Review Article

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USE OF NEUROTOXIN IN MYOFACIAL AND OTHER CONCOMITANT PAIN

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ABSTRACT

Botox is a highly purified protein, presynaptic neuromuscular blocking agent extracted from Clostridium Botulinum bacteria. Since 1989, this toxin is used in treatment of strabismus, hemifacial spasm, blepharospasm, cervical dystonia. It is also used in cosmetic application mainly for dynamic wrinkles and glabellar lines. Nowadays, this toxin has become the most widely known use in various chronic pain syndromes. Due to relative safety, potency and reversibility of its effects, this toxin has become an attractive treatment option. In this review, we discuss the role of Botulinum neurotoxins in management of different pain conditions.

KEYWORDS: Botox; Myofacial pain; Neurotoxin

INTRODUCTION

Since the discovery, the use of botulinum toxins has gone from deadly poison to versatile therapeutic agent. In 1897, Van Ermangen, identified the toxin as the offending agent that caused a fatal food poisoning, botulism. In 1949, it was shown that Botulinum toxin type A blocked transmission at the neuromuscular junction (NMJ). In 1989, the US Food and Drug Administration (FDA) approved Botulinum toxin for use in treating strabismus, blepharospasm, and hemifacial spasm.[1] The toxin was named after the Latin word for sausage, "botulus," because it was associated with sausage poisoning. The syndrome is known as "Botulism" and is associated with food poisonings (mostly home-canned foods) or exposure of open wounds to contaminated soils.[2] 3 types of toxins presently are available around the world: Botox (Allergan, Inc, USA), Dysport (Ipsen Ltd, UK). Botox is the most thoroughly studied, widely used, and potent of the Botulinum Toxin. Botox is a lyophilized Botulinum toxin synthesized in bacterial culture as a single long chain protein nicked by bacterial proteases to produce the free toxin. It is purified by acid precipitations to a crystalline complex which consist of an active and hemagglutinin protein. The complex is dissolved in a solution of saline and albumin and sterile filtered before vacuum drying. It is marketed as the vacuum-dried form 100 U of Botulinum Toxin in a complex of 900 kd with 0.5 mg of human albumin and 0.9 mg of sodium chloride. The 100-U vial represents approximately 1 mg of actual neurotoxin protein. Myobloc (Botulinum Toxin B) is produced by fermentation of Clostridium botulinum type B (Bean strain) as a noncovalently associated neurotoxin complex with hemagglutinin and nonhemagglutinin proteins. After the fermentation process, the neurotoxin complex is purified through a series of precipitation and chromatography steps.[1]

MECHANISM OF ACTION

Each Botulinum Toxin is a 150-kd chain with the heavy (100 kd) and light (50 kd) components linked by a single disulfide bond. The toxin works at the neuromuscular junction through four-step process.

1. The toxin dissociates from the complex and attach to the target site and the step is mediated by the carboxyl-terminal portion of the heavy chain binding to a specific acceptor site on the presynaptic nerve membrane.
2. The free toxin is internalized into an acidic vesicle.

3. The light chain is released into cytosol.
4. The light chain disrupts the specific target fusion protein complex preventing acetylcholine release. Botulinum Toxin A cleaves SNAP-25 (synaptosomal-associated protein of 25 kd), synaptobrevin-II and Syntaxin. Recovery of Neuromuscular junction (NMJ) function occurs when an axonal sprout and end plate elongation bypass around the deactivated NMJ. After about 1 year, the original NMJ recovers, and the axonal sprout and end plate extension disappear.[1]

ACTION OF BOTOX IN PAIN RELIEF

Botox decreases hyperactivity of the muscle and checks excessive muscle spindle activity. The toxin also retrograde the neuronal uptake in central nervous system. There is a decrease release of calcium-dependent substance P in the dorsal horn of spinal cord and in the brain. The toxin also decreases nociceptive neuropeptides and increases encephalin release in the dorsal horn.[3]

