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Chronic Migraine: Role of CGRP antagonists and Botox

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Abstract.

Chronic migraine (CM) is characterized by the International Headache Society classification (ICHD-3) as headache that occurs for greater than or equal to 15 days a month, lasting 4 or more hours. For chronic migraine patients, the goal with prophylactic treatment is to prevent future attacks and reduce the migraine frequency and severity. OnabotulinumtoxinA is the most universally accepted medication for the treatment of chronic migraine; and if successful, reduces migraine frequency up to 50%. The goal of CGRP (Calcitonin-gene-related peptide) antagonists is to reduce the frequency of chronic migraines by targeting the CGRP protein that is elevated during a migraine attack. The aim of this study is to further explore the effectiveness of combining CGRP antagonists and Botox for the treatment of chronic migraine. We will analyze data to confirm or deny that migraine frequency is further reduced with the use of both medications.

Key Words: Chronic migraine, medication, CGRP, CGRP-antagonists, OnabotulinumtoxinA, wear off

Introduction.

Chronic migraine (CM) is characterized by the International Headache Society Classification (ICHD-3) as headache that occurs for greater than or equal to 15 days a month, for greater than 3 months, lasting 4 hours or more (Agostoni et al.,2019). The neurologic condition is genetically linked and can be highly disabling. Chronic migraine is the most common type of daily headache seen by specialists in an outpatient setting. Patients that suffer from CM, typically also suffer from other psychiatric and medical conditions. Due to this comorbidity, it is at times difficult to diagnose. CM is less common that other types of migraine variants, but it is associated with greater disability, interference with everyday activities (i.e. work and school) and impacts quality of life. For chronic migraine patients, the goal with prophylactic treatment is to prevent future attacks and reducing the migraine frequency and severity. However, there are fewer approved therapies than there are for episodic migraine (Aurora et al.,2014)

There are multiple orally administered medications that can be used in the treatment of CM. These medications include, beta-blockers (propranolol, nadolol, timolol), anticonvulsants (topamax, valproate), tricyclic antidepressants (amitriptyline, nortriptyline), antihypertensives (candesartan), and calcium channel-blockers (flunarizine). Typically, these medications are used when migraine frequency has increased, and patients have failed acute rescue treatment such as triptans (sumatriptan, rizatriptan, naratriptan etc.) and other over the counter medications. The main objective of prophylactic medications should be to reestablish the ability to function and improve the quality of life of those with CM

Migraine Therapies.

Botox (onabotulinumtoxinA) is considered when patients have failed multiple other prophylactic preventatives and headache frequency and severity are high. The prophylactic

effects were initially observed by a plastic surgeon who treated patients cosmetically for wrinkles, and an open-label study involving 106 patients with headaches was conducted (Binder et al.,2000) which showed that there was a positive benefit. OnabotulinumtoxinA is one of the only prophylactic medications universally used in the treatment of chronic migraine. Botulinum toxin is a natural product synthesized by an anaerobic bacterium called *Clostridium botulinum.* The primary action is to block the pre-synaptic release of acetylcholine at the neuromuscular junction, which results in temporary paralysis of the muscles. The secondary action involves the inhibition of a range of neurotransmitters and inflammatory cells. For significant benefit, onabotulinumtoxinA is injected every 3 months or 12 weeks. The recommended reconstituted dose is between 155 to 195 units per visit. Botox is typically injected to at least 31 injection sites across various muscles in the head, face and neck.

