

CASE REPORT

Botulinum Toxin A Improved Burning Pain and Allodynia in Two Patients With Spinal Cord Pathology

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ABSTRACT

Objective. To report the effect of botulinum toxin A in two patients with burning pain and allodynia of spinal cord origin.

Design, Setting, Patients. Two patients with spinal cord lesions at the cervical level (tumor and stroke) experienced exquisite skin sensitivity and spontaneous burning pain in dermatomes corresponding to the cord lesions. Botulinum toxin A (Botox®) was injected subcutaneously at multiple points (16 to 20 sites, 5 units/site) in the area of burning pain and allodynia.

Results. Both patients reported significant improvement in spontaneous burning pain and allodynia in visual analogue scale and clinical measures. The analgesic effect of botulinum toxin A lasted at least 3 months and was sustained over follow-up periods of 2 and 3 years with repeated administration at 4-month intervals.

Conclusion. Subcutaneous application of botulinum toxin A relieved central burning pain and allodynia in two patients with spinal cord pathology.

Key Words. Pain; Spinal Cord; Botulinum Toxin A; Botox

Introduction

Botulinum toxin A (Botox®, Allergan Inc., Irvine, CA) reduces pain in a variety of medical conditions. Over 70% of patients with cervical dystonia report marked improvement of associated neck pain [1,2]. Botulinum toxin A is highly effective against muscle spasms associated with medical disorders causing spasticity [3]. Other painful syndromes with a favorable response to botulinum toxin A include myofascial pain [4], whiplash neck injury [5], headaches, and some forms of low back pain [6,7]. Although, initially, the analgesic effects of botulinum toxin A were attributed to its

antispasmodic effect through anticholinergic mechanisms, more recent data indicate a variety of mechanisms of local and central pain modulation, including modification of neurotransmitter signaling, peptide release, and nociceptive fibers [8–10].

We report a sustained analgesic response for allodynia and burning dysesthesias after subcutaneous administration of botulinum toxin A in two patients with focal spinal cord pathology. To our knowledge, this is the first report of botulinum toxin A effectiveness in a centrally mediated pain syndrome.

Case Reports

Patient 1

A 55-year-old female complained of severe burning pain over the elbows, upper forearms, and the medial aspects of both lower arms for 6 years.

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The pain was described as “excruciating” with an intense burning quality “as if hot charcoal was applied directly to the skin.” Although the pain was bilateral, she complained of more severe symptoms on the left. Minimal contact with this region, particularly near the elbow, consistently produced worsening of her intense pain. Medications, including tricyclic antidepressants, anticonvulsants, nonsteroidal anti-inflammatory drugs, and opioids, failed to improve pain. In her last visit, she stated, “life is becoming unbearable,” and “I cannot live like this.”

The patient’s past history was significant for the onset of progressive weakness of both legs and loss of sensation in lower limbs 7 years ago. Six years prior to presentation, she underwent partial resection of an intramedullary spinal cord angioma at C7. Pain began a few months before surgical intervention but intensified significantly after surgery. For the past 2 years, pain was described as “unbearable.”

On examination at our center, the patient was noted to hold her arms in constant abduction

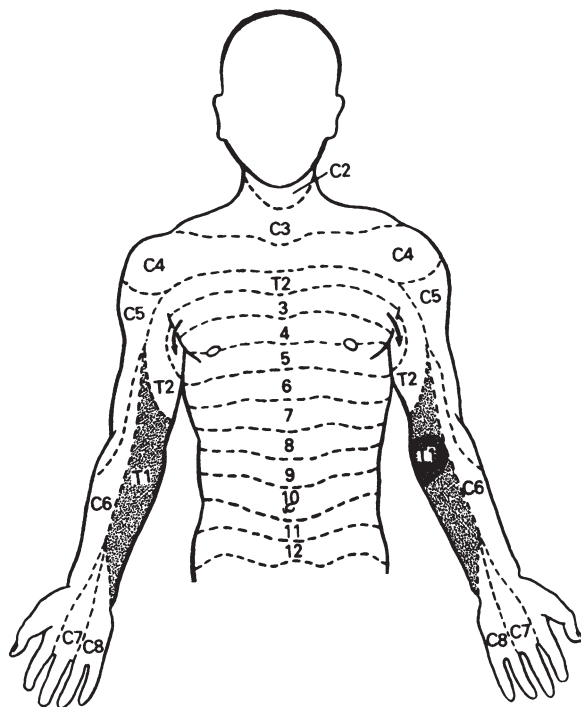


Figure 1 Shown are the regions of skin exquisitely sensitive to touch before botulinum toxin A injection, corresponding to the T1 and a small part of the T2 dermatome. Skin sensitivity and spontaneous burning pain were more prominent on the left side. After botulinum toxin A injection on the left side, only a small region close to the elbow (dashed) remained slightly sensitive to pressure.

