

**Application of inevitable botulinum toxin in migraine: A Review**

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Abstract

Botulinum Toxin is acclaimed to be the most catastrophic of all the poisons, today this toxin has emerged as a boon in the field of medical sciences because of its multiple uses and has fabulously enhanced the practices of nation's dermatologist, neurologists and pain specialists. This toxin has a tremendous track record of more than ten years of spectacular efficacy and remarkable safety profile with least side effects. In April 2002, US FDA has approved this toxin for cosmetic use and in 2004 it also got the approval for Hyperhidrosis. From past fifteen years various controlled trials have been done and they revealed the use of botulinum toxin in Chronic Migraine and as well as chronic tension type headaches. Herein we review the history, biochemical aspects, mechanism of action and clinical evidences which prove its use in migraine.

Key- Words: Clostridium Botulinum, Migraine, Botulinum toxin, Episodic migraine, Headache.

Introduction

Migraine is a neurological painful disease characterised by altered bodily perceptions, severe headache, vomiting, nausea sensitivity to light, depression. This word is derived from old French *migraigne*¹. Globally, 15% of the population is affected by the migraine. The prevalence of this disease is more in women than men². Men are more prone to this disorder before puberty and risk for women increases by 2 to 3 folds after puberty³. According to the World Health Organisation, migraine has been listed among the first twenty diseases causing disability. According to International Headache Society, there are certain specified criteria which define migraine such as repetitive attacks of headache lasting 4 – 72 hours in the form of unilateral pain, throbbing pain increases on movement along with nausea, vomiting, photophobia, phonophobia, and anorexia⁴. Current therapy of migraine has number of side effects such as myocardial infarction, heart stroke, uncontrolled arterial hypertension, Raynaud's syndrome.

In 2006, FDA put out a warning about the triptans as these drugs leads to Serotonin syndrome characterised by the features like seizures, dilated pupil, and blood pressure problems. Serendipitous discovery of Botulinum Toxin (BTX) by a Plastic Surgeon Dr Williams reveal its worthy use in the treatment of chronic pain⁵. Clostridium botulinum is a bacterium that produces the toxin botulin, the causative agent in botulism. It is a major group of gram positive bacteria and it has been included in the genus clostridium. It was first recognized and isolated in 1896 by Emile van Emergon and is commonly found in soil and damp environment. Clostridium botulinum are highly heat resistant, for inactivation it requires humid heat temperature of more than 120 C. First therapeutic use was reported by Alan B Scott M D in the patients suffering from Strabismus⁶. Since then this toxin has been employed in the treatment of various human diseases.

History and biochemical aspects

Botulism has been known ever since the early 1800's. A German poet and district medical officer Justinus Kerner recognized the food borne toxin and named it as Botulism derived from the Latin word *boulus* which means sausage, so it is also known as sausage poisoning. In 1895, there was a remarkable discovery of causative agent Clostridium botulinum by Van Ermengem while having a funeral dinner with smoked ham in the small Belgian village of Ellezelles⁷. In 1928, P Tessmar Snipe and Hermann Sommer for the first time purified this toxin. In 1949, Burgen's group

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discovered the blocking action of neuromuscular transmission

by *Clostridium botulinum*. Modern botulinum toxin was pioneered by Alan B Scott and Edward J Schantz. Various antigenically exotoxins are exhibited by this toxin A, B, C1, C2, D, E, F⁸. Out of all these type Botulinum toxin A (BTX-A) is the most potent, followed by the type B, E and F. All toxins are inactive, single polypeptide chain with zinc dependent endopeptidase light chain of molecular mass of 50kDa bound to heavy chain of 100kDa linked by the disulfide bond as a complex in the hemagglutinin and non toxin proteins⁹ as shown in figure 1. Fermentation of *Clostridium botulinum* after getting cleaved liberates the botulin toxin into the culture. Further, it is purified and crystallized with ammonium sulphate by diluting it with human serum albumin and finally lyophilisation is done and it is sealed in the vials and refrigerated. Before injecting, BTX-A is reconstituted with 1-5 ml of preservative free saline. Shaking of the contents should be avoided as bubbling and rigorous agitation can lead to denaturation of the contents. The reconstituted solution should be refrigerated at 2- 8 ° C and should be administered within 3- 4 hours. Botulinum toxin B preparation does not require reconstitution and is stable for up to 21 months in a refrigerator¹⁰. In table 1, there is a list of botulinum products available in the market approved by US FDA.

