DOI: https://doi.org/10.36811/ijapr.2019.110001 **IJAPR: February-2019: Page No: 01-04**

International Journal of Anesthesiology and Pain Research

Mini Review Open Access

Botulinum Toxin Treatment for Painful Diabetic Neuropathy A Review

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***Received Date:** Feb 16, 2019 / **Accepted Date:** Feb 23, 2019 / **Published Date:** Feb 25, 2019*

Cite this article as: Bahman Jabbari, Yasaman Safarpour. 2019. Botulinum Toxin Treatment for Painful Diabetic Neuropathy A Review. Int J Anesthesi Pain Res. 1: 01-04.

Introduction

Diabetic neuropathy (DN) is one of the most common peripheral nervous system disorders. It affects 16% of individuals with type I (young onset) diabetes and 25-26% of individuals with type II (late onset) diabetes [1]. Pain and numbness of the feet and, in advanced cases, weakness in the feet or hands are the usual symptoms. These symptoms are typically more prominent in the lower limbs. The skin in the affected areas is sensitive to touch (hyperesthesia); sometimes touch evokes pain (allodynia). The pain of diabetic neuropathy may develop spontaneously or may be provoked by touch or motion. Pain often interferes with patient's rest and sleep and has typical characteristics of a neuropathic pain i.e having a sharp and burning quality. Dorsum of the foot and toes are most commonly affected in diabetic neuropathy. On examination, the patients demonstrate decreased sensations (heat, cold, touch, position) in the affected limb. Diabetic neuropathy (DN) is usually bilateral and presents in form of a polyneuropathy.

Treatment of DN consists of avoiding sugar, lowering serum glucose levels with medications and treating pain. Both pharmacological and non-pharmacological measures have been employed to manage the pain in DN. Table 1 shows recommended and not-recommended approaches according to the guidelines published by the American academies of Neurology and Physical Medicine and Rehabilitation [2]. The levels of efficacy in this table (A: definitely effective, B: probably effective) are based on published guidelines (A level: requiring two class I and B level: requiring one class I or two class II studies) [3].

In more recent years, other agents have been found helpful in relieving the pain of DN in both humans and animal models. In human, the efficacy cannabinoids inhalation [4], to relive the pain of diabetic neuropathy has been shown in a small randomized, double blind, placebo-controlled study. In rats, several studies suggested that epigallocatechin-3-gallate (EGCG), the active component of green tea, can relieve neuropathic pain including the pain of DN [5].

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From Bril et al. [3], - PMR 2011

Table 1 Summary of recommendations

	Recommended drug and dose	Not recommended
Level A	Pregabalin, 300-600 mg/d	
Level B	Gabapentin, 900-3,600 mg/d	Oxcarbazepine
	Sodium valproate, 500-1,200 mg/d	Lamotrigine
	Venlafaxine, 75-225 mg/d	Lacosamide
	Duloxetine, 60-120 mg/d	Clonidine
	Amitriptyline, 25-100 mg/d	Pentoxifylline
	Dextromethorphan, 400 mg/d	Mexiletine
	Morphine sulphate, titrated to 120 mg/d	Magnetic field treatment
	Tramadol, 210 mg/d	Low-intensity laser therapy
	Oxycodone, mean 37 mg/d, max 120 mg/d	Reiki therapy
	Capsaicin, 0.075% QID	
	Isosorbide dinitrate spray	
	Electrical stimulation, percutaneous nerve stimulation ×3-4 weeks	

Botulinum Toxin Treatment of Pain in Diabetic Neuropathy (DN)

In animal models of local pain, injection of the botulinum toxin A or B into the skin of the painful area can relieve pain and block local accumulation of pain neurotransmitters such as glutamate and calcitonin gene related peptides [6]. Apart from the peripheral mechanism, presence of botulinum toxins A and B target proteins in spinal cord sensory neurons after peripheral injection, strongly suggests an independent central mechanism [7]. OnabotulinumtoxinA (Botox) was approved for chronic migraine in Europe and the US in 2010. In recent years, a large number of clinical trials have strongly suggested the efficacy of botulinum toxins in a variety of pain disorders [6].

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 1,1989 (the year botulinum toxin was introduced into the market) to February 1st ,2019. The search words included botulinum toxin, botulinum neurotoxin, diabetes, diabetic neuropathy and neuropathic pain.

Results

This search identified a total of forty five manuscripts, of which 5 manuscripts were directly relevant to the search subject (Table 2). Four manuscripts represented, randomized, double-blind, placebo-controlled clinical trials. Three of these four studies were of parallel design, while one had a cross-over design. All

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studies used type A toxin- three used Botox, one Xeomin and one Dysport. Of four studies with neuropathic pain (foot), the mode of injection was intradermal in three; the toxin was employed in small doses using a grid-like pattern over the dorsum of the foot. In one patient, the toxin (Botox) was injected directly into the lumbar plexus. One double - blind study evaluated the efficacy of intramuscular toxin injection in relieving calf and foot cramps associated with diabetic neuropathy (table 2). The toxin dose used was 100 units in four and 50 units in one study. The response of neuropathic pain was evaluated by visual analogue scale (0-10) and that of muscle cramps by changes in frequency and intensity of cramps. All 4 studies of neuropathic pain in DN demonstrated significant pain relief after botulinum toxin treatment. In the study of Restivo et al. [7,8], intramuscular injection of the toxin reduced the frequency and intensity of cramps substantially. None of the studies demonstrated any serious adverse effects.

Table 2: Published manuscripts on the subject of BoNT treatment of painful diabetic neuropathy.

Authors and date	Type of study	Number of patients	Toxin and dose in units(U), mode of injection	Results
Restivo DA et al. 2018 [9]	Double blind, Placebo controlled, parallel design	50	Xeomin 30 or 100 U IM	Significant reduction of intensity and frequency of calf and foot cramp in the toxin group
Moon et. al.2016	Single case	1	Botox, 100 units- Lumbar plexus	Significant pain reduction for 4-5 months.
Ghasemi et al. 2014 [10]	Double blind, placebo controlled, parallel design	40	Dysport, 100 U, ID	30% of the patients in toxin group became pain free (P<0.001). Except cold, all sensations improved
Chen et. 2013 [11]	Double blind, placebo controlled, parallel design	18	Botox 50 units ID	Significant reduction of tactile and mechanical sensation in the toxin group
Yuan et al. 2009 [12]	Double blind placebo controlled, cross-over design	18	Botox, 100 units ID	At 4 and 12 weeks, Toxin group demonstrated significant decrease in VAS score.

VAS: Visual analogue Scale - SC: subcutaneous- ID: intradermal - IM: intramuscular

Conclusion

The data from high quality studies of Botulinum toxin A in DN is encouraging and suggest the efficacy of all type A toxins in relieving both neuropathic pain and painful cramps in DN. Lack of significant adverse effects, prolonged effect (3-4 months) after one set of injections versus daily use of oral analgesic agents, makes botulinum toxin treatment desirable to patients. Larger randomized clinical trials are necessary to

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support this conclusion and demonstrate the long-term efficacy and safety of botulinum toxin treatment in painful diabetic neuropathy.

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