

## Severe Post-herpetic Neuralgia Successfully Treated with Botulinum Toxin A: Three Case Reports

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Sir,

Herpes zoster is a disease that can significantly impair quality of life for affected individuals. Anyone infected with varicella (chickenpox) virus in childhood is at risk for reactivation of dormant virus and the onset of zoster disease, although it occurs with increasing frequency in the elderly as a result of waning of cell-mediated immunity. The most common complication of herpes zoster is post-herpetic neuralgia (PHN), which can cause chronic and debilitating pain (1). In some patients, pain persists for weeks or even years after regression of the rash. We report here three cases of PHN, which were relieved by botulinum toxin type A (BTX-A).

### PATIENTS AND METHODS

Based on previous trials (2–4), we recruited two men and one woman, with severe PHN resistant to usual therapeutic modalities in order to evaluate the efficacy of BTX-A in this condition. Written informed consent was obtained from each patient. The patients' mean age was 67 years (age range 63–70 years), while mean duration of PHN was 2.5 months. Herpes zoster had been diagnosed in all patients based on the presence of unilateral dermatomal clinical findings in our clinic. Former treatment approaches included non-steroidal anti-inflammatory drugs (NSAIDs), codeine, gabapentin and tricyclic antidepressants as well as topical anaesthetics resulting in no or slight pain reduction. Patients' characteristics and clinical data are summarized in Table I. Clinical evaluations were performed on the day of treatment administration, which was defined as baseline, and at weeks 2, 4, 6, 8, 10 and 12 after treatment. At each visit a visual analogue scale (VAS) was used to evaluate the degree of pain as perceived by the patient (0: painless; 10: maximum pain).

The therapeutic procedure for all patients was as follows: dilution was made by adding 4 ml of sodium chloride to each sterile vial containing 100 units of BTX-A (BOTOX®; Allergan Corporation, Irvine, CA, USA), resulting in a concentration of 25 U/ml. The volume of the injection was 0.2 ml (5 units of botulinum toxin) per route. A total of 20 routes (100 units) was

Table I. Patients' demographic and clinical data of post-herpetic neuralgia (PHN)

Pat. no.	Age (years)	Affected dermatomes	PHN duration (months)	Previous treatments
1	68	T6, T7	3	Topical anaesthetics, NSAIDs, codeine
2	70	T5	2.5	NSAIDs, gabapentin, tricyclic antidepressants
3	63	T6, T7	2	Topical anaesthetics, NSAIDs, tricyclic antidepressants

NSAIDs: non-steroid anti-inflammatory drugs.

Table II. Visual analogue score (VAS) of pain at baseline and follow-up visits (weeks) after botulinum toxin therapy

Pat. no.	VAS score						
	baseline	2 w	4 w	6 w	8 w	10 w	12 w
1	8	2	2	2	2	4	4
2	10	3	3	3	3	5	5
3	7	1	1	1	1	3	3
Mean	8.3	2	2	2	2	4	4

performed in every individual. The solution was injected subcutaneously, in a chessboard fashion, over the affected area.

### RESULTS

All patients complained of stinging pain during the BTX-A procedure, which persisted for the next 3 days. Erythema was also observed at the injection sites for 24 h.

Table II shows the change in VAS score over the follow-up period. Mean VAS score dropped from 8.3 at baseline to 2 at the first follow-up visit (week 2). At week 10 pain was described as stronger but bearable by all patients; mean VAS score increased to 4 and remained at that level at week 12.

Pain relief started gradually within a mean period of 72 h and reached maximum response within a mean period of 7 days. The mean duration of the analgesic effect of BTX-A was 64 days. However, pain, after its reappearance, was milder and bearable to all patients.

### DISCUSSION

PHN-associated pain is considered neuropathic. After reactivation of varicella zoster virus, leading to inflammation of dorsal root ganglia, significant alteration occurs in the nociceptive pathways, to spontaneous discharge, and lower activation thresholds. Pain and temperature detection systems are hypersensitive to light mechanical stimulation, leading to severe pain (allodynia) (6–9). Allodynia may be related to formation of new connections involving central pain transmission neurons. Previous studies have shown that hyperactivity of A-β afferents following nerve injury can result in touch-evoked pain and spontaneous pain via presynaptic activation of C afferent terminals. However, the precise mechanism of allodynia remains obscure (10).

The therapeutic approach of PHN involves the early use of antiviral drugs. Other treatment modalities, such as topical analgesics (lidocaine patch 5% and capsaicin),

tricyclic antidepressants, gabapentin, and opioid analgesics, are often necessary. The combination of different treatment options is a common practice, while no single therapy is completely effective (11, 12). For individuals with treatment-refractory PHN, non-pharmacological approaches may be considered and a pain-management specialist should be consulted. In addition, studies have demonstrated that herpes-zoster vaccine significantly reduces the morbidity due to herpes-zoster and PHN in older adults (13).

The minor pain relief with usual treatments in our patients, in combination with the beneficial effect of BTX-A reported in the literature (2–4), led us to the decision to try BTX-A administration. BTX-A blocks the release of acetylcholine by cleaving synaptosome-associated protein-25, which participates in the formation of the exocytic SNARE complex, which is essential for the fusion of acetylcholine-containing vesicles with the pre-synaptic membrane (14). The local peripheral BTX-A injection may result in a reduction in various substances that sensitize nociceptors. This anti-nociceptive effect is associated with the inhibition of formalin-induced glutamate release and a possible reduction of the peripheral nociceptive input by inhibiting the release of substance P and calcitonin-gene-related peptide, which play a significant role in neurogenic inflammation (14). However, some investigators believe that the beneficial effect of BTX-A in treating neuropathic pain is related not only to acetylcholine inhibition but also to a blocking action on the parasympathetic nervous system. The retrograde uptake of BTX-A into the central nervous system is believed to influence the substance P and enkephalin levels in the spinal cord and nucleus raphe. In addition, there is evidence of an inhibition potential on the sensory system, since BTX-A has been shown to have a direct effect on afferent fibres, resulting in a blockade of autonomic pathways (4).

Temporary erythema, which was observed immediately after the procedure and faded away within the first 24 h, could be explained by the repetitive, multiple injections in a limited area. Taking into account that BTX-A reduces neurogenic inflammation, we would expect less erythema on the next treatment occasion.

The encouraging results of this small clinical study lead us to conclude that BTX-A could be an alternative therapeutic modality in treating PHN in the future. However, further randomized, controlled trials are needed to confirm the analgesic efficacy of BTX-A, and to determine its role in the overall treatment of patients with PHN.

*The authors declare no conflicts of interest.*

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