Mechanism of action

The general mechanism of action can be divided into two phases as shown in figure 2. In Phase 1, binding of the active ingredient in the toxin to the cell membrane of the nerve¹¹ and then through pinocytosis, it is internalised followed by the cleavage of the chain. At this stage, the toxin is activated; the light chain gets circumscribed by the vesicle and binds to the series of SNAP proteins which is responsible for the release of Acetylcholine. The activated chain cleaves SNAP-25 and blocks the nerves from releasing Acetylcholine¹². In Phase 2, a new nerve ending appear and get connected to the new muscle after 3-4 months and regains their ability to cause muscle contractions. In this way, Nerve muscle communication is restored. In migraine pain relief, as such there is no direct effect on central nervous system as this 150 kDa molecule cannot cross the blood brain barrier¹³, but preclinical studies has revealed that BTX decreases the neuronal release of calcium dependent substance P released^{14,15}. It also reduces the release of nociceptive neuropeptides that is glutamate, calcitonin gene related peptide¹⁶⁻¹⁹. Some studies show that BTX A is transported along the axons into the brainstem and exert its effect centrally²⁰. The inhibition of nociceptive

mediators ceases the afferent input to CNS, inflammatory signals to the sensitised regions²¹.

Botulinum toxin: A Seminal discovery

Botulinum toxin was the first biological poison licensed for the human use. It was in April 2002, the toxin got the approval for its cosmetic use in treating glabellar lines, crow's feet, nasolabial folds and perioral lines in year 2002 which was followed by the approval for digital and palmar hyperhidrosis²². Facial revitalization by the botulinum toxin has revolutionized the treatment of ageing²³. This toxin has shown promising results in treating various neurological diseases as shown in table 2. In 1940 and 1950's, migraine was considered as psychosomatic disorder²⁴. Kalper and Kalper performed an open label study over five patients with a dose of 75 U of botulinum toxin A being injected into the multiple sites. Out of them, four patients exhibited a remarkable improvement in the migraine hence embarking upon a new journey for this wonder drug²⁵. The efficacy of BTX-A was well evaluated in a double blind placebo controlled study by Relja et al²⁶. In 2000, Silberstein et al conducted a similar study by injecting the BTX in forehead and temple regions of brain. The patients were divided in two groups, one receiving 25 U and 75 U of BTX respectively. They concluded 25 U of drug to be safe and effective dose²⁷. Binder et al in a non randomized open label trial of 106 patients, reported a complete response in 51% of patients having migraine within four months. Ten patients who were treated in the acute phase of the migraine attack responded completely within 1-2 hours²⁸. Schmitt et al showed only a slight benefit in patients suffering from chronic tension-type headaches following the first month of treatment with botulinum-A injections. Studies produced since then, however, have indicated that benefits appear following 180 days, which equates to at least 3 treatments with botulinum-A. It should be noted that in Schmitt's study, only 20 units of botulinum-A was injected per treatment and none of the injection sites included muscles in the neck²⁹. A case report published in 2002 showed dramatic improvement in the symptoms of status migrainosus with a single dose of 25 U at single pain site³⁰. Eross et al used a dose range of 25 U to 75 injected at multiple sites in 54 such patients of chronic and episodic migraine and observed that the pain effects were reduced and improvement lasted up to 3 months³¹. Mauskop et al also supported the above finding with a dose of 25 to 200 U and found it to be effective³². BTX was also evaluated for the treatment of the intermittent and chronic type of migraine by Mauskop A and was found useful for this indication³³. Krusz

