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Epilepsy Control in Patients with Chronic Headaches Receiving Onabotulinum Toxin, Type A (Botox)

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Editorial

Botulinum is a neuro toxin produced by gram-positive bacillus C. *botulinum* of the 7 serotypes of the Botulin toxin (A, B, C1, D, E, F, G) A and B are commercially available. Since the introduction of Botulin in 1992 it has been used for several indications including limb spasms, blepharospasm, cervical dystonia, and prophylaxis in adult patients with chronic migraine headaches, overactive bladder with urge incontinence, severe axillary hyperhidrosis, strabismus, cervical dystonia and limb spasticity. Botulinum toxin acts as an acetylcholine releasing inhibitor and a neuromuscular blocking agent.

We have two patients in our practice with history of epilepsy, who were receiving Botulinum toxin A for migraine headaches prophylaxis, and were observed to remain seizure-free since they were started on botulinum toxin injections. Patient 1 is a 66-year-old male with history of epilepsy, secondary to concussion, PTSD, coronary artery disease, chronic sinusitis, cirrhosis of liver, chronic headaches secondary to motor vehicle accident in 1970, and vestibular neuritis, bilateral shoulder pain was followed by neurology service since January 2004. Seizures started after he sustained a head injury when he was hit by a semi-truck and remained unconscious for 9 days. He was on Dilantin and phenobarbital initially for the treatment of seizures. He was intolerant to both medications and hence Dilantin and phenobarbital were discontinued and was started on carbamazepine. He was experiencing Seizures about 1-2 times per month. He had tonic-clonic seizures without aura. Botox injections were started on January 21, 2004 for chronic migraine headaches. He was still on carbamazepine when he was receiving Botulinum injections. He was receiving injections every 3-4 months. He took himself off seizure medications on December 9, 2005. Since then he remained seizure-free. EEG on February 21, 2008 was unremarkable. MRI of the brain in July 2008 was normal.

Patient 2 is a 35-year-old female with history of hypothyroidism, narcotic use disorder, nicotine use, major depression, back pain and epilepsy. She had epilepsy since 2006 and was placed on Topiramate 200 mg daily. She had tonic-clonic seizures every week. She was noncompliant with Topiramate. She had history of chronic headaches. Botox injections were started in July 2009 for migraine headache prophylaxis. Her migraine headaches improved. Seizure frequency has decreased. Last seizure was in November 2011. She had no recurrence of seizures since then.

Epilepsy is a condition in which a person can have recurrent unprovoked seizures due to underlying disease processes. It is the second most common neurological condition in the primary care setting after headaches. Epilepsy affects about 0.5% of population in United States and at about 44 new cases of epilepsy per ten thousand individuals per year. More than one third of the populations with epilepsy are estimated to have pharmaco resistant epilepsy. Seizures are paroxysmal, abnormal, and excessive neuronal activity in the brain resulting in sudden attacks of involuntary behavior or sensory experiences. Life time risk of seizure in an individual is about 10%.

Treatment of epilepsy includes antiepileptic drugs. The selection of the drug depends upon the type of seizures. The doses gradually increased until seizures are controlled or when the patient develops side effects. If seizures continue despite of maximum tolerated dose of medicine a second drug is added. Its Doses are increased depending on the requirement and tolerance.

Botulinum toxin causes paralysis by inhibiting acetylcholine release at the neuromuscular junction. This is accomplished in three steps. First, the toxin binds the nerve. Second, the toxin

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is internalized into the nerve. Third, the toxin is cleaved by internal proteolytic enzymes, and the degradation by-products interfere with the normal process of vesicle fusion to the plasma membrane. This results in the inhibition of the exocytosis of acetylcholine. Due to chemo denervation of neurons, absence of skeletal muscle activity or autonomic control of target organs such as sweats glands occur. Botulinum neurotoxin A and E targets SNAP -25, which is a competent specific to excitatory synapsis and can inhibit generation of seizures.

Botulinum toxin has not been used to prevent seizures in routine practice. Literature search revealed that there was no evidence of increased risk of seizures in Juvenile cerebral palsy in children receiving Botox therapy [1]. There was a study in which botulinum neurotoxicity A2 reduced the incidence of seizures in mouse models of temporal lobe epilepsy. In this study Botulinum toxin A was chosen as it was more stable and had long term activity. The repeated injections of Botulinum toxin A2 into the hippocampal region of mouse brain reduced grand mal seizures in half population of mice [2]. Researchers concluded that Botulinum neurotoxicity A2 prevented epileptic seizures and can be studied as a new antiepileptic agent. In another study involving rat animal models, injection of botulinum neurotoxin E into the hippocampus reduced neuronal cell death in the brain. They observed that botulinum neurotoxin E prevented the up regulation of the apoptotic proteins which are seen in the hippocampal neurons following induction of the seizures with kainic acid [3]. In a similar study on mouse model, status epilepticus was induced by injection of kainic acid in the hippocampal region. Injection of botulinum toxin E prolonged the duration of latent period but did not block the occurrence of spontaneous seizures [4]. This demonstrated that botulinum toxin in the administration before or after status epilepticus was found to be neuroprotective. In another rat model study Botulinum neurotoxin A and B were locally delivered to amygdala –kindled rats and was noted to have behavioral seizure measured reduction by a both toxin, and prolonged inhibition of brain excitability [5]. These studies indicate that botulinum neurotoxin infusion into the seizure focus of the brain had reduced seizures in mouse models. A case report on botulinum toxin use in two patients with ictal pain revealed reduction of pain from painful partial motor seizures [6].

In The two cases mentioned above patients were noted to have decreased frequency of seizures since there were started on Botulinum toxin injections and eventually remained seizure-free. Botulinum toxin has proven to be safe and effective treatment choice for several conditions. Many animal models studies confirmed reduction of seizures with administration of botulinum toxin.

These intriguing findings rises, many questions that need to be answered. Is there a therapeutic benefit of botulinum toxin in humans with seizures or was it an incidental finding? If there is a therapeutic benefit what will be the dose of botulinum toxin administered? How often it should be given? Can the Botulinum toxin be used alone or in adjunct to other antiepileptic drugs? Is there a role of infusion of botulinum toxin into the seizure focus in humans? Further studies needs to be conducted in humans regarding the application of botulinum toxin as a therapeutic agent or as an adjuvant therapeutic agent to the anti-epileptic drugs in patients with epilepsy to remove possibility of serendipity.

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