away from her garments, to prevent contact with the painful region. Pertinent neurological findings consisted of prominent hyperalgesia throughout the T1 and part of the T2 dermatomes bilaterally, with exquisite sensitivity to touch about the elbows (Figure 1). The level of pain was rated at 8–10 on the visual analog scale (VAS). There was bilateral leg weakness (4/5) involving the hamstrings and quadriceps muscles and mild weakness of the interossei (4/5). Vibration sense was diminished in both ankles and knees. A Babinski sign was present on the left side. A magnetic resonance imaging (MRI) scan of the cervical and thoracic cord demonstrated residual angioma at the C7 and T1 levels. With the patient’s consent, she was treated with 100 units of botulinum toxin A in divided doses, subcutaneously in the region of her pain on the left side. The patient reported significant improvement of spontaneous pain and skin sensitivity on the left side 1 week after treatment. The intensity of spontaneous pain as rated on her VAS decreased from 8–10 to 2–3, with an 80% decrease in the frequency of more severe episodes of spontaneous pain. Rubbing of garments against her left elbow no longer caused discomfort, and tapping the skin over the left elbow produced only mild discomfort. There was no change in the severity of pain on the right side. Subsequent nonblinded administration of botulinum toxin A to the right side produced a similar analgesic effect. The analgesic effect lasted for approximately 3 months. Over the next 3 years, treatment with botulinum toxin A at 4-month intervals provided similar pain relief. Eventually, the pain lessened to such a degree that she elected to discontinue treatments.

Patient 2

A 33-year-old female was admitted to the hospital after 7 days of left-sided head and neck pain, nausea, and vertigo and 2 days of right-sided weakness. She had a history of severe migraines since age 19, requiring treatment with ergot drugs and propranolol. An MRI scan shortly after the onset of symptoms demonstrated an area of increased T2 signal involving the three upper cervical cord segments and the lower medulla. The findings were consistent with an acute infarct. On examination, there was a right hemiparesis, more prominent in the upper extremity (4/5). Cranial nerves were intact. Extensive investigation for an etiology revealed no abnormality except a high serum cholesterol level (320–350 mg/dL). An angiogram showed a 90% reduction in the lumen of the right vertebral artery, suggestive of spasm.

Over the ensuing weeks, the patient developed exquisite sensitivity of the skin over the right posterior neck extending to the right shoulder region. Touching these areas produced severe discomfort and not infrequently brought tears to her eyes. Three months later, she was referred to our clinic for pain management due to the failure of analgesic medications. On examination, touching the skin on the back of the neck and the right shoulder produced significant discomfort. She complained of constant burning pain in that area, which interfered with sleep and many activities of daily living. Physical examination showed significant recovery of the hemiparesis and MRI demonstrated residual changes from her ischemic insult at the cervicomedullary region.

We administered a total of 80 units (100 units/mL) of botulinum toxin A subcutaneously at 16 sites, eight in the right lower neck and eight in the right shoulder region. Ten days later, she reported significant reductions in skin sensitivity and spontaneous burning pain. The effect lasted for approximately 3 months. Over the next 2 years, repeated botulinum toxin A injections every 4–6 months produced similar results. Thereafter, the burning pain and skin sensitivity subsided but she complained of annoying stiffness of the right lower neck and shoulder muscles. This was treated successfully with intramuscular injections of botulinum toxin A in the right splenius capitis (60 units) and trapezius muscles (40 units).

Discussion

Pain related to spinal cord lesions can be classified as mechanical, radicular, visceral, or central. Of these, central pain is the most common and difficult to modify. It is often characterized as burning, aching, and/or tingling experienced below the level of the lesion [11].

