Botulinum Toxin in Migraine

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INTRODUCTION

Migraine is a common, chronic, paroxysmal, debilitating neurologic disorder with widely varying symptoms, affecting up to 16% of the general population.1 It is very likely, but as yet not proven beyond doubt that hereditary factors are important in the individual’s susceptibility to migraine attacks. The relatively recent characterization of the anatomy and physiology of the pain-sensitive innervation of the cranium provides a framework to understand the manifestations and treatment of migraine. The effect of migraine on the life-style of sufferers can lead to loss of function and limit the number of working days. A certain percentage of patients need preventive treatment in order to decrease the sufferings. The aim of preventive medication is to lessen the severity and frequency of attacks and to reduce the disability. Different kinds of medication with proven efficacy namely beta-blockers such as metoprolol and propranolol, calcium channel blockers such as flunarizine, several 5-HT, antagonists and amitryptiline and mainly used in combination or alone in migraine prophylaxis. Recently antiepileptic drugs (valproic acid, topiramate, gabapentin) have been evaluated for the prophylaxis of migraine.2 A certain number of migraineurs still cannot be treated satisfactorily despite the presence of a number of effective prophylactic medications.

CURRENT USAGE OF BOTULINUM TOXIN (BTX)

Botulinum toxin type A (BTX), one of the most poisonous biological substances known, is used for treatment of a myriad of human neuromuscular disorders characterized by involuntary contraction of striated or smooth muscle. Although BTX is approved by the US FDA and labeled for strabismus,3 hemifacial spasm4 and blepharospasm5 in 1989, it was demonstrated as safe and effective appropriate therapy for torticollis (cervical dystonia),6 spasmodic dysphonia,7 spasmody dysphonia,8 some cases of oromandibular dystonia and writer’s cramp.9,10 The beneficial effect of BTX has been shown in spasticity,11 rectal sphincter spasm with fissure,12 and achalasia.13 Since its introduction into clinical use in the early 1980s, BTX has been demonstrated to provide an effective and safe therapy for focal and segmental dystonia as well as other disorders manifested by inappropriate contraction of muscles. The list of areas treated has expanded to include dystonic and nondystonic involuntary movements, including those excessive muscle contraction accompanying stroke, demyelinating disease, tremor, and cosmetic condition.14,15 Reported benefits in hyperhydrosis16 has proven that BTX can inhibit overactive non-motor as well as motor peripheral acetylcholine neurons. In addition to reducing muscle hyperactivity and spasm, BTX-A treatment often reduces the pain associated with cervical dystonia, achalasia, and rectal fissures. Evidence suggests that it may be beneficial in the treatment of chronic low back pain associated with muscle spasm.17 Recently it has been used in reducing drooling of saliva in Parkinson’s disease.18

CONSIDERATION OF ROLE OF BTX-A IN HEADACHE

Some of the current migraine preventive therapies often have limited efficacy and adverse effects. The therapeutic effect of botulinum toxin in headache was observed coincidentally.19 The rationale for this new indication was met initially with great deal of scepticism, because the toxin’s mechanism of action, cholinergic chemodenervation does not fit the pathophysiological concept of migraine and the other forms of headache. Meanwhile a fair number of studies have been published which indicate efficacy for botulinum toxin and recommend its use for the treatment of migraine and tension type headache.

Possible mechanism of action of botulinum toxin as antinociceptive agent

The potential efficacy of BTX in the treatment of migraine raises interesting questions regarding the role of muscle contraction in the pathophysiology of migraine and the mechanism of action of botulinum toxin in pain disorders in general. Pericranial muscle tension may contribute to the development of chronic daily headache, and tension type headache. Elimination of pericranial muscle tension by injecting Botox may reduce associated myalgia and counteract headache. The disablement. Different kinds of medication with proven efficacy namely beta-blockers such as metoprolol and propranolol, calcium channel blockers such as flunarizine, several 5-HT, antagonists and amitryptiline and mainly used in combination or alone in migraine prophylaxis. Recently antiepileptic drugs (valproic acid, topiramate, gabapentin) have been evaluated for the prophylaxis of migraine.2 A certain number of migraineurs still cannot be treated satisfactorily despite the presence of a number of effective prophylactic medications.

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Recent research has shown that in addition to its effect at the neuromuscular junction by inhibiting the release of acetylcholine, it may have anti-nociceptive effects due to its action on pain carrying C and A delta fibres as well as its effects on reducing cholinergic transmission at the perivascular nerve endings.17 Botox is an enzyme that acts as zinc (Zn²⁺) endopeptidase and proteolysis of one or more neuronal proteins is probably the case of the intracellular lesion that inhibits neurotransmitter release.18,19 Animal
studies have demonstrated that botulinum toxin may reach the CNS through axonal flow from inoculations of to muscle. There is typically a delay of 24 to 72 hours between administration of toxin and onset of clinical effect and hence it is conceivable that the delay in onset of clinical effects is related to a delayed effect of the protease on substrate metabolism or a proximal spread of toxin as noted in experimental systems.

