A New Treatment for Refractory Chronic Daily Headache

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Patients who experience headaches on a daily or almost daily basis and who have been unresponsive to the wide range of commonly prescribed headache treatments are said to suffer from Refractory Chronic Daily Headaches (CDH).

Common treatments today include the use of two or more "preventive medications" such as anti-seizure and anti-hypertensive medication, daily or near daily triptan medications (which increase serotonin release and block the release of neuropeptides in the trigeminal nerve), long-acting opioids, botulin toxin injections and nerve blocks (Robbins, 2014).

It is widely believed that chronic daily headaches originate in the brainstem through an interaction with the trigeminal nerve, the major pain pathway to the head and scalp (Mayo Clinic). In this paper we propose a previously undescribed pathophysiologic mechanism for CDH. Our hypothesis is that many patients who experience CDHs suffer from a form of visually induced trigeminal dysphoria and that the primary source of this dysphoria is untreated ocular misalignment.

We will discuss a treatment that utilizes spectacles with contoured prismatic correction and review data from a prospective pilot study that demonstrates the efficacy of this treatment in a subset of patients with CDH.

METHODS

This study was conducted from September of 2012 to June of 2013 through the joint efforts of Neurology Associates, LLC and the offices of Dr. Jeff Krall in Sioux Falls, South Dakota.

Candidates for this study were a highly selected group of individuals who suffered from refractory CDH. Interviews were conducted prior to testing. Individuals who gave a history of long-standing daily or almost daily headaches and who were resistant to other traditional therapeutic modalities underwent testing using a new proprietary testing device, called the neurolens® Measurement Device.

A BRIEF DESCRIPTION OF THE *NEUROLENS MEASUREMENT DEVICE*:

The neurolens Measurement Device is a novel device, designed to measure binocular misalignment of the peripheral and central visual tracking systems. With this device, coordination of central binocular vision is tested first and measured without peripheral stimulation. Two independent central dots viewed at optical infinity are introduced on the measurement device viewing screen while the eyes are alternatingly occluded. If there is no imbalance of central fusion, the dot appears stationary during alternating ocular occlusion. If there is an imbalance of central fusion (a phoria), the central dot seems to dance as each eye moves to fix on the central dot following alternating occlusion. The neurolens Measurement Device tracks the movement of each eye and automatically relocates the targets until no perceived movement of the central target or eye movement is detected. Horizontal misalignment of central fusional balance is then measured in pixels. Once neutralization is accomplished, the central dot is seen as stationary during alternating occlusion.

With the central dot visible and aligned with central fusion, several very compelling peripheral targets are then introduced independently to both the right and left eyes. These independent targets stimulate cortical fusion of one's peripheral field of vision due to their size and movement while allowing central vision to remain monocular. Any change in binocular alignment of the central vision is in response to fusion from peripheral binocular stimulation. If there is no disparity between the alignment of central vision and the peripheral alignment of the fused binocular images, the central dot remains stationary. If there is disparity between central fusion and the alignment of the peripheral tracking system, the dot begins to dance and vibrate. This imbalance is then tracked and the neurolens Measurement Device automatically relocates the central target to align with the center of peripheral fusion. The deviation is measured in pixels on the monitor. This procedure is then repeated to measure the central and peripheral alignment of objects viewed at near.

Measurements taken from the neurolens Measurement Device device were then used to guide the manufacture of glasses with contoured prisms, designed to correct the measured imbalance. Patients found to have an imbalance based on evaluation with this instrument were entered into the study and were given spectacles with the calculated contoured prismatic correction. A unique proprietary manufacturing technique allows the power of the contoured prismatic correction to vary from distance to near vision.

The primary measure of efficacy in this study was the validated Headache Impact Test (HIT6) score (Yang, 2011). This questionnaire, which quantitates severity of headache symptoms, was performed before and after treatment. In addition, demographic information, including age, gender and duration of follow-up at the time of the post treatment testing, was collected.

RESULTS

DATA ANALYSIS OVERVIEW

186 patients with severe headaches for which other treatments were ineffective were enrolled in this study. Patients received neurolens spectacles with contoured prismatic correction, based on measurements from the neurolens Measurement Device, for treatment of headache symptoms.