CGRP (calcitonin gene-related peptide) is a protein that acts like a neurotransmitter. It is present on the trigeminal ganglia nerve in the brain. CGRP antagonists are the first migraine-specific preventive medication group developed. The first of which was approved by the FDA in May 2018.The three main medications currently on the market are Aimovig (erenumab-aooe), Emgality (galcanezumab-gnlm) and Ajovy (fremanezumab-vfrm). These new medications have less side effects - for example, they do not cause vasoconstriction, which is a major limitation in the use of triptans (Edvinsson, 2017). They directly treat part of the underlying mechanism of migraines. They aim to reduce the frequency and severity of episodic and chronic migraine. Although new to the market, CGRP antagonists' have shown promising results in the treatment of CM and EM (episodic migraine) as well. Research has shown that the levels of CGRP circulating in the body are elevated in patients with chronic migraine. Anti-CGRP medications target the molecules and are associated with lowering the circulating CGRP levels during a

migraine attack (Agostini et al.,2019). The antagonists block the inflammatory molecule CGRP, and keep it from escalating even further, therefore, reducing the chances of future migraine attacks.

Literature Review

Melo-Carrillo (2019) looked to explore the effects of Botox injections on the activation of meningeal nociceptors by cortical spreading depression (CSD). CSD is associated with significant failure of brain ion homeostasis, efflux of excitatory amino acids from nerve cells, increased energy metabolism and changes in cerebral blood flow (Lauritzen, 2011). This paper was interesting because it looked at the different mechanisms of onabotulinumtoxinA and CGRP antagonists and which fibers each one targets. The authors understood that a migraine begins with the activation of the nociceptors that supply the meninges. Medications that prevent the activation of the nociceptors will be effective in reducing migraine frequency. They examined myelinated C- and unmyelinated A&-meningeal nociceptors' responses in female rats. Melo-Carrillo (2019), was the first study to find out if the activation of meningeal nociceptor by a stimulus that originates in the CSD rather than the outside of the BBB can be attenuated by extracranial injections of onabotulinumtoxinA. The study concluded that there is a possibility that the mechanism of Botox in preventing headache involves mild but lengthy reduction in the firing of the unmyelinated C- fibers but suggested that more research be done on the thinly myelinated A&- fibers. They also found that the mechanism of action of Botox differs from that of a CGRP antagonist. This is interesting as it informed the current research, that CGRP antagonists and Botox can be beneficial in treating chronic migraine. In their clinical study, Zhang et al (2016) showed that when Botox is injected directing to the dura, it can inhibit naïve C-fiber meningeal nociceptor responses to mechanical nociception, reverse and prevent their

sensitization by inflammatory mediators. There is evidence that onabotulinumtoxinA can reduce the frequency of migraine into the range seen with episodic migraines (Aurora, 2010). Further treatment with CGRP antagonists could reduce the frequency of migraines. Both treatment options can be used together as they have different mechanisms and ultimately provide relief for the patient.

Edvinsson and Goadsby (1990) looked for CGRP in patients during a migraine attack, taking blood samples from the jugular vein- near the point of release in the brain- instead of the arm. The study confirmed the notion that CGRP is released in significant amounts in the body during a migraine attack and was the only neuropeptide released during the headache phase. In his research study, Edvinsson (2017) looked at the history of the trigeminal pathway, the role of CGRP in migraine attacks and the messenger molecules involved. This was interesting because it is well known that CGRP plays a role in a number of intracranial brain regions associated with chronic migraine. Edvinsson did however, believe that these regions are not the direct targets of effective CGRP treatment. He postulated that the targets of CGRP are located outside the brain blood barrier. These regions include intracranial and extracranial, dural mast cells, blood vessels and other peripheral parts of the trigeminal pathway. The trigeminal ganglion plays a major role in primary headache pathophysiology. Multiple studies have found that there are CGRP containing nerve fibers within the trigeminal ganglion. Migraines involve the activation of the trigeminal system and dilatation of cranial vessels. It is hypothesized that trigeminal-targeted preventative treatments counteract the impingement of nociceptive input from highly sensitized trigeminal neurons on brain stem second order neurons, thus preventing central sensitization, a key pathophysiological mechanism of chronic migraine (Agostoni, 2019).

