ISSN: 0976-7126

INTERNATIONAL JOURNAL OF PHARMACY & LIFE SCIENCES

Application of inevitable botulinum toxin in migraine: A Review

Ashok Kumar*, Rishbha Sharma, Anroop Nair and Gautam Saini
M.M. College of Pharmacy, M.M. University, Mullana, (Haryana) -India

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 men [2]. Men are more prone to this disorder before puberty and risk for women increases by 2 to 3 folds after puberty [3] .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 anorexia [4]. Current therapy of migraine has number of side effects such as myocardial infarction, heart stroke, uncontrolled arterial hypertension, Raynaud's syndrome.

*** Corresponding Author:**
E-mail: ashokmmcp@rediffmail.com
Mob.: +919896551284

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 pain [5]. Clostridium botulinium 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 botulinium 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 Strabismus [6]. 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 *botulus* 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 Ellezelles [7]. In 1928, P Tessmar Snipe and Hermann Sommer for the first time purified this toxin. In 1949, Burgen's group

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, F [8]. 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 proteins [9] 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, B T X - 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 º 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 refrigerator [10]. 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 nerve [11] 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 Acetylcholine [12]. 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 barrier [13] , 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 peptide [16-19]. Some studies show that BTX A is transported along the axons into the brainstem and exert its effect centrally [20].The inhibition of nociceptive mediators ceases the afferent input to CNS, inflammatory signals to the sensitised regions [21].

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 hyperhidrosis [22]. Facial revitalization by the botulinium toxin has revolutionized the treatment of ageing [23]. 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 disorder [24]. 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 drug [25]. The efficacy of BTX- A was well evaluated in a double blind placebo controlled study by Relja et al [26]. 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 dose [27]. 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 hours [28]. Schmitt et al showed only a slight benefit in patients suffering from chronic tension-type headaches following the first month of treatment with botulinium-A injections. Studies produced since then, however, have indicated that benefits appear following 180 days, which equates to at least 3 treatments with botulinium-A. It should be noted that in Schmitt's study, only 20 units of botulinium-A was injected per treatment and none of the injection sites included muscles in the neck [29]. A case report published in 2002 showed dramatic improvement in the symptoms of status migrainous with a single dose of 25 U at single pain site [30]. 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 months [31]. Mauskop et al also supported the above finding with a dose of 25 to 200 U and found it to be effective [32]. BTX was also evaluated for the treatment of the intermittent and chronic type of migraine by Mauskop A and was found useful for this indication [33]. 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]. Blumenfed evaluated 271 patients and found a response in 80% of such patients with a fixed dose of 63.2 U [35]. 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 U [36]. 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 pain [37]. Other controlled trials reported in the medical literature in the year of 2003 were supportive of our findings [38-44].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 D et al on the patients having chronic headache and they did not receiving any other medication [47]. 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 observed [48]. 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 attacks [49].Some authors have questioned the use of BTX A for migraine prophylaxis [50-54]. 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 headache[61]. In 2010,Mauskop conducted double blind placebo controlled trials, which confirmed the efficacy of Botulinum Toxin A to treat chronic migraine [62]. 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 patients [63]. 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 months [66]. 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 instabilities [67]. This toxin is gaining uphold by showing its ability to manage problems in the field of gastroenterology as it treats achalasia [68], anal fissure[69],sphincter oddi dysfunction [70] in gynecology treats vagnismus [71] and in urology cures detrusor instability [72],detrusor sphincter dyssynergia [73]and chronic prostate pain[74].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.