Of the 186 patients, 7 were lost to follow-up. Of 179 patients with follow-up data, the estimated mean decrease in HIT6 score was 7.64 units, with a 95% confidence interval of (6.46, 8.82). The two-sided p-value against the hypothesis of no-effect was highly statistically significant with a P-value < 0.0001. Multivariate regression models indicated an association of change in HIT6 score with initial HIT6 score. Self reported efficacy indicated that 146 of the 179 patients (81.6%) had a positive response to the treatment. In addition 69.66% of patients stated that they had reduced headache medications since wearing neurolens spectacles.

CHARACTERIZATION OF STUDY POPULATION

PATIENTS WITH FOLLOW-UP (N=179)

The average age of the study cohort was 39.7, where the youngest participant was 14 and the oldest 74. The study cohort was primarily female (n=144, 81.6%). 84.4% of the study cohort had an initial HIT6 score of 60 or higher, with a mean HIT6 score of 64.7 (SD 5.8). The mean days to follow-up were 88.2 (SD 91.4) and the median was 51. The minimum days to follow-up was 12, and the maximum was 411.

PATIENTS LOST TO FOLLOW-UP (N=7)

The average age of the cohort lost to follow-up was 37.9, where the age ranged from 20 to 50. 6 of the 7 patients were female (85.7%) and 6 of the 7 patients (85.7%) had an initial HIT6 score of 60 or higher, with a mean HIT6 score of 66.0 (SD 9.2). Overall, the patients lost to follow-up were very similar to the study cohort, indicating that there was likely no substantial bias introduced through loss of follow-up.

REVIEW OF RESULTS

The following tables and plots demonstrate several facets of the data.

Figure 1 demonstrates patients' responses to the basic question: "Headaches are _____ after wearing lenses". This question was asked before and after treatment.

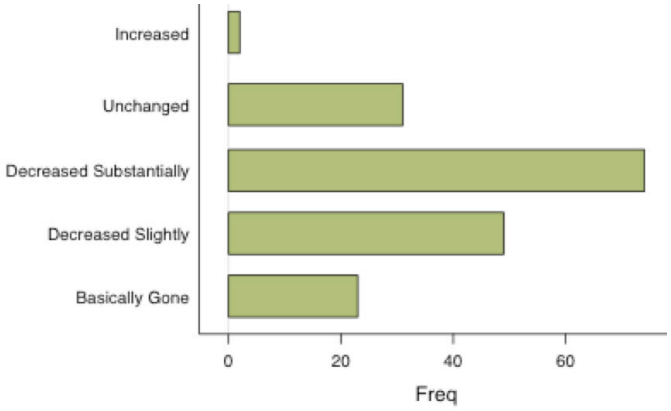

Figure 1: Relative Severity of Headaches Pre and Post-treatment

The results also are tabulated below:

Basically Gone	Decreased Substantially	Decreased Slightly	Unchanged	Increased
23 (12.8%)	74 (41.3%)	49 (27.4%)	31 (17.3%)	2 (1.1%)

Table 1. Relative Severity of Headaches Pre and Post-treatment

Of the 179 patients only 33 did not respond indicating a positive response rate to treatment. Positive responses regarding reduction of headaches were given in 81.6% of patients.

Figure 2 is a graphical depiction of the reallocation of patients to generally lower categories of symptoms following treatment.

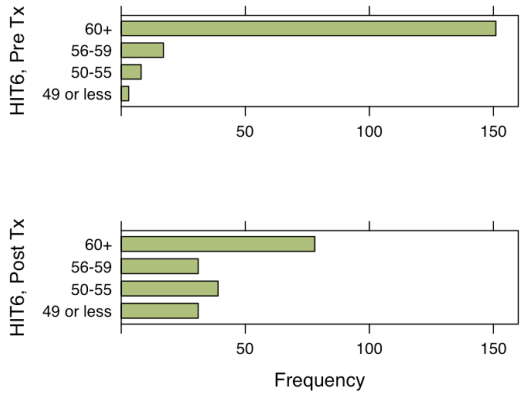

Figure 2: Reduction of Severity of Headaches Pre and Post Treatment

This is also illustrated in Tables 2-4 below, which quantify the reallocation of patients to lower HIT6 score categories.