A variety of treatment approaches can be tried for such pain. Pharmacologic efforts using tricyclic antidepressants, anticonvulsants, nonsteroidal analgesics, opioids, epidural steroids, and radio-frequency stimulators can succeed on occasion. Ablative surgical procedures, such as dorsal root rhizotomy, also offer pain relief in selected patients, but failures are not uncommon, and the resultant deafferentation at a higher level will occasionally worsen the dysesthesia [12].

In recent years, based on the results of animal studies in addition to the known anticholinergic effect, a number of other mechanisms have been proposed for the analgesic effects of this agent:

- Botulinum toxin A inhibits the release of substance P from the dorsal root ganglia of the rat [8] and iris sphincter of the rabbit [9]. Substance P is believed to sensitize primary afferents and promote local release of histamine and bradykinin, both known to excite nociceptors [13].
- Botulinum toxin A significantly reduces the inflammatory phase (second phase) of pain when injected into a rat's paw 5 days prior to formalin injection [10]. This effect has been attributed to both a direct effect on C fibers (possibly via inhibition of neuropeptide release) and a local anti-inflammatory effect.
- Intramuscular injection of botulinum toxin A reduces muscle spindle discharge and feedback to the gamma motor neurons [14]. In chronic pain conditions, "wide dynamic range neurons" of the spinal cord become hypersensitive and perceive non-nociceptive stimuli (such as conveyed by muscle spindles) as nociceptive [15]. Furthermore, in chronic pain conditions (central and peripheral), A-alpha fibers can sprout, contacting spinal cord nociceptive neurons of the dorsal horn, resulting in misperception of tactile and mechanical stimuli as nociceptive [16].
- Botulinum toxin A impairs sympathetic transmission by inhibiting preganglionic cholinergic sympathetic fibers [17]. The sympathetic nervous system plays a recognized role in maintaining both peripheral and central pain. Long-standing neuropathic pain results in ingrowth of sympathetic postganglionic axons into dorsal root ganglia, where they encircle the dorsal root ganglia cells [18].
- Botulinum toxins A and B have been shown to block glutamate exocytosis from synaptosomes [19]. One group of investigators implicated Group I metabotropic glutamate receptors in the development of central pain [20]. Peripherally, glutamate accumulates in tissues affected by chronic pain. Centrally, herniated disc material has been shown to produce large amounts of glutamate, presumably affecting pain signaling in the dorsal root ganglia [21]. Chronic painful tendons have significantly higher levels of glutamate than normal tendons [22].

To our knowledge, sustained improvement of segmental pain of spinal cord origin after subcutaneous administration of botulinum toxin A has not been reported previously. In these two patients, duration of the favorable effect (3–4 months) and persistence of the response after

repeated injections support a causative effect. The treatment was free from side effects and, in particular, caused no muscle weakness.

The mechanism of our patients' pain relief remains speculative. Central sensitization of spinal cord neurons is known to play a major role in the persistence of neurogenic pain resulting from peripheral nerve injury [23]. We propose that spinal cord lesions causing chronic central pain sensitize the peripheral nociceptors through antidromic depolarization and this "peripheral sensitization" maintains and enhances the central pain. Botulinum toxin A may alleviate central pain by reducing neurogenic inflammation and unwanted activity of certain peripheral neurotransmitter(s) [10,19,20]. Another possibility is a central effect, that is, upon spinal cord neurons. Some animal data suggest that botulinum toxin A (or its metabolites) may reach the spinal cord when injected intramuscularly. In one experiment, administration of radiolabeled botulinum toxin A in a cat's hamstring muscle resulted in radiostaining of the sciatic nerve, sciatic nerve roots, and hemi-cord ipsilateral to the side of the injection [24]. In a human application, one study showed evidence of impaired neuromuscular transmission (jitter and blocking in electromyogram) in muscles far from the site of botulinum toxin A administration [25]. This finding could only be explained by a direct effect upon intramedullary neurons, either through retrograde transmission or through circulation.

In conclusion, we have shown satisfactory analgesic effects in two patients with central pain following subcutaneous administration of botulinum toxin A. This observation warrants conducting a controlled study with this agent for central pain. If effective, this approach has significant advantages over the majority of current treatment strategies in that it renders no systemic side effects (at current doses) or addictive potential and is minimally invasive.

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