USE OF BOTOX IN PAIN TREATMENT

Chronic Daily Headache

CDH (Chronic Daily Headache) is defined as headache disorders that exists for more than 15 days per month for more than 3 months in the absence of structural or systemic disease and is linked to significant disability. Alteration from episodic to chronic headache may alter the central nociceptive system. Central sensitization of trigeminovascular neurons are inhibited by Botox, which is a fundamental aspect in the development and maintenance of migraine headaches.[4]

Myofascial pain syndrome (MPS)

MPS is a regional pain syndrome defined by the presence of a localized, hyperirritable trigger point (TP), a palpable knot or mass (usually 3 to 6 mm in diameter) in a taut band of muscle. An active TP is defined as a well-localized, highly irritable taut band within skeletal muscle fibers that responds with a twitch response and remote, referred pain distribution pattern to palpation arising from central convergence and facilitation.[1] The Toxin can be used in myofacial pain related to bruxism. Bruxism is an awake or sleeps parafunctional activity which is strongly detrimental for all the stomatognathic structures, being responsible for tooth wear, periodontal tissue lesions, articular and/or muscular damage. A study was done in Padova, Italy on the patients diagnosed as Myofacial pain related to Bruxism. Efficacy of Botulinum Toxin A to reduce myofascial pain symptoms, were not significant in some cases. Descriptive analysis showed that improvements in both objective (range of mandibular movements) and subjective (pain at rest, pain at chewing) outcome variables were higher in the botox group than in the placebo patients.[5] Some authors demonstrated bite strength reduction with Botulinum toxin aid in pain relief.[6]

Neuropathic pain

A study on chronic neuropathic pain demonstrated an analgesic effect of Botulinum Toxin A injected subdermally in the area of mechanical hyperalgesia with post-traumatic and post herpetic pain.[7]

Temporomandibular Joint Disorders

The TMJ connects the mandible with temporal bone of skull and serves many functional purposes like mastication, deglutition. Temporomandibular disorder is a collective term for the pathological conditions of TMJ. Symptoms of TMD are difficulty in speaking, sleeping and eating. Headache, hyper and hypomobility of the joint, jaw dysfunction, orofacial pain. 20% to 25% of patient seeks professional care to get relieve. Clinical studies have demonstrated the use of Botulinum toxin in neurological disorders associated with hyperactivity of skeletal muscles.

Messeter & temporalis Hypertrophy

The facial deformity is due to excess muscle bulk and over activity of muscles. Injection of Botulinum toxin has been shown atrophy and reduction in muscle bulk.

Joint Pain

A recent study reported an analgesic effect in osteoarthritis, rheumatoid arthritis, refractory shoulder pain with intraarticular injection.[3] The reduction in joint pain persists for 3 to 12 months after the first injection and 3 to 8 months after repeat injections.[8]

Cervical Dystonia

Cervical dystonia (CD) is a common form of focal dystonia which frequently misdiagnosed movement disorder. Based on positioning, this condition described as torticollis (neck rotation), anterocollis (head-forward flexion or pulled forward), retrocollis (head-posterior extension or

pulled backward), or laterocollis (head tilt or lateral flexion). Multiple clinical trials support the use of botulinum toxins for the treatment. Today, botulinum toxins injection is considered a first line treatment for cervical dystonia in adult patients to reduce the severity of neck pain.[2]

SIDE EFFECTS

The possible side effects:[3]

Around the eyes / face:

Burning and pain, Diplopia, Ptosis, Tearing, Eyelid swelling and bruising.

For injections around the throat / cervical dystonia:

Neck weakness, Dysarthria, Dysphasia, Hoarseness, Drooling, Singing difficulty.

For injections in the arms or leg / treatment of Focal dystonia (e.g. writer's cramp):

Wrist drop, Arm / Hand weakness, Foot drop.

Rare side-effects:

Fever, Chills, Headache, Nausea, Muscle soreness, Light-headedness, Hypertension, Weakness, Difficulty breathing, Diarrhea, Abdominal pain.