Researchers have hypothesized that recurring migraine episodes and comorbid conditions, such as medication overuse or anxiety/depression, may lead to dysfunction of pain modulation pathways. This then causes reduced nociceptive thresholds and atypical release of nociceptive molecules (Aurora, 1990). Proper brain function requires that all the chemicals are at optimal levels, and all nerve pathways are faultless. In the event any of these things are interrupted, migraine may occur. Imaging studies have shown activation of regions that contain numerous neurons and nerve fibers, multiple neurotransmitters that are connected to synapses and receptors. Due to the complexity of this pathway, it is important that it is fully understood. Multiple methods of combating the CGRP receptors that are released at a migraine attack could prove beneficial.

According to a study performed by Masters-Israilov and Robbins (2019), a majority of the chronic migraine patients who received onabotulinumtoxinA experienced the phenomenon of *wear off.* This phenomenon is documented by those who experience it approximately 2-4 weeks before their next scheduled treatment. The study included 143 patients who have chronic migraine and were treated with onabotulinumtoxinA. Their results showed that 62.9% of the sample documented wear off (n=90) The researchers indicated that almost two-thirds of the CM population who receive onabotulinumtoxinA will experience wear off. These conclusions suggest that clinicians should increase the number of units administered to hinder the phenomenon from ocurring. Zidan et al, (2019) found that CM patients have reported a period of increased headache frequency and severity before their next treatment. Their research study found that the response to onabotulinumtoxinA is not uniform and that the current regimen of treatment-12 weeks- allows for a period of vulnerability during which migraines attacks can occur. The results indicated that most of the participants experienced the start of *wear off* at week

8 of their cycle. According to the researchers, the period of vulnerability can be at the start and end of a treatment cycle. The presence of wear off can be identified if there is a quantitative increase in the use of abortive medications/therapies or emergency room visits to treat the migraines. Bridge therapies such as nerve blocks, intravenous injections, intramuscular ketorolac injections (Masters-Israilov & Robbines, 2019) have been used to alleviate migraine attacks. CGRP antagonists should also be considered by clinicians as one of the possible bridge therapy options as it directly treats part of the underlying mechanism of migraines. It will also prove beneficial due to the fact that CGRP antagonists are administered once a month (30 days), therefore it will put the wear off phenomenon at bay until the next treatment with onabotulinumtoxinA.

The aim of this study is to further explore the effectiveness of the combination of CGRP antagonists and onabotulinumtoxinA for the treatment of chronic migraine. This study will analyze data to confirm or deny that migraine frequency and severity are further reduced with the use of a CGRP antagonist medication. Each medication has different mechanisms that target or act on different receptors within the brain. Concurrent treatment can prove beneficial and further clinical studies should be conducted to further investigate the use of the medications for the treatment of chronic migraine.

Method.

This study looked at 24 respondents to a survey sent out to a convenience sample of chronic migraine patients attending a headache program. The survey was sent out by the office of the Medical Director of the Headache Program. The survey was distributed for 4-6 weeks. Using descriptive analysis and visualizations, we used the responses/data collected to investigate, and answer if the addition of a CGRP antagonist provided further reduction of migraine frequency.

Results.

After six weeks of data collection, 24 surveys were completed and returned. The surveys were handed out to patients in a Headache Program after their individual Botox procedures. Patients were informed that the surveys were anonymous. The survey had 8 questions that we estimated would take 2- 4 minutes to complete.

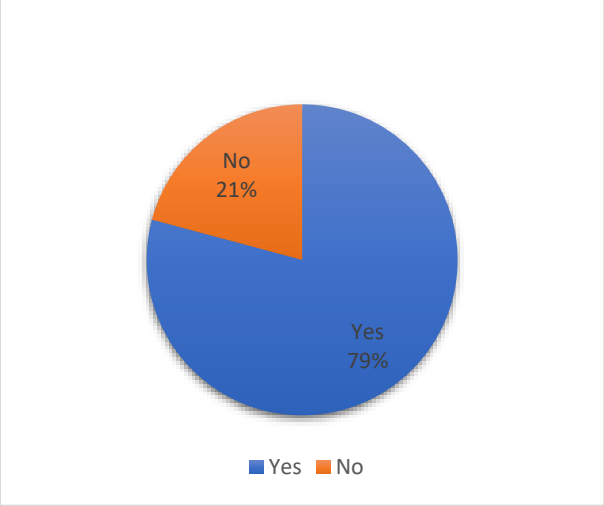

Figure 1.