49 or less	50-55	56-59	60+
3 (1.7)	8 (4.5)	17 (9.5)	151 (84.4)

Table 2. Initial HIT6

49 or less	50-55	56-59	60+
31 (17.3)	39 (21.8)	31 (17.3)	78 (43.6)

Table 3. Final HIT6

	49 or less	50-55	56-59	60+
49 or less	2 (66.7)	0 (0)	1 (33.3)	0 (0)
50-55	2 (25)	4 (50)	1 (12.5)	1 (12.5)
56-59	8 (47.1)	2 (11.8)	3 (17.6)	4 (23.5)
60+	19 (12.6)	33 (21.9)	26 (17.2)	73 (48.3)
Total	31 (17.3)	39 (21.8)	31 (17.3)	78 (43.6)

Table 4. Initial HIT6 (Row) vs. Final HIT6 (Col)

Figures 3 and 4 illustrate the relationship of change in HIT6 score as a function of the initial HIT6 score.

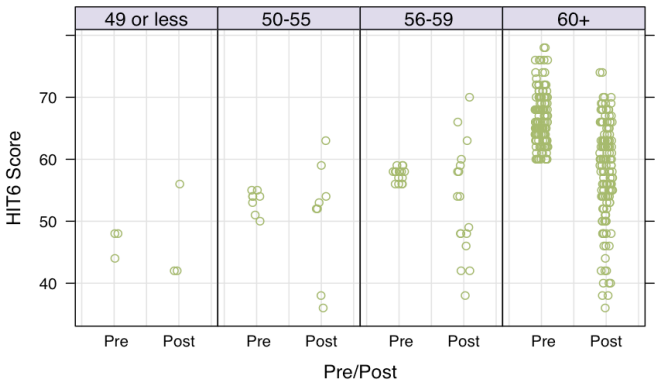

Figure 3: Change in HIT6 score as a function of the initial HIT6 score.

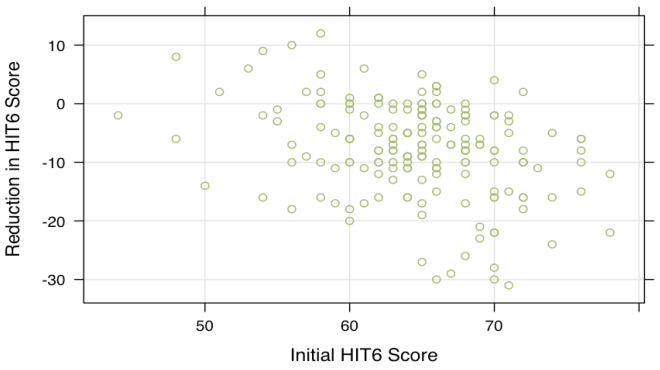

Figure 4: Scatter plot of HIT6 difference from pre to post treatment vs. Initial HIT6 Scores. These data indicate that the reduction is roughly linear with initial HIT6 score.

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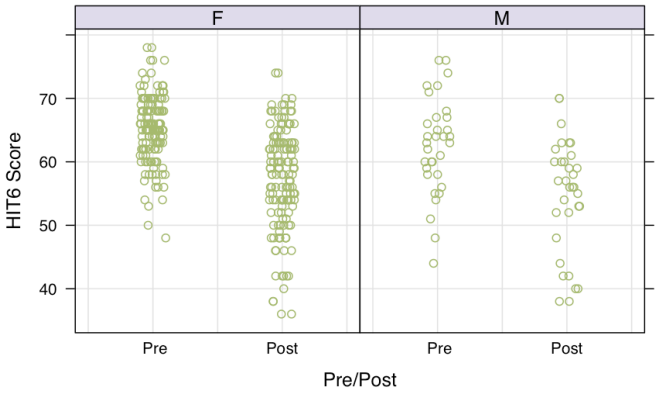

Figure 5: Pre and Post HIT6 scores separated by gender. These data suggest that the magnitude of change in HIT6 is similar between males and females.

Figure 5 indicates that the magnitude of change in HIT6 is similar between males and females.

The overall mean difference in HIT6 by Pre/Post treatment was 7.64 with a 95% confidence interval of (6.46, 8.82). The two-sided P-Value against a null hypothesis of no effect was <0.0001 (Note that since this is a population for which other treatments were ineffective, the null hypothesis of no effect is the appropriate null hypothesis to test).

A multivariable linear regression was performed to assess the following: relationship of change in HIT6 by Initial HIT6 (continuous), gender, age (categorized by quartile) and follow-up days (categorized by quartile).

Table 5 lists the ANOVA table describing the overall effect of these factors, with Age and Initial HIT6 score statistically significantly associated with change in HIT6. The significance of the age factor was driven largely by a smaller estimated difference in the 40-49 group. For initial HIT6 it was estimated that the HIT6 difference would be 4.92 units larger for an initial HIT6 score that was 10 units higher.