References

1. Migraine [Internet].2010[revised 2010 Jan 27]. Available from: http://en.wikipedia.org/wiki/Migraine.
2. Lipton R.B., Stewart W.F., Diamond S., Diamond M.L., Reed M. (2001). Prevalence and burden of migraine in the United States:

data from the American Migraine Study II, Headache. 41; 646–657.
3. Stewart W.F., Linet M.S., Celentano D.D., Van Natta M., Ziegler D. (1991). Age and sex specific incidence rates of migraine with and without visual aura, Am. J. Epidemiol.134; 1111–1120.
4. International Headache Society. (2004).The International Classification of Headache Disorders, Cephalalgia. 24(Suppl. 1); 9-160 .
5. Mathew NT. (2008). Preventive treatment of migraine, Acta Neurol Colomb. 24 ; S53-S71.
6. Scott A.B. (1981). Botulinum toxin injection of eye muscles to correct strabismus, Trans Am Ophthalmol Soc. 79 ; 734–770.
7. Erbguth F.J. (2004). Historical notes on botulism, Clostridium botulinum, botulinum toxin, and the idea of the therapeutic use of the toxin, Mov Disord. Suppl 8 ; S2-6.
8. Neuenschwander M.C., Pribitkin E.A., Sataloff R.T.(2000).Botulinum Toxin in Otolaryngology: A review of its actions and opportunIties for use.79(10);788-799
9. Huang W., Foster J .A ., Rogachefsky A.S. (2000).Pharmacology of Botulinum toxin, Journal of the American Academy of Dermatology. 43(2); 249-259
10. Dastoor S. F., Misch C.E., Wang H. L. (2007). Botulinum toxin to enhance facial macroesthetics: a literature review, J Oral Implantol .33 (3) ; 164-71
11. Aoki R . (1998). The development of Botulinum: its history and pharmacology, Pain digest . 8 ; 337-44
12. Aoki K. R. (2005) . Review of a proposed mechanism for the antinociceptive action of botulinum toxin type A, Neurotoxicology. 26 ; 785–793.
13. Dressler D., Saberi FA.., Barbosa ER..2005 Botulinum toxin: mechanisms of action, Arq
14. Neuropsiquiatr. 63; 180-185
15. Van den Bergh P., Beukelaer M D., Deconinck N. (1996). Effect of muscle denervation
16. on the expression of substance P in the ventral raphe-spinal pathway of the rat, Brain Res. 707 ; 206-12.
17. Ishikawa H., Mitsui Y., Yoshitomi T., Mashimo K., Aoki S., Mukuno K.,Shimizu K. (2000). Presynaptic effects of botulinum toxin type A on the neuronally evoked response of albino and pigmented rabbit iris sphincter and dilator muscles, Jpn J Ophthalmol. 44(2) ; 106-109
18. Cui M., Li Z., You S., Khanijou S., Aoki R. (2002) Mechanisms of the antinociceptive effect of subcutaneous Botox: inhibition of peripheral and central nociceptive processing , Arch Pharmacol .365 ; R17.
19. Morris J.L ., Jobling P., Gibbins I.L.(2001). Differential inhibition by botulinum neuro-toxin A of cotransmitters released from autonomic vasodilator neurons, Am J Physiol Heart Circ Physiol .281 ; 2124-32.
20. Durham P.L., Cady R., Cady R. (2004) . Regulation of Calcitonin Gene-Related Peptide secretion from Trigeminal nerve cells by Botulinum Toxin type A: Implications for Migraine therapy, Headache. 44 ; 35-43
21. Tugnoli V., Caponone J.G., Eleopora R., Quatrale R., Sensi M., Gastaldo E., Tola M.R., Geppetti P. (2007) . Reduces capsaicin-evoked pain and neurogenic vasodilatation in human skin, PAIN .130 ; 76-83
22. Aoki K.R. (2003) .Evidence for antinociceptive activity of Botulinum toxin type A in pain management, Headache . 43 ; S9-S15.
23. Wiegand H ., Wellhoner H.H. (1977).The action of botulinum A neurotoxin on the inhibition by antidromistimulation of the lumbar monosynaptic reflex. Naunyn Schmiedebergs , Arch Pharmacol . 298 ; 235-238
24. Solomon B A., Hayman R .(2000) . Botulinum toxin type A therapy for palmar and digital hyperhidrosis, Journal of American Academy of dermatology.42 (6); 1026-1029
25. Hallett M. (1999). One man's poison—clinical applications of botulinum toxin, N Engl J Med. 341 ; 118–120
26. Jackson M., Barbuto J.P. (2008). Botulinum, migraine, and the American Academy of Neurology: an antidote to anecdote,J Manag Care Pharm .14(5) ; 465-67.
27. Klapper J.A., Klapper A. (1999). Use of Botulinum toxin in chronic daily headaches associated with migraine, Headache Quart. 10; 141-143
28. Relja M .A ., Korsic M. (1999).Treatment of tension-type headache by injections of Botulinum toxin type A: double-blind placebo controlled study, Neurology. 52 ; A 203.
29. Silberstein S., Mathew N., Saper J., Jenkins S.(2000). Botulinum toxin type A as a