The p-value of 0.004, ($p < 0.5$) indicates that there is strong evidence against the null hypothesis and therefore is statistically significant.

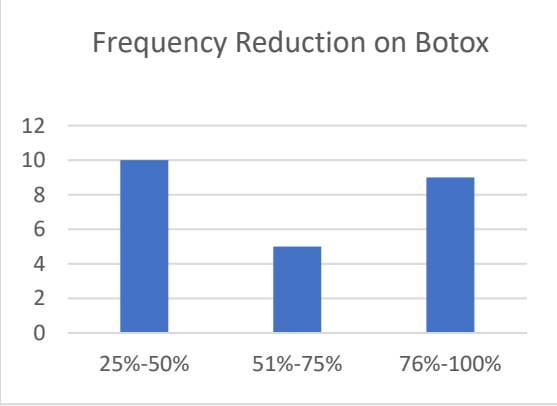

Figure 2.

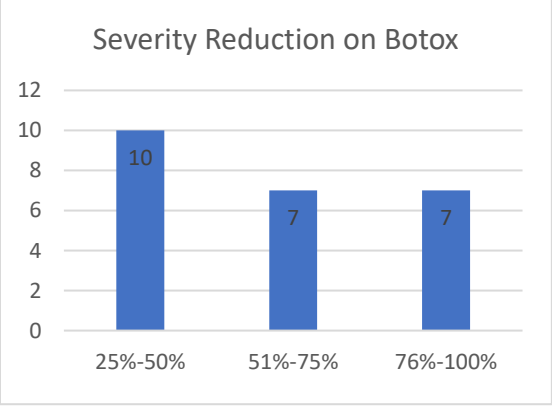

Figure 3.

The images above show that the majority of the sample population have reduction in frequency and severity in varying percentages on Botox (OnabotulinumtoxinA).

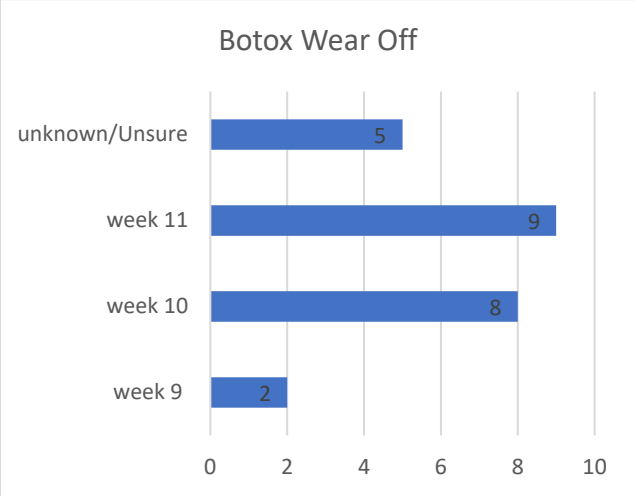

Figure 4

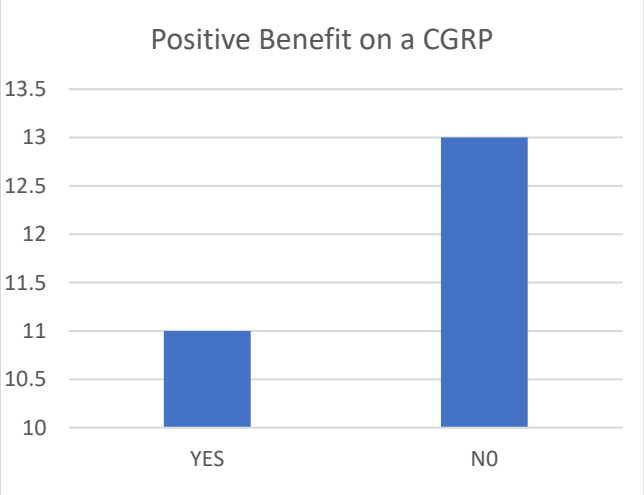

Figure 5.