injected BTX A in posterior cervical sites with a dose of 100 U which resulted in decreased pain symptoms and headache by 70%³⁴. Blumenfeld evaluated 271 patients and found a response in 80% of such patients with a fixed dose of 63.2 U³⁵. On the contrary, the same author conducted a retrospective, open label trial over 208 patients, with a dose of 50 to 100 U of the BTX A, and found effective dose to be 100 U³⁶. Relja conducted a double blind placebo controlled trials over 32 patients for the assessment of BTX A on the life and on the use of triptan. Results showed the reduction in the use of other medication, total dose of triptan and features of pain³⁷. Other controlled trials reported in the medical literature in the year of 2003 were supportive of our findings³⁸⁻⁴⁴. In 2005, two largest double controlled studies were done by Mathew *et al*⁴⁵ and Silberstein *et al*⁴⁶ over 702 and 571 patients respectively for 11 months, which showed a statistically significant decrease in the frequency of headache and other pain symptoms were observed as compared to the placebo. Silberstein *et al* took BTX A in various dose units and concluded that 150 U of BTX A per treatment is the effective dose. This is significantly more than the 20 units used in Schmitt's study. Another prophylactic study was done by Dodick *et al* on the patients having chronic headache and they did not receiving any other medication⁴⁷. This author explored the effect of low dose of BTX A in sequential, randomised, controlled studies of 418 patients having a past record of moderate to severe migraine attack. In first part of study, patients were randomised to the BTX A or placebo at dose units of 7.5U, 25U, 50U. In second part, consecutive treatment was done by 25 U and 75U and finally patients were randomised to placebo. A significant decrease in frequency of migraine attacks was observed⁴⁸. Moshe Jakubowski *et al* injected BTXA intramuscularly across pericranial and neck muscles in 63 patients, among them 39 responded with a significant decline in migraine attacks⁴⁹. Some authors have questioned the use of BTX A for migraine prophylaxis⁵⁰⁻⁵⁴. Studies mentioned in the Table No. 3 observed that Botulinum toxin failed to show its effect in episodic migraine, as there was no reduction in the frequency of migraine attacks. In 2008, American Academy of Neurology published that Botulinum toxin is ineffective in the treatment of episodic migraine and chronic tension type headache⁶¹. In 2010, Mauskop conducted double blind placebo controlled trials, which confirmed the efficacy of Botulinum Toxin A to treat chronic migraine⁶². Karman Ahmed *et al* did retrospective study to assess the tolerability and efficacy of BTX A in 10 patients of age 11 -17 years giving 100 U and 40 % of them

showed a significant decrease in severity of headache in paediatric patients⁶³. Experimental studies as shown in Table 4 account for the effectiveness of this toxin in chronic migraine. On, 15 April 2010 US FDA approved Allergan anti wrinkle Botulinum for treating chronic migraine headache as it has shown its effect within a duration of 3 months⁶⁶. The treatment of migraine with this toxin decreases the need of other expensive drugs like triptans as well as the side effects shown by them. It proves to be the cost effective technically simple, easy to administer and long lasting treatment are advantages offered by this treatment.

Conclusion

Botulinum Toxin is a versatile authentic tool used for the diagnostic and therapeutic purposes in the various diseases. It has been enthusiastically employed in curing the multiple disorders such as dystonias, aesthetic improvement of facial features crow's feet, glabellar lines, nasolabial folds, detrusor instabilities⁶⁷. This toxin is gaining uphold by showing its ability to manage problems in the field of gastroenterology as it treats achalasia⁶⁸, anal fissure⁶⁹, sphincter oddi dysfunction⁷⁰ in gynecology treats vaginismus⁷¹ and in urology cures detrusor instability⁷², detrusor sphincter dyssynergia⁷³ and chronic prostate pain⁷⁴. With its mild and reversible side effects, botulinum toxin is very well accepted by the patients. It is a good choice of drug in older age group suffering from chronic pain as it has no side effect as sedation and disorientation. It is a perfect drug given to the migraineurs who have contraindications for triptans and ergotamine. BTX A is not yet approved for treating episodic migraine. Mechanism of action is not yet clear so there is lot of work has to be done for the elucidation of its direct mechanism of action in chronic migraine. In pain management, use of the botulinum toxin is equivocal so understanding the limitations and identifying as well as managing the complications is paramount. Migraine varies from patient to patient so utmost important steps should be taken to enhance the patient's reliability and to reduce the psychological burden of the disease. This toxin has a wide therapeutic index with least side effects and has proved its efficacy by showing gratifying results in all the clinical studies till date.