migraine preventive treatment,for the BOTOX migraine clinical research group ,Headache. 40 ;445-450.
30. Binder W.J., Brin M.F., Blitzer A., Schoenrock L.D., Pogoda J.M. (2000). Botulinum toxin type A (BOTULINUM) for treatment of migraine headaches: an open-label study, Otolaryngol Head Neck Surg. 123(6) ; 669-76.
31. Schmitt W.J., Slowey E., Fravi N., Weber S., Burgunder J.M.(2001). Effect of Botulinum toxin A injections in the treatment of chronic tension-type headache: a double blind, placebo controlled trial, Headache. 41; 658–664.
32. Poungvarin N. (2001) .The first world report of botulinum A toxin injection for status migrainosus , J Med Assoc Thai . 84 ; 1199-1203.
33. Eross E.J., Dodick D.W. (2002).The effects of botulinum toxin type A on disability in episodic and chronic migraine , Neurology .58 ; A497.
34. Mauskop A. (2002). Long-term use of Botulinum toxin type A in the treatment of episodic and chronic migraine headaches, Headache. 42; 454-455.
35. Mauskop A. (2002).The use of botulinum toxin in the treatment of headaches, Curr Pain .6 ; 320-323.
36. Krusz J. (2002). Intradermal botulinum toxin, type A, for cervicogenic migraine[abstract],
37. Headache .42;405
38. Blumenfeld A. (2003). Botulinum toxin type A as an effective preventive treatment in headache, Headache. 43;576
39. Mathew N., Kaup A ., Kailasam J. (2003).Botulinum toxin type A modifies chronic migraine; further long-term (3 years) experience with up to ten sets of treatments , Headache . 43;576
40. Relja M.A .(2003). Botulinum toxin type-A reduces acute medication (triptans) use in migraine patients, Neurology .60 ;147
41. McAllister P. (2003) Patient-reported improvements in headache and change in headache medication usage in a cohort treated with botulinum toxin type-A (Botulinum). Headache; 43 ; 577.
42. Tepper S.J., Bigal M .E ., Sheftell F.D ., Rapoport A. M.(2004). Botulinum Neurotoxin type A in the preventive treatment of refractory headaches: a review of 100 consecutive cases Headache. 44 ; 794-800
43. Miller T., Denny L. (2003). Botulinum toxin A (Allergan) for chronic intractable headache: equally effective with or without concomitant neck pain, Headache 43; 577.
44. Tomosovic J., Sabo T. (2003). Improvement of intractable headache in adolescent females after craniocervical injections of BTX-A (Allergan). 43;579 .
45. Loder E. (2003). Botulinum toxin treatment of headache and neck pain associated with stiff-person syndrome. 43;509
46. Troost T., Rosenberg J.R., Wiles R. (2003). Improvement in intractable headache with repeated botulinum toxin type A treatment, Neurology. 60; A323 - A324.
47. Sebastian F.T., de Bruijn M. (2003). Treatment of chronic tension-type headache with botulinum toxin; a double-blind placebo controlled clinical trial, Neurology. 60;148.
48. Mathew N.T., Frishberg B.M., Gawel M., Dimitrova R., Gibson J., Turkel (2005).C. Botulinum toxin type A (Botulinum) for the prophylactic treatment of chronic daily headache: a randomized, double-blind, placebo-controlled trial, Headache. 45; 293–307.
49. Siberstein S.D., Stark S.R., Lucas S.M., Christie S.N., De Gryse R.E., Turkel C.C. Botulinum toxin type A for the prophylactic treatment of chronic daily headache: a randomized, double-blind, placebo-controlled trial, Mayo Clinic Proceedings.80(9);1126–1137.
50. Dodick D.W., Mauskop A., Elkind, A.H., DeGryse R. .,Brin M .F., Silberstein S.(2005). Botulinum toxin A for the prophylaxis of chronic daily headache: subgroup analysis of patients not receiving other prophylactic medications: a randomized, double-blind, placebo-controlled study. Headache 45(4); 315-324.
51. Elkind A. H., Carroll P O ., Blumenfeld A., DeGryse R ., Dimitrova R.(2006). Study Group. Series of Three Sequential, randomized, controlled studies of repeated treatments with Botulinum Toxin Type A for Migraine prophylaxis,The Journal of Pain. 7(10); 688-696.
52. Jakubowski M., McAllister P.J., Bajwa Z.H., Ward T.N., Smith P., Burstein R. (2006). Exploding vs. imploding headache in migraine prophylaxis with Botulinum Toxin A,