**Efficacy of botulinum toxin in clinical trials**

A number of clinical traits are underway to assess the efficacy of botulinum toxin type A injections into the pericranial muscle in patient with chronic tension type headache and migraine. The following clinical trials have demonstrated the efficacy of Botox A in migraine prophylaxis and in tension-type headache.

i) Silberstein S et al carried a double blind, placebo (vehicle) controlled study of 123 subjects having three arms, randomized to receive single administration of Botox type A 25 units and 75 units. Compared with placebo treatment, subjects in the Botox type A treatment groups showed significantly fewer attacks per month, the attacks were reduced in severity, there was a reduction in number of days needing acute migraine medications and a lower incidence of migraine associated vomiting. All treatments were generally well tolerated and there were no serious treatment-related adverse events. All treatment-related adverse events were transient and include blepharoptosis, diplopia and injection site weakness - an expected drug effect.

ii) Binder WJ et al carried a non-randomized, open label study of 106 patients; predominantly female, and main outcome measures were determined by severity and duration of response. Among 77 true migraine subjects treated prophylactically, 51% reported complete response with a mean response duration of 4.1 months; 38% reported partial response with a mean response duration of 2.7 months. Seventy percent of 10 true migraine patients treated acutely reported complete response with improvement 1 to 2 hours after treatment. No adverse effects were reported.

iii) Wheeler AH carried out a study in four patients of chronic, predominantly tension-type headaches associated with pericranial muscle tension who were refractory to prolonged conventional treatment by injecting botulinum toxin type A in pericranial muscle. This alleviated myalgia and reduced the severity and frequency of headache with a concomitant reduction in subsequent intervention of medical and physical therapy.

iv) Pounvarin N reported the first ever documented publication in the world concerning the use of botulinum toxin A (BTX) injection for status migrainosus. A 58 years old man, a sufferer of migraine without aura for 20 years presented with severe throbbing headache and refractory to paracetamol, aspirin, ergotamine, mefenamic acid, and diazepam was administered 25 international units of Botox - A into Fung Chou point (Classical Chinese acupuncture point for migraine). Dramatic response was observed within one hour of injection and status migrainosus was aborted within 10 hours. He was headache-free and had no further attack of migraine for another two months.

v) Ghosh B et al used botulinum toxin type A prospectively in two patients of chronic daily headache by injecting over 11 different sites in pericranial muscles. Both the patients started improving 10 days after injection and they are symptom-free four months after injection with no adverse effects.

**Current suggestions regarding the use of botulinum toxin**

1. Prophylactic treatment of migraine headache, transformed migraine / chronic daily headache
2. Acute treatment of migraine headache
3. To abort attack of status migrainosus

Dosage range: The ideal final dose has not been arrived at. Till such time 25 to 75 units. The injections are given once in every 3 to 4 months interval or as and when the effect wanes off.

Sites to be given (Figs. 1 and 2): Multiple sites of pericranial muscles namely over frontalis (4 sites), temporalis (2 sites), glabellar site (Corrugator : 4 sites, Procerus : one site), suboccipital regions of head and neck (2 sites).

Expected onset of benefit after BTX - A therapy is usually 15 days to one month post-treatment when given as prophylactic therapy. The need for daily prophylactic medication is diminished by botulinum type toxin and side effects from daily prophylactic medications are also reduced. The need for acute treatment and the severity of attacks of

![Fig. 1: Injection sites over the frontalis, temporalis and glabellar regions](image)
migraine is reduced substantially. Side effects of botulinum toxin type-A are minimal, local and usually very transient. Overall it appears to be a promising area of research. It is probably too early to recommend it as in the routine management of chronic migraine and related disorders.

CONCLUSION

Migraine imposes a substantial burden on society as measured by direct and indirect costs. Because the indirect costs greatly exceed the direct cost and since migraine is often undertreated, improvement in treatment should reduce individual suffering and work loss in a cost-effective manner. Use of a therapeutic modality such as botulinum toxin provides a scope for side-effect-free management in some cases of difficult-to-treat headache sufferers. For some unknown reason, the effect is better in some patients than in others.

REFERENCES


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**Book Review**

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KP Misra

This indeed is a fascinating book by Dr. KP Misra, his 9th, who has more than 35 years experience in medicine and cardiology in India and USA. He is a renowned cardiologist, a great orator, teacher, author and a humanist involved in socio-cultural activities.

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