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Botulinum Toxin Treatment in Post Herpetic Neuralgia a Review

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Introduction

Herpes zoster results from reactivation of childhood chicken pox virus during adulthood. Eruption of small vesicles over the skin with typical distribution along the course of the nerve routes or peripheral nerves is the characteristic symptom of the disease. The lesions can involve the face, trunk or limbs or affect more than one region. When on the trunk, large parts of the body may be involved. Skin lesions are often accompanied by intense itch. After a few weeks, the vesicles dry up and leave scars and areas of e skin discoloration. Some patients with herpes may develop pain (post-herpetic neuralgia) during or shortly after healing of skin lesions, but majority of the patients experience the pain weeks or months later. The pain of herpes zoster is one of the most severe pains known to mankind. It is often described as sharp and jabbing , felt in the distribution of the involved nerves. The percentage of patients who develop pain after shingles, is highly dependent on the age at the onset of their symptoms; 5% among individuals younger than 60 and 20% among patients who are 80 years of age or older [1]. In adults, vaccination against shingles reduces the incidence of post-herpetic neuralgia. In many patients, pain lasts for months or even years, incapacitating the affected patient.

Treatment

Argoff, [2] based on the guidelines of American Academy of Neurology and European Federation of Neurological Societies describes tricyclic antidepressants, gabapentin, pregabalin, and the topical lidocaine 5% patch as first line of treatment in PHN. Opioids, tramadol, capsaicin cream, and the capsaicin 8% patch are recommended as either second- or third-line therapies. Serotonin-norepinephrine reuptake inhibitors, the anticonvulsants carbamazepine and valproic acid are also partially effective. In refractory patient's short course of oral steroids, invasive procedures such as sympathetic blockade, intrathecal steroids, and implantable spinal cord stimulators have been studied and have been helpful in some patients.

Botulinum Toxin Treatment

Animal studies of the past [2-3] decades have clearly shown that injection of the botulinum toxins A and B into the skin blocks local accumulation of pain neurotransmitters and pain modulators such as glutamate and calcitonin gene related peptides. More recent studies have strongly suggest that the analgesic effects of local BoNT injection in the animal models of pain has an additional central mechanism. Botulinum toxins B and A have been traced to the spinal cord sensory neurons after peripheral injections in to the muscles [3,4]. The positive results of PREEMPT studies led to approval of on a botulinum toxin A (Botox) for chronic migraine in Europe and US in 2010. Since then a large number of clinical trials strongly suggests efficacy of Botulinum toxins in a variety of pain disorders [5].

Method of the Review

The published literature on the use of botulinum toxins in postherpetic neuralgia was reviewed, using Medline and Ovis SP search engines. The search included all English manuscripts published between January 1st, 1989 (the year that botulinum toxin was introduced into the market) to February 1st, 20019. The search

Table 1: Published manuscripts on the subject of BoNT treatment in post-herpetic neuralgia.

Authors and date	Type of study	Number of patients	Toxin and dose in Units (U), mode of injection	Result
Ding XD et al 2019	Open label Prospective	59	Prosigne 50-100 U SC	Marked pain reduction in 46.5% of patients
Jain et al 2017	Case series	2	Dysport, 500 U, SC	Pain in VAS dropped to 2 and 3 after two weeks
Moon et al 2016	Single case	1	Botox, 50 units, into lumbar plexus	Pain measures at baseline as 8-10 in VAS deopped to 2-3 after injection
Apalla et al 2013 [6]	Double blind, placebo controlled	30	Botox, 100U SC	At least 50% reduction of VAS score in 13 pts in toxin group (P< 0.001)
Li & Xio 2015	Single case	1	Bobtulinum toxin -A? 100 units SC	Reduction of VAS from 8-9 to 2-3 Ophthalmic PHN
Emad et al 2012	Cas series	15	Botox 15U every 2 cm, SC	Baseline VAS 6.4 – at week 4: 3.7 (P<0.03)
Xiao et al 2010 7	Double blind, placebo controlled	60, 20 per arm-Toxin, placebo, Lidocaine	Prosigne Varied- less than 200 U SC	VAS score diminished in all three arms but more in Toxin arm.
Sotrion et al 2009 [10]	Case series	3	Botox,100 U SC	Pain dropped from 8-10 in VAS to 1-3 between post-injection weeks 2-8
Liu et al 2006	Single case	1	Botox, 100U SC	Pain severity reduced to 1 from 10 in VAS.
Turk et al 2005	Case series	8	Botox 100 U SC	Reduced pain

VAS: Visual Analogue Scale; SC: Subcutaneous

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words included botulinum toxin, Botulinum neurotoxin , Herpes Zoster and Post-herpetic Neuralgia.

Results

A total of 37 manuscripts were identified. Of these, 10 studies specifically studied the effect of botulinum toxins on post herpetic neuralgia (Table 1). Two studies, represented high quality, randomized, blinded, placebo controlled clinical trials [6,7].

All studies reported marked improvement of pain following local botulinum toxin injections. No serious side effects were reported. Like other indications of BoNT therapy, analgesic effects of injected toxins in PHN usually lasted [3-6] months after one injection.

Injection Technique

With exception of one study (Moon et al 2016- Table 1), all other studies injected BoNT subcutaneously, covering the involved area in a grid- like pattern. In case of Botox, the toxin which was mostly used, the dose per injection site varied from 2.5 to 5 units with 1-5cm distance allowed among injection sites. Prosigne, (Chinese toxin) have units roughly comparable in strength to Botox. Injections are done usually after application of an anaesthetic cream (for instance Emla cream) or an anesthetic spray (or both) to the involved area.

Conclusion

Two blinded, high quality studies indicate that local injection of botulinum toxin-A (Prosigne) relieves the pain of PHN. This is supported by the rest of the literature, which uniformly suggests efficacy of other type A toxins (Botox and Dysport) in this pain disorder. Larger randomized, blinded trials specially with US or Europe approved type A and B toxins (Botox, Dysport, Xeomin, Myobloc) are necessary to support efficacy and analgesic effect of local BoNT injections in PHN.

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