Pain.125 (3); 286- 295.
53. Evers S., Olesen J. (2006). Botulinum toxin in headache treatment: the end of the road, Cephalalgia. 26 (7); 769-71.
54. AteŞ Y. (2006). Botulinum toxin for the treatment of headaches: a review of Current practices and evidence-based data, Agri.18(3);5-11.
55. Gupta V.K. (2006). Botulinum Toxin— a treatment for migraine? A systematic review, Pain Med. 7(5); 386-94.
56. Pakalnis A., Couch J. (2008). Headache therapy with botulinum toxin—form over substance, Arch Neurol. 65(1) ; 149
57. Roach E.S. (2008). Questioning botulinum toxin for headache—reality or illusion, Arch Neurol. 65(1) ; 151-52.
58. Aurora S.K., Gawel M ., Brandes J.L., Pokta S., VanDenburgh A.M. (2007).Botulinum toxin type a prophylactic treatment of Episodic migraine: a randomized, double-blind, placebo-controlled exploratory study, Headache. 47(4); 486-99
59. Vo A.H., Satori R., Jabbari B., Green J., Killgore W.D.S., Labutta R., Campbell W.W.(2007)Botulinum toxin type A in the prevention of migraine: a double-blind controlled trial , Aviat Space Environ Med .78(5);B113-B118
60. Relja M., Poole A.C., Schoenen J., Pascual J., Lei X. (2007).Thompson C. A multicentre, double blind, randomized, placebo-controlled, parallel group study of multiple treatments of botulinum toxin type A (BoNTA) for the prophylaxis of episodic migraine headaches, Cephalalgia .27 (6); 492-503.
61. Saper J.R., Mathew N.T., Loder E.W., DeGryse R., VanDenburgh A.M. (2007).A double- blind, randomized, placebo-controlled comparison of Botulinum toxin type a injection sites and doses in the prevention of episodic migraine. Pain Med. 8(6); 478-85.
62. Mitchell M.P., Schaecher K., Cannon H.E., Speckman M. (2008). Humanistic, utilization and cost outcomes associated with the use of botulinum toxin for treatment of refractory migraine headaches in a managed care organization, J Manag Care Pharm.14(5);442 - 50.
63. Shuhendler A. J., Lee S., Siu M., Ondovcik S., Lam K., Alabdullatif A., Zhang X., Machado M., Einarson T. R.. (2009). Efficacy of Botulinum Toxin Type A for the Prophylaxis of Episodic Migraine Headaches: A Meta analysis of randomized, double-Blind, Placebo-Controlled Trials, Pharmacotherapy. ; 29 (7) ; 784-791
64. Naumann M, So Y, Argoff CE, Childers M. K., Dykstra D.D. ,Gronseth G.S.,Jabbari B., Kaufmann H.C., Schurch B ., Silberstein S.D.,Simpson D.M. (2008).Botulinum neurotoxin in the treatment of autonomic disorders and pain (an evidence based review):report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology, Neurology. 70 (19) ;1707-14.
65. Mauskop A.(2010). Botulinum neurotoxin in the treatment of headache disorders ,Handbook of Clinical Neurology. 97 Chapter 17, Pages 217-232
66. Ahmed K., Oas K. H., Mack K. J.,Garza I. Experience With Botulinum Toxin Type A in Medically Intractable Pediatric Chronic Daily Headache Pediatric Neurology,2010 Nov; 43(5): 316-319
67. Aurora S.K., Dodick D.W., Turkel C.C., DeGryse R.E., Silberstein S.D., Lipton R.B., Diener H.C., Brin M.F.(2010). PREEMPT 1 Chronic Migraine Study Group. OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 1 trial, Cephalagia: An International Journal of Headache.30 (7); 793-803.
68. Diener H.C., Dodick D.W., Aurora S.K., Turkel C.C., DeGryse R.E., Lipton R.B., Silberstein S.D., Brin M.F.(2010).PREEMPT 2 Chronic Migraine Study Group. OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 2 trial, Cephalagia: An International Journal of Headache. 30(7):804-14
69. Samson., Kurt . 2010. Fda approves Botulinum Toxin A for severe Chronic migraine: Training on how and when to use is key experts say. Neurology Today 4; 10(21);1-13
70. Carruther J.A., Lowe N.J., Menter M.A., Gibson J., Nordquist M., Mordaunt J.(2002). A multi-center, double-blind, randomized, placebo controlled study of the efficacy and safety of botulinum toxin type A in the

