Abstract
Botulinum neurotoxin A (BoNTA) is rapidly gaining acceptance for management of spasticity secondary to spinal cord injury (SCI). Due to its increased usage, more undesirable effects and complications have come in light. Unwanted distant and/or generalised muscle weakness is possible following BoNTA administration in SCI population causing temporary neurological and functional decline. Physicians should carefully perform a clinical assessment of every patient individually for risks stratification. Additional studies for adult population evaluating adverse-effects of high dose of BoNTA treatment for spasticity management are indicated.

Key words: Botulinum neurotoxin A, adverse events, spasticity, spinal cord injury, distant muscle weakness.

Introduction:
Spasticity is a velocity-dependent increase in tonic stretch reflexes with exaggerated tendon responses.1 It is one of the most common consequences of spinal cord injury (SCI). One year post-injury, about 78% of patients demonstrate spasticity with more than half requiring pharmacological interventions.2 Botulinum neurotoxin is gaining rapid acceptance for spasticity management due to several advantages. It avoids sedation, common with oral antispasticity medications. No surgical intervention is required. It provides an option of focal spasticity management. It is equally effective as phenol3 but technically simpler to administer, less painful, and without any side-effects like dysesthesia. Due to its increased usage, more undesirable effects have come in light. Here, I have described a case elucidating distant and generalised muscle weakness as a potential side-effect of botulinum neurotoxin A (BoNTA) in a patient with SCI with brief literature review.

Case Report:
A 35-year-old man sustained C5 burst fracture secondary to a diving accident. His injury was little more than one year old when he was evaluated at our centre for outpatient neurorehabilitation. He was diagnosed C4 ASIA impairment scale C. During the rehabilitation course, his progress was hampered due to spasticity (3/4 on modified Ashworth scale) in bilateral hip adductor and ankle plantar-flexor muscles even after receiving oral baclofen, 80 mg/day. Therefore, it was decided to address spasticity with Botox®. A total of 800 units (~10 units/kg; 200 units in thigh adductors, 150 units in gastrocnemius – both heads, and 50 units in tibialis posterior in each extremity) were injected using an EMG-guided technique. Each 100 units were diluted with two ml of preservative-free normal saline. Patient tolerated the procedure well. A week later, he was admitted in a hospital for cellulitis followed by septic arthritis of the left elbow. He was treated with intravenous cephalosporin. His infection never progressed to cause compartment compression syndrome and his 2-week hospital stay was uneventful. One week post-discharge, upon his return to the clinic, patient complained for left wrist extension weakness and increased difficulty to transfer. It evolved over past one week. He denied for dysphagia or dysphonia. As per his hospital records, patient did not acquire left wrist weakness during his hospital stay. On physical examination, cranial nerves evaluation was normal. His left elbow infection was resolved but he developed
generalised truncal weakness along with noticeable deterioration in muscle strength of left wrist extensors. It deteriorated from 4/5 to 1/5 on Medical Research Council scale (Fig 1). There was no prominent change in strength of other left upper extremity muscles especially brachioradialis, supinator, and finger extensors. Sensory examination was also at baseline. Spasticity in hip adductors and ankle plantar-flexor muscles was decreased to 1+ on modified Ashworth scale. Patient demonstrated decreased sitting balance due to truncal weakness. His abilities for pressure relief and bed-to-wheelchair transfer were also markedly impaired due to wrist extension weakness. He was referred for laboratory, electrodiagnostic, and imaging studies. Electrodiagnostic study was performed three weeks after onset of left wrist weakness. It was positive for ulnar nerve entrapment at the right elbow. Nerve conduction study (NCS) of radial nerve did not show latency increase or decrease in amplitude or conduction velocity across the left elbow. Electromyography (EMG) was performed in left brachioradialis, supinator, extensor digitorum and extensor indicis. It showed normal activities at needle insertion as well as at rest along with no denervation potentials. Magnetic resonance imaging (MRI) with contrast of the cervical, thoracic and lumbar spine and laboratory work-ups demonstrated no acute pathology (Fig 2). He was continued on outpatient rehabilitation programme. He gradually regained functional strength of his left wrist extensors and trunk muscles. His functional ability to transfer, pressure relief, and sitting balance also improved.

**Discussion:**

Our patient developed generalised weakness with prominent weakness in left wrist extension, approximately three weeks after BoNTA administration. Multiple plausible aetiologies were considered including radial nerve injury at the elbow level, syringomyelia, cord tethering and cord/root compression secondary to infection, tumour or disc herniation. Since radial nerve

![Fig 1: Muscle Strength in Upper Extremities as per American Spinal Injury Association (ASIA) Classification](image-url)
Injury at the elbow level was one of the differential diagnoses, an electrodiagnostic study was ordered. Absence of conduction block at the elbow level as well as lack of denervation potentials effectively ruled out left radial nerve injury including neuropraxia or axonotmesis. Likewise, physical examination did not demonstrate prominent weakness in other muscles supplied by radial or posterior interosseous nerve except the wrist extensors. Unremarkable spine MRI and laboratory work-up exclude radiculopathy, myelopathy, or other acute aetiologies. Along with left wrist weakness, patient also developed generalised weakness which is a documented side-effect of BoNTA. His muscle strength improved within 14-16 weeks. All information can collaboratively deduce BoNTA as a causative factor for unwanted muscle weakness.