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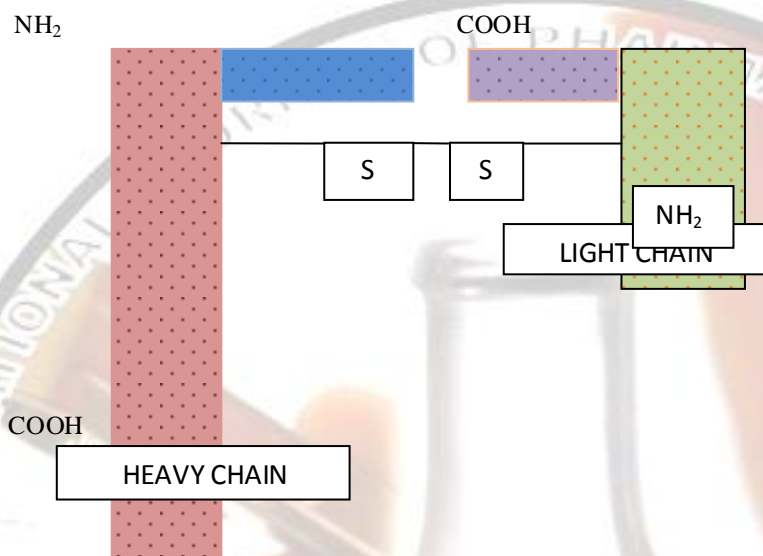


Fig. 1: Structure of botulinum toxin having light chain and heavy chain linked by disulfide bond

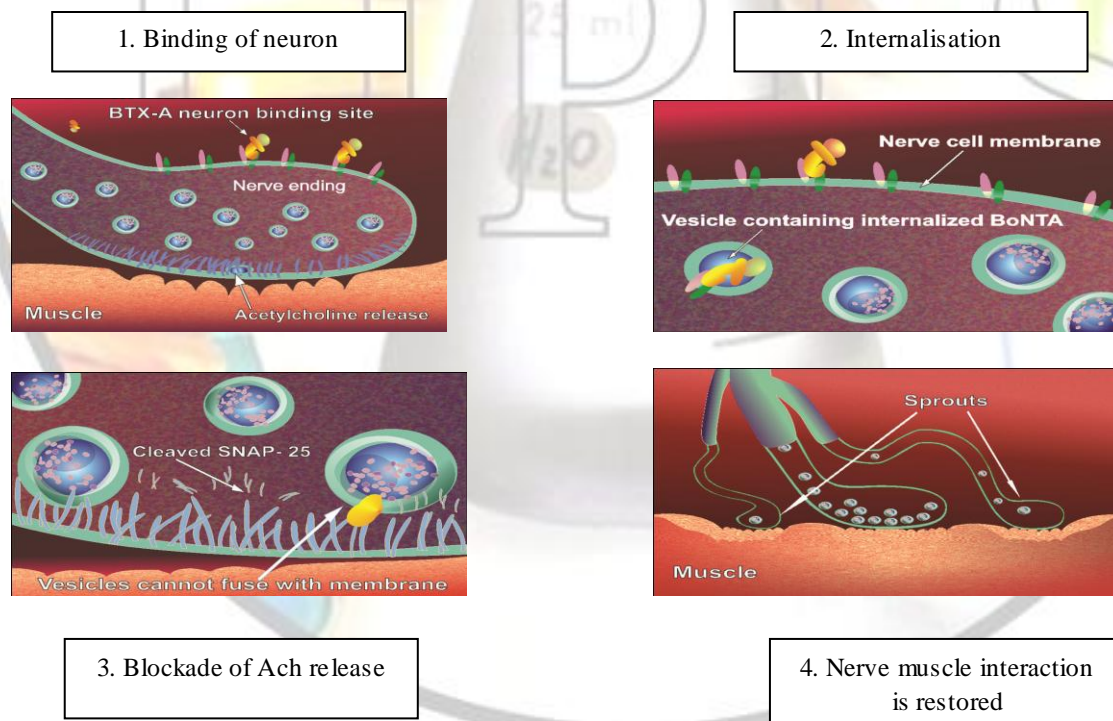


Fig. 2: Mechanism of action of btx-a divided into two phases: blockade of ach release and restoration of nerve muscle co- ordination