treatment of glabellar lines, J Am Acad Dermatol. 46 ; 840-9.

71. Martinek J., Spicak J. (2003). A modified method of botulinum toxin injection in patients with achalasia: a pilot trial, Endoscopy .35 (10) ;841-844.
72. Maria G., Cassetta E., Gui D., Brisinda G., Bentivoglio A.R.,Albanese A.(1998). A comparison of botulinum toxin and saline for the treatment of chronic anal fissure,N Engl J Med .338(4) ; 217-220.
73. Banerjee B., Miedema B., Saifuddin T., Marshall J.B. (1999). Intrasphincteric botulinum toxin type A for the diagnosis of sphincter of Oddi dysfunction: A case report. Surg Laparosc Endosc Percutan Tech .9(3) ; 194-196.
74. Brin M.F., Vapnek J.M. (1997). Treatment of vaginismus with botulinum toxin, Lancet .349; 252-253.
75. Werner M ., Kuschel S. , Schmid M. D. , Schuessler B .(2006). Efficacy of Botulinum Toxin A in the Treatment of Female Idiopathic Detrusor Overactivity Incontinence: Long-Term Results of a Prospective Non randomised Study, Eur Urol.5(11);667-696.
76. Yokoyama T., Kumon H., Smith CP., Somogyi G.T. (2002).Botulinum toxin treatment of urethral and bladder dysfunction, Acta Med Okayama .56 ; 271–7.
77. Maria G., Brisinda G., Civello I.M., Bentivoglio A.R., Sganga G., Albanes A. (2003).Relief by botulinum toxin of voiding dysfunction due to benign prostatic hyperplasia: results of a randomized, placebo-controlled study, Urology. 62 (2) ; 259–64