The p-value of 0.683 (p >0.5) indicated that there is statistical significance and thus failing to reject the null hypothesis. Of the 24 responses, n=11 did experience positive benefit and n=13 did not.

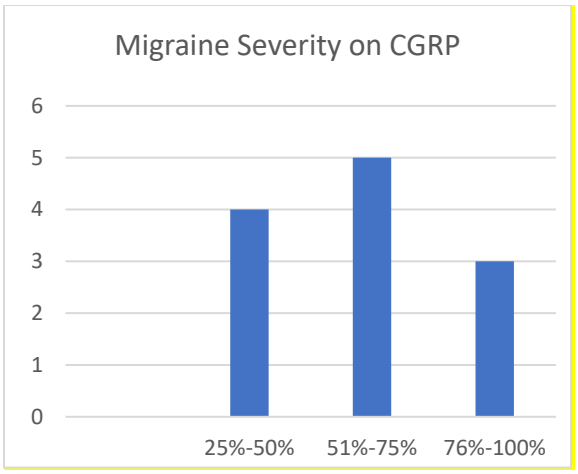

Figure 6.

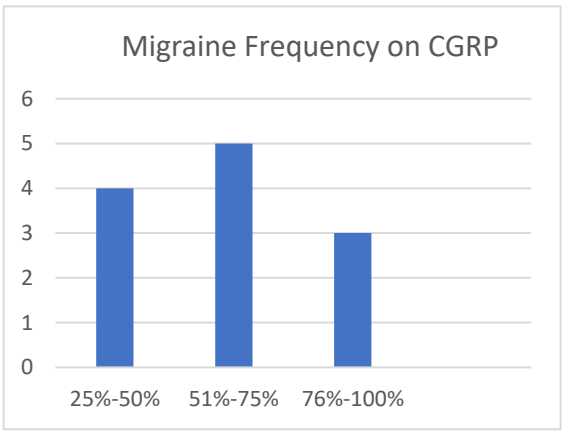

Figure 7.

The images above illustrate the percentage of the further reduction of migraine frequency and severity on CGRP antagonists.

Discussion.

For several years, there have been very few migraine specific medications on the market, leaving patients with limited treatment options for chronic migraine. CGRP antagonists recently joined onabotulinumtoxinA as an FDA approved treatment for CM. The goal for chronic migraine patients being treated with onabotulinumtoxinA and CGRP antagonists, is to bring down the migraine frequency and severity to a level that has them characterized as episodic migraine (4-14 days a month).

The results were as expected regarding the question of onabotulinumtoxinA *wear off*. CM patients do experience the wear off phenomenon and therefore will need bridge therapy of some kind. Of my sample population, 79% experienced the phenomenon (Figure 1). There was a total of 19 respondents who did experience *wear off* and a total of 5 who did not. This corroborates the research done by Masters-Israilov & Robbins (2019) and Zidan et al. (2019). This study was also interested in documenting where in the treatment cycle *wear off* typically occurred. Treatment with onabotulinumtoxinA is not uniform and the current approved regimen

of every 12 weeks, leaves room for a period of vulnerability for those prone to *wear off*. The results indicated that patients in our sample population experienced *wear off* either within the tenth week or the eleventh week. Therefore, patients are vulnerable to rebound migraines 1-2 weeks before their next treatment. For CM sufferers, this is a large gap and going without relief would proof detrimental to the patient's health. During this time, bridge therapies such over the counter medications, and prophylactic medications-such as beta blockers, antihypertensives, anticonvulsants, antidepressant, etc.- are used to minimize the migraine attacks. CGRP antagonists taken monthly would be an effective addition to reduce the amount of rebound migraines that could occur during the *wear off* period or possibly completely eliminate the period.