Table 1: List of us FDA approved botulinum products

S/ No.	Brand name	Manufacturing company	Drug name	Disorder
1.	BOTOX	Allergan, Irvine, Calif of USA	OnaBotulinum Toxin A	Cervical Dystonia, Severe primary axillary hyperhidrosis, Strabismus, Blepharospasm, Chronic migraine
2.	DYSPORT	Ipsen , French pharmaceutical company	AboBotulinum toxin A	Glabellar lines, Cervical Dystonia
3.	MYCOBLOC	Elan pharmaceutical Company ,Europe	RimaBotulinum Toxin B	Cervical dystonia
4.	NEUROBLOC	Elan pharmaceutical company, Europe	RimaBotulinum Toxin B	Cervical dystonia

Table 2: Therapeutic uses of botulinum toxin in the field of neurology

S/No.	Disorder
1.	Strabismus – Muscle contracture and there is increase in intraocular pressure of eye.
2.	Blepharospasm - Uncontrolled twitching of the muscles of the eyelids by paralysing the eye muscles.
3.	Spasticity-Increase in the velocity dependent tonic stretch reflexes.
4.	Cervical dystonia-Abnormal strangling and twirling contractions in head and neck areas.
5.	Oromandibular dystonia-Forceful contractions of muscles of jaw,lips,tongue
6.	Spasmodic dystonia-Constrictions of vocal cords.
7.	Limb dystonia/Writer's cramp – Abnormal forced gripping of the writing instrument
8.	Parkinson's disease-Alteration in the release of the chemical neurotransmitter Dopamine in brain
9.	Whiplash-Injuries caused by the sudden distortion of the neck, hyperextension of the neck injuries

Table 3: Clinical trials between the action of BTX and placebo on migraine frequency and severity

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S/No.	Studies	Type of study	Number of Patients	Outcomes	Results
1.	Aurora et al ⁵⁵ (2007)	Double blind placebo controlled exploratory study	369 patients/11 months	Migraine frequency	–
2.	Vo et al ⁵⁶ (2007)	Double blind placebo controlled study	32 patients/3 months	Migraine frequency and severity	–
3.	Relja et al ⁵⁷ (2007)	A multicentre, double blind, randomized, placebo controlled, parallel group study.	495 patients/9 months	Migraine frequency	–
4.	Sapra et al ⁵⁸ (2007)	Multicentre, double blind, randomized, placebo controlled, parallel group study.	32 patients/3 months	Migraine frequency	–
5.	Mitchell et al ⁵⁹ (2008)	Retrospective analysis of data from January 1,2003 and October 31,2006	Survey done on 54 patients	Impact of BTX A on life and its assessment of use and overall cost	Improvement in disease specific symptoms in refractory migraine but medical costs were found to be high.
6.	Adam J. Shuhendler et al ⁶⁰ (2009)	Meta analysis of eight randomized double blind placebo controlled study	1601 patients/3 months	Migraine frequency	–

-No significant difference was observed

Table 4: Phase iii research evaluating migraine prophylaxis therapy showing the effectiveness OF BTX in chronic migraine

Researchers	Phase	Subject	Subject dose	Outcomes	Result
Aurora SK et al ⁶⁴ (2010)	PREEMPT (Phase3 study)	24 week double blind parallel group placebo controlled phase followed by 32 week open label phase	OnaBotulinum toxin injected in the unit dose of 155 U-195U, n =341 or placebo n=338 two cycles	Migraine Frequency	Significant decrease in the headache and migraine days. No reduction was observed in the episodic migraine
Diener HC et al ⁶⁵ (2010)	PREEMPT (Phase3 study)	24-week, double-blind, placebo-controlled phase, followed by a 32-week, open-label phase	OnabotulinumtoxinA injected in the unit dose range of155U-195U; n = 347 or placebo (n = 358) every 12 weeks for two cycles.	Migraine frequency	Significant decrease in the headache and concluded that OnaBotulinumtoxin A is safe and effective in the use of chronic migraine