INJECTION TECHNIQUE

Muscles	Dosage of Type A (Botox) (Units)	Dosage of Type B (Myobloc) (Units)
Temporalis	5-25 U	1000-3000 U
Masseter	25-50 U	1000-3000 U
Medial Pterygoid	5-25 U	1000-3000 U
Lateral Pterygoid	5-10 U	1000-3000 U

Table I shows Masticatory muscles and dose ranges of toxins. Dilution of 5 U per 0.1 ml. of normal saline except masseter at 10 U per 0.1 ml.[9]

FACTORS IN CHOOSING INJECTION TECHNIQUE

- **Dose:** Depends on intensity of pain, muscle size, activity of muscles.
- **Location of Injection:** There is no scientific evidence which results from pain relief if injection is given in "Trigger points". Injection is mostly done where there is symptomatology.
- **Needle size:** Small gauge needle is used preferably 30 gauge. 27 gauge is preferable for masseter.
- **Adjunctive anesthesia:** EMLA can be applied before injection as topical agent to avoid pain from injection.

ARGUMENTS AGAINST THE USE OF BOTOX

The decision of selecting the treatment for any condition is based on etiology more than the involved symptoms. Wheeler *et al*. tested placebo against Botulinum Toxin in chronic neck pain and found no difference. In another study, comparison of Botulinum toxin was done with isotonic saline for TMJ myofacial pain, the results showed no relevant effect of Botulinum Toxin. The author addressed several reasons of not using the toxin for treatment of MPDS:

1. The action of the toxin is only to relief the symptoms and doesn't address the etiology.
2. Toxin therapy is a temporary therapy and muscle function returns back in a month and require retreatment.
3. The current recommendation of American Association for Dental Research for treating patient with MPD stated that "…unless there are specific and justifiable indications to the contrary, treatment of TMD patients should be based on the use of conservative, reversible, evidence-based therapeutic modalities". And according to author Botulinum Toxin doesn't fulfill the above statement.[10]

CONCLUSION

Botulinim toxin is useful in treatment of myofacial pains. The Botulinum toxin seems to be a promising option due to its safety, reversibility and high potency. Limited literature was found in the effect of Botulinum Toxin in TMD and Bruxism. Clinical studies of the toxin on pain syndromes and in some pain conditions have shown contradictory results. There still needs a further research regarding the continued use of the toxin.

BIBLIOGRAPHY

1. Mike A. Botulinum toxins in pain management. Phys Med Rehabil Clin N Am. 2003;14:805-20.
2. Michael S. Botulinum Toxin Injections: Emerging Uses in Non-Surgical Spine Treatment and Pain Management. J Spinal Res Foun. 2011;6(1):45-54.
3. Ko G. How Botox Works for the Treatment of Chronic Pain. http://www.neuropathicpain.ca/
4. Coetzee C, van der Merwe E. Uses of Botulinum Toxin A (Botox®) In Current Medicine. SA Pharma J. 2008;44-6.

5. Luca GN, Daniele M, Salamone, Luigi S, Stefano T, Giuseppe F. Efficacy of Botulinum Toxin in Treating Myofascial Pain in Bruxers: A Controlled Placebo Pilot Study. J Craniomandibular Pract. 2008;26(2):1-10.
6. Schwartz M. Treatment of Temporomandibular Disorders with Botulinum Toxin. Clin J Pain. 2002;18(6):198-203.
7. Erisela Q, Anders FF, Troels SJ. The role of botulinum toxin in management of pain: an evidence based review. Curr Opin Anaesthesiol. 2010;23:602-10.
8. Maren LM, Jasvinder AS, Dennis D. Long Term Effects of Intra-articular Botulinum Toxin A for Refractory Joint Pain. Neurotox Res. 2006;9(2,3):179-88.
9. Position Paper on Botulinum Toxin (Botox) Injection for treatment of Chronic Myofascial pain. 2004;1-5.
10. Daniel ML. Botulinum Toxin A in the Treatment of Myofascial pain and Dysfunction: The case against its use. J Oral Maxillofac Surg. 2012;70:1240-42.

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