A on ankle muscles in children who were idiopathic toe-walkers. In their study of five children (mean age of four years), each child was injected with BoNT-A in the gastrocnemius and soleus muscles. By twenty days following injection, the authors concluded that, following treat-

**Plantar Fasciitis**

Heel pain secondary to plantar fasciitis affects at least 1 million Americans and is a frequent cause for visits to foot and ankle surgeons and podiatric practitioners. Pathologic findings include: (1) contracture of the plantar fascia, (2) attribution fibrosis and/or periostitis of the plantar fascial origin from the calcaneus, (3) shortening of the quadratus plantae muscle and short toe flexors, and (4) contracture or shortening of the Achilles tendon. No evidence strongly supports the effectiveness of any treatment modality for plantar fasciitis, and most patients improve either without specific therapy or after nonoperative treatment. Shoe inserts, custom orthoses, and stretching exercises may be beneficial and should be the first step in treatment. Although no data support the use of nonsteroidal anti-inflammatory drugs, the effectiveness of such drugs in managing other musculoskeletal conditions makes them reasonable choices for adjunctive therapy. For patients who do not improve after initial nonoperative treatment, BoNT-A injections represent a viable alternative to corticosteroid injections.

Botulinum neurotoxin-A treatment of plantar fasciitis is directed at reducing painful forces on the plantar fascia, facilitating lengthening of the contracted structures, and decreasing nociceptive signals. Injections are performed in the painful fascia and perioisteum (25 U in 0.5 mL of saline solution) and in the quadratus plantae and short toe flexors (75 U in 1.5 mL of saline solution). The injections are accompanied by a home stretching program and night-splinting. A recent prospective randomized study demonstrated that injections of BoNT-A into the plantar region significantly decreased the pain associated with recalcitrant plantar fasciitis (p < 0.0005) (see Appendix).

**Safety Issues**

Botulinum neurotoxin-A has a long-established safety profile and has been approved by the Food and Drug Administration for more than seventeen years to treat a variety of medical conditions. In 2002, approval was granted for its aesthetic use for glabellar lines. There are more than 3000 publications on BoNT-A in scientific and medical journals, and the results of dozens of clinical trials involving more than 10,000 patients have been used to establish its safety profile. Recently, however, the Food and Drug Administration announced in an “Early Communication” that it was reviewing certain serious adverse events following the use of botulinum toxins for spasticity management in patients with juvenile cerebral palsy. This posting is a routine step that is typically used to provide early information regarding safety or other related reviews, often before any conclusions are, or can be, made. The posting of this information does not mean that there is a causal relationship between the products and the adverse events. Al-
though overdosage of BoNT-A can lead to hypersensitivity reactions, respiratory arrest, cardiovascular events, and even death, the results of our literature review as well as the outcomes of patients treated at our institution suggest that the dosage used for musculoskeletal applications does not put patients at risk for any of these serious complications. In our more than twenty years of experience with BoNT-A treatment of musculoskeletal disorders, we have not seen any cases of systemic toxicity, permanent weakness, or death. Adverse events observed included pain at the injection site, cramping, and transient weakness. Key points for a safe and successful application of BoNT-A are knowledge of indications, contraindications, labeling warnings, adverse events, and dosage recommendations.

Conclusions

After its introduction as a therapeutic agent in the early 1980s, BoNT-A has gained popularity in multiple fields of medicine. More recently, studies at our institutions as well as other studies reported in the literature have shown the applicability of this treatment modality for patients with cerebral palsy, multiple sclerosis, flexion and extension contractures of the knee and hip, and idiopathic clubfoot. Looking ahead, a variety of “off-label” uses of the toxin are being evaluated. These uses are based on the theoretical considerations related to the effects of the toxin on muscle units and to the potential for tendon protection and its positive impact on fixed muscle contractures when injections are coupled with bracing, therapy, or surgery.

Appendix

Tables listing pertinent references and a table listing dosage recommendations of muscles commonly injected with BoNT-A are available with the electronic versions of this article, on our website at jbjs.org (go to the article citation and click on “Supplementary Material”) and on our quarterly CD/DVD (call our subscription department, at 781-449-9780, to order the CD or DVD).

References

23. Seyler TM, Marker DR, Koman LA, Jinnah RH, Bhave A, Mont MA. Botulinum toxin type A injections for the management of flexion contractures following total knee and hip, and idiopathic clubfoot. Looking ahead, a variety of “off-label” uses of the toxin are being evaluated. These uses are based on the theoretical considerations related to the effects of the toxin on muscle units and to the potential for tendon protection and its positive impact on fixed muscle contractures when injections are coupled with bracing, therapy, or surgery.

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