ISSN: 0976-7126

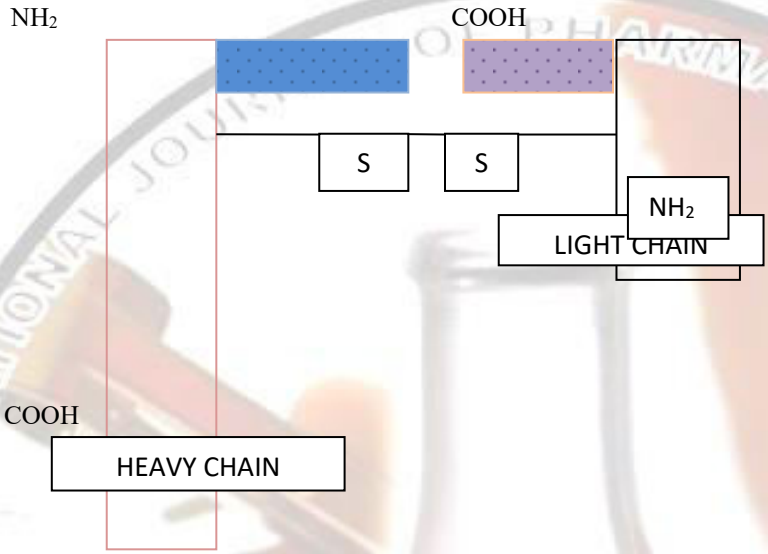

Fig. 1: Structure of botulinum toxin having light chain and heavy chain linked by disulfide bond

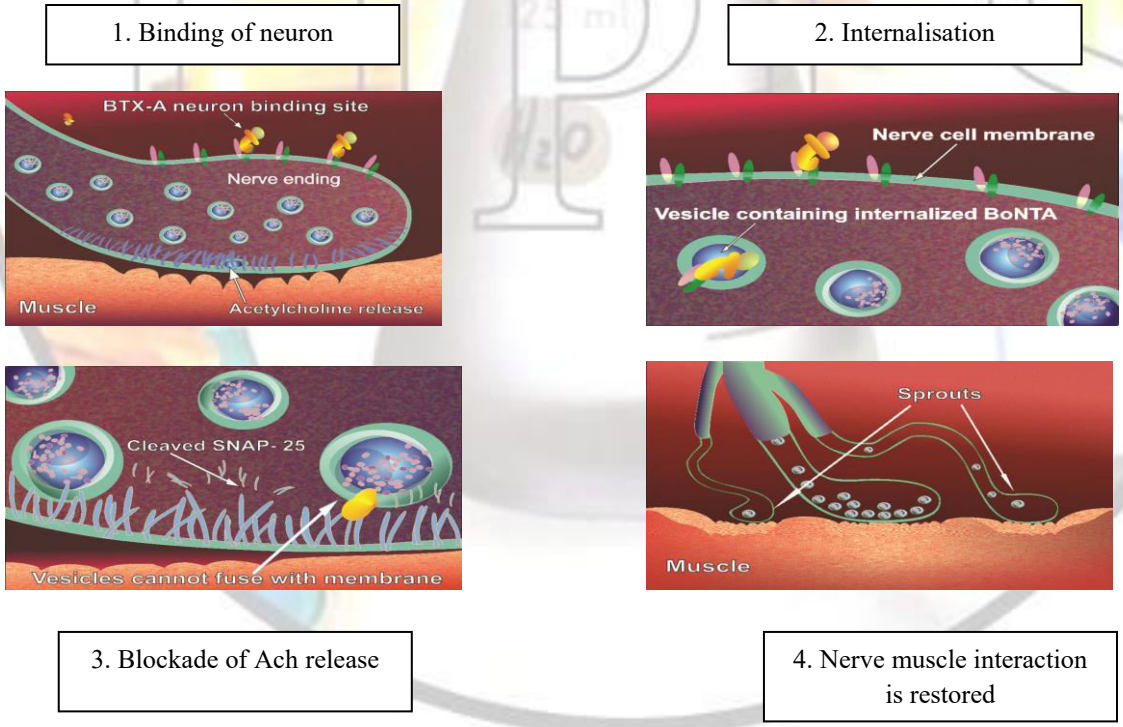

Fig. 2: Mechanism of action of btx-a divided into two phases: blockade of ach release and restoration of nerve muscle co- ordination

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.	Bleopharospasm - 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-Contractions of vocal cords.
7.	Limb dystonia/Writer's cramp – Abnormal forced griping 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

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 =341or 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