ONABOTULINUMTOXIN A EFFECT ON CUTANEOUS ALLODYNIA IN CHRONIC MIGRAINE

Introduction:
Migraine is one of the most prevalent diseases worldwide, yet is has a high rate of disability. Chronic migraine has a signficant impact on quality of life and disability, and is associated with increased depression, anxiety, insomnia and fatigue.[1] OnabotulinumtoxinA therapy is one of few available therapies for chronic migraine. Phase III Research Evaluating Migraine Prophylaxis Therapy (PREEMPT) 1 and PREEMPT 2 trials, two class I multicenter studies assessing efficacy of onabotulinumtoxinA in chronic migraine were published in 2010.[2] These trials demonstrated the efficiency and tolerability of OnabotulinumtoxinA in Chronic migraine. However, the mechanism by which OnabotulinumtoxinA reduces migraine days in chronic migraineurs is not fully understood. In addition to myorelaxant effects OnabotulinumtoxinA causes inhibition of excitatory neurotrasnmitter release from both motor and sensory neurons.[3] OnabotulinumtoxinA has also been shown to decrease interictal CGRP levels in chronic migraine patients [4], and may have an indirect effect on inhibition of peripheral and central sensitization in trigeminovascular neurons, thought to be associated with onabotulinumtoxinA effect in chonic migraine.[5]
Cutaneous allodynia (CA), a symptomatic presentation of central sensitization, is skin pain provoked by non noxious stimuli. Migraine patients often report symptoms of cutaneous allodynia, especially during migraine attack, but also interictally.[6] Burstein et al compared cutaneous pain thresholds in 44 patients with episodic migraine before and during migraine attacks, and showed decrease in pain thresholds acutely during attacks not only ipsilateral head but also contralateral head and both forearm.[7] Schwedt et al used similar techniques to compare pain thresholds in episodic migraine, chronic migraine and control subjects, confirming that both migraine groups patients were more sensitive to thermal stimuli compared to controls in interictal stage.[6]

Aims/Hypothesis: Our clinical experience suggests that chronic migraine patients with cutaneous allodynia may respond better to OnabotulinumtoxinA therapy than those without cutaneous allodynia. We aim to test the effect of 3-cycles of OnabotulinumtoxinA on interictal mechanical pain thresholds and allodynia symptom severity in chronic migraineurs. We hypothesize that OnabotulinumtoxinA "responders" will show reduced allodynia symptom severity and increased mechanical pain thresholds (reduced sensitivity to cutaneous mechanical stimulation as pain), compared to baseline pre-OnabotulinumtoxinA therapy assessments. We expect that OnabotulinumtoxinA "non-responders" will not have significant change in allodynia symptoms or pain thresholds. We also expect that "non-responders" may have lower baseline allodynia symptom severity compared to "responders."

Methods: All procedures are approved by the University of Utah IRB.

Subjects: We will enroll 30 patients ages 18-80 years, seen in the University of Utah headache clinics with an ICHD-3-beta diagnosis of chronic migraine and scheduled for OnabotulinumtoxinA therapy based on their physician's assessment. Exclusion criteria included any skin lesion or scar around the area determined for sensory assessment.
Clinical Assessment/Questionnaires: Migraine Disability Assessment (MIDAS)[8], Headache Impact Test (HIT-6)[9], Allodynia Assessment(ref), PHQ-9[10], GAD-7[11] will be assessed before the first OnabotulinumtoxinA treatment cycle, and again after the third OnabotulinumtoxinA treatment.
Sensory assessment: Cutaneous mechanical pain thresholds will be assessed using von Frey hairs (VHF) (20 calibrated filaments; Bioseb) according to previously published methods(cit ref for Burstein); testing will occur before the first OnabotulinumtoxinA treatment and again 4-6 weeks after the third OnabotulinumtoxinA treatment.

Power Analysis: Based on preliminary data, to detect variation on the order of 1⁄2 of a standard deviation for mechanical thresholds using a conservative effect size of 0.5 and alpha of 0.05, 19 subjects would be required to allow for power > 0.80.

Analysis: Based on our experience with sensory threshold testing data distributions, nonparametric tests are planned, though we will be alert to the possibility of normally distributed data and will substitute parametric tests as appropriate. Wilcoxon matched pairs signed-rank sum test for comparing across paired results, Kruskal-Wallis one-way ANOVA for comparing multiple groups, and the Mann-Whitney test will be used for comparing two groups. Values of $p<0.05$ will be considered statistically significant, except where correction for multiple comparisons is needed, where Bonferroni correction will be utilized.

Results: Thuso far, we have enrolled and completed baseline testing on about 15 subjects, with pending follow-up evaluations. We plan to have preliminary data collected and analyzed the time AHS meeting in Boston.

Discussion: OnabotulinumtoxinA therapy is a very effective and highly tolerated therapy for chronic migraine. However, the mechanism of action in chronic migraine remains poorly understood. Cutaneous allodynia isa common clinical presentation of chronic migraine ictally and interictally, which may predict therapy responsiveness. The improvement on cutanous allodynia with OnabotulinumtoxinA therapy would supports an effect on central senstization. By the end of third cycle we will compare the demographic, clinical and allodynia response differences of the patients which will give us more information regarding patient selection for onabotulinumtoxinA therapy.

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