The data showed that 11 respondents (Figure 5) experienced a positive response on a CGRP antagonist, while 12 respondents either had not started or did not experience a positive benefit. This was a surprising result as this research study's hypothesis was to show that the combination of an anti-CGRP medication and onabotulinumtoxinA would further reduce migraine frequency and severity. The p value was 0.683, indicating that there was no statistical significance to the study. The observed values did not differ significantly from the expected values. Therefore, for this question, the null hypothesis was accepted. We concluded that majority patients on CGRP antagonists within the sample population, did not experience positive benefit. We were unable to demonstrate that the addition of CGRP-antagonists to current onabotulinumtoxinA patients would be significantly beneficial to their treatment.

Among the patients that did experience positive benefit on a CGRP-antagonist, we looked to see if there was additional benefit in migraine frequency and severity reduction. For successful treatment of CM, patients should have greater or equal to 50% reduction in migraine

frequency - on average would be 8-9 migraine days - or at least 100 hours reduction in severity. Our results corroborated this statement as shown in figures 2 and 3. For those chronic migraine patients, onabotulinumtoxinA is an effective treatment option and many would agree that continuation is medically necessary. For successful treatment on a CGRP antagonist, chronic migraine patients should also have their migraine days decreased by 50%. The results indicated that majority of the sample population experienced over 50% additional reduction in migraine frequency and severity (Figures 6 &7). The study believed CGRP antagonists, could offer considerable improvements over existing drugs as they were specifically designed to act on the trigeminal ganglion, which plays a major role in primary headache pathophysiology.

Conclusion.

Though this study was not able prove its hypothesis, we encourage further research on the topic. I would recommend that researchers collect data on patients who experience a positive benefit on onabotulinumtoxinA at the baseline but need additional reduction in total migraine days. An additional recommendation is that a larger population of chronic migraine patients who are on both onabotulinumtoxinA and a CGRP antagonist be recruited. This current study was able to show that there was some benefit with the addition of the CGRP antagonist to the treatment regimen. Future research should collect data multiple time to investigate if there is consistent significant improvement in patients. Through various studies discussed within this paper, there is proof that the two medications target different fibers in the brain and have differing mechanisms and, therefore can be used concurrently. It would be beneficial to clinicians that come up with multiple methods of combating the CGRP receptors that are released at a migraine attack.

Additional research into the use of both onabotulinumtoxinA and CGRP antagonists is needed to show the efficacy and the medical necessity in treating chronic migraine. Further research is necessary to determine that CGRP antagonists are the answer to overcoming the wear off phenomenon that occurs towards the end of a standard 12-week cycle of onabotulinumtoxinA injections. This research may help elucidate the mechanism of the action of both CGRP antagonists and onabotulinumtoxinA; and possibly implement methods that allow more consistent response for chronic migraine sufferers.

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Appendix

Survey Questions

1. How long have you been treated for chronic migraine?
    a. 0-5 years
    b. 6-10 years
    c. 11-15years
    d. 16 or more years
2. Do you experience Botox *wear off*?
    a. Yes
    b. No
3. If yes, when in treatment cycle do you usually experience *wear off*?
    a. Week 9
    b. Week 10
    c. Week 11
    d. Unknown/Unsure
4. What percentage would you say your migraine *frequency* decreased on Botox **alone**?
    a. 25% -50%
    b. 51% -75%
    c. 76% -100%
5. What percentage would you say your migraine *severity* decreased on Botox **alone**?
    a. 25% -50%
    b. 51% -75%
    c. 76% -100%

6. Do you experience positive benefit on a CGRP medication? (Aimovig, Emgality or Ajovy)

   a. Yes

   b. No

7. What percentage would you say your *frequency* ***further*** decreased with the addition of a CGRP?

   a. 25%-50%

   b. 51%-75%

   c. 76%-100%

8. What percentage would you say your *severity* is ***further*** decreased with the addition of a CGRP?

   a. 25%-50%

   b. 51%-75%

   c. 76%-100%