Reports suggesting unwanted muscle weakness following BoNTA injection are commonly published for cerebral palsy but sparsely for SCI. To this author’s knowledge, only one report has been published till this date. BoNTA has been utilised successfully since the late 1980s to treat limb spasticity. It irreversibly binds to presynaptic neurons at the neuromuscular junction within hours of administration. It actively cleaves peptides necessary for membrane-bound acetylcholine release. The peripheral blockade of neuromuscular activity causing focal muscle weakness is a desirable therapeutic effect. Though BoNTA has good safety and tolerability profile, one of the undesirable systemic effects is unwanted muscle weakness. Occasionally, the toxin tends to spread causing regional, distant or generalised muscle weakness. Regional weakness manifests in adjacent anatomical area to the injection site e.g., dysphagia/dysphonia after injections in neck muscles for cervical dystonia or diplopia/facial palsy after BoNTA treatment for blepharospasm. Distant muscle weakness occurs in anatomically separate and remote sites. In animal studies, BoNTA has been shown to spread 30-45 mm from the injection site. Higher dose, an incorrect injection technique, and higher dilution may potentiate spread of the toxin. Its effects on neuromuscular transmission distant to the injected site have been demonstrated by single-fibre electromyography showing increased jitter and blocking. Although these changes suggest disturbance in neuromuscular transmission, they do not explain the cause of the disturbance. Besides, clinically they are not always associated with muscle weakness. Premorbid conditions like amyotrophic lateral sclerosis or neuromuscular junction disorders (e.g., myaesthenia gravis or Lambert-Eaton syndrome) may increase possibilities of unwanted muscle weakness. It is possible that decreased function of alpha motor neurons makes these patients more susceptible to BoNTA. Patients treated concomitantly with agents interfering with neuromuscular transmission (e.g., aminoglycosides, curare-like agents) should also be observed closely for the same reason. In the present case, the patient neither had above mentioned pre-existing conditions nor received agents impairing neuromuscular transmission.

There are several hypotheses regarding modes affecting BoNTA diffusion. Retrograde axonal spread is one of the proposed physiological modes of diffusion in literature but there are no solid evidences to support. Wiegand suggested a theory of retrograde axonal spread to corresponding spinal cord segments using radioactive BoNTA. On the contrary, Koman et al provided an indirect evidence to nullify that theory by demonstrating no change in “pre- and post-BoNTA” H-reflex. The H-reflex is a well-standardised measure of central synaptic activity. Therefore, they concluded that BoNTA had no significant “central” effect. Systemic spread of BoNTA can also be possible by entering into a vascular system. Another mode of BoNTA diffusion to the distant sites can be systemic vascular spread. Nonetheless, it is a standard practice to aspirate before administration to prevent intravascular injections. Besides if the toxin enters the venous system, the manifestations will be much quicker; which did not happen in this case. Capillary uptake may be possible and needs to be explored further. There may be many factors affecting BoNTA diffusion.
Unwanted Muscle Weakness Following Botulinum – Tapan N Joshi

causing systemic effect: lack of injection guidance, higher weight-adjusted dose, dilution (volume) and total cumulative dose. Underlying comorbidities may also make subjects predisposed to systemic involvement.\textsuperscript{13,16} There is not a single factor that has emerged as a potential cause. Needle guidance ascertains a placement of a needle and an end-organ to be injected. Therefore, lack of guidance may increase chances of systemic spread. Higher weight-adjusted dose is another possible factor for systemic spread causing distant/generalised weakness. Crown et al\textsuperscript{17} demonstrated no relationship between high dose (21 units/kg) and distant muscle weakness. The European consensus group has also suggested 30 units/kg of BoNTA as a safe upper limit for spasticity management.\textsuperscript{18} Our patient received about 10 units/kg of his body weight which is considered very safe by most published studies and yet, he developed unwanted muscle weakness. A possible explanation can be ‘an indirect overdose’ of BoNTA. In chronic SCI, there is a decrease in lean muscle mass secondary to muscle atrophy and its replacement with fatty tissue.\textsuperscript{19} Therefore the requirement of BoNTA can be less than the calculated weight-adjusted dosage, causing indirect overdose but its effect is not universally seen in every patient with chronic SCI. Higher dilution has shown to increase spread across the muscular plane\textsuperscript{10} but at the same time, Lee et al\textsuperscript{20} has shown no clinical effect in term of excessive weakness with different dilutions. Dilution used in our case is standard for spasticity management involving large muscle groups. Another possible reason could be the total cumulative dose of BoNTA injected.\textsuperscript{13} The patient was injected with 800 units of Botox\textsuperscript{®} which is arguably a high dose for the first time treatment and it could be a possible reason for distant and generalised weakness. Although, total dose of 800-1200 units of Botox\textsuperscript{®} is safely used for spasticity management in young adults more than 45 kg of body weight.\textsuperscript{21} In the present case, the dose was titrated based on the practitioner’s experience and the patient’s clinical condition. He was already on 80 mg/day of oral baclofen while receiving rehabilitation interventions and yet he had significant spasticity, 3/4 on modified Ashworth scale. Besides, many of our spinal cord injured subjects were treated safely and successfully with a high dose of BoNTA. This was our first case of unwanted distant muscle weakness along with generalised weakness in a patient with SCI. It remains unclear why only left wrist extensors became markedly weak. Recently, the European consensus group has also suggested further studies to identify the side-effects of high doses of BoNTA treatment in adults.\textsuperscript{22}

**Conclusion:**

Botulinum neurotoxin has evolved as a widely used therapeutic measure for spasticity management. Serious side-effect like unwanted generalised and/or distant muscle weakness is uncommon but possible. Our understanding of risk factors as well as pathogenesis of distant muscle weakness is limited. It should be discussed prior to the treatment. Physicians should carefully perform a clinical assessment of every patient individually for the benefit-risk profile. Additional studies for adult population evaluating adverse-effects of high dose of BoNTA treatment for spasticity management are recommended.

**References:**