Factor	Df	Sum Sq	Mean Sq	F value	Pr(>F)
Initial HIT6	1	1266.976	1266.976	23.18856	< 0.001
Gender	1	49.73542	49.73542	0.910272	0.341397
Follow-up Days	3	151.9422	50.64741	0.926963	0.429049
Age	3	762.0053	254.0018	4.648813	0.00377
Residual	170	9288.458	54.63799	NA	NA

Table 5. ANOVA table for multivariable model

STUDY STRENGTHS AND LIMITATIONS

STRENGTHS

The strengths of the study include that it incorporated a large number of patients (n=186) with minimal loss to follow-up (n=7). Those that were lost to follow-up were demographically (and clinically, as measured by their HIT score) very similar. The study population contained patients for whom other treatments were ineffective, providing an opportunity to demonstrate efficacy in a challenging population. The composition of the study population (age, gender, initial HIT6 score) was comparable to existing studies helping to facilitate cross-study comparisons.

LIMITATIONS

The study was a one-arm study, so a direct comparison to existing treatments was not possible to control for potential experimental confounders or concurrent coincidental effects. The study was somewhat observational in nature, whereby facets such as strict inclusion criteria or fixed follow-up times was not employed.

SUMMARY OF DATA ANALYSIS

The study demonstrated a mean reduction in HIT6 scores of 7.64 that was highly statistically significant ($p < 0.0001$) and had a narrow 95% confidence interval (6.64, 8.82). These results are highly suggestive that the treatment is efficacious in a population for whom other conventional headache treatments were ineffective, a fact that is further substantiated by the high treatment response rate of 81.6% (146 of 179). The data further show that patients who suffered from the most severe headache symptoms reported the greatest benefit in terms of symptom relief.

DISCUSSION:

This paper describes a pilot study conducted to evaluate a new treatment for patients with Refractory Chronic Daily Headaches (CDH). Treatment involves the use of spectacles with a contoured prism correction. The basis of the treatment is the hypothesis that one pathophysiologic mechanism for CDH may be chronic irritation of the trigeminal nerve caused, not only by uncorrected heterophorias and deficiencies of accommodative convergence, but also by imbalances of the peripheral and central visual tracking systems. In order to understand the science that serves as the foundation for this hypothesis, it is useful to review what is known about the relationship between peripheral and central visual processing, saccadic and smooth pursuit eye movements, peripheral and central visual tracking, trigeminal nerve mediated extraocular muscle proprioception and CDH.

OVERVIEW PERIPHERAL AND CENTRAL VISION

The evolution of the visual system of vertebrates represents a delicate balance between the biologic advantages of self-preservation and food acquisition. Creatures that graze, but are preyed upon by more aggressive species, have eyes on the sides of the head to provide a panoramic view of their surrounding. Human beings, living as hunters and gathers, evolved a visual system with eyes forward that optimize binocularity, visual tracking and acuity (Duke-Elder, 2013). The integrative "software" of the human brain gives one the illusion that vision is clear in all fields of gaze. This, however, is an illusion. Unlike a digital photographic image that provides a uniformity of detail and clarity because of a uniformity of pixel distribution, human vision is constructed of two concentric circles with higher levels of clarity existing only in the center of gaze. This central clarity reflects the high density of photoreceptors clustered in the fovea. The peripheral circle of vision is less clear because of the rapid drop off of photoreceptor density in the peripheral retina.

When one looks at one's hand at arm's length, the size of the thumbnail is roughly the size of our foveal image (Godlove, 2013). Clarity of the vision drops off precipitously outside this small central circle. Roughly one degree away from the area of central vision, visual acuity is reduced by 50% (Green, 1970). It has been demonstrated, moreover, that less than one ten-thousandth of the total visual field can be processed with foveal clarity by the brain at one time (Carpenter, 1988).

In order to allow functional vision in a world of constant motion, the eye must move constantly with the peripheral circle of vision serving as a primary tracking and homing device. Peripheral tracking brings objects of regard close enough to the center of vision for the central tracking system to capture the image and provide enhanced clarity (Duke-Elder).

UNDERSTANDING THE RELATIONSHIP BETWEEN PERIPHERAL AND CENTRAL VISUAL PROCESSING SYSTEMS

The peripheral vision develops before central vision in human infants. At birth, myelinated fibers form rod cells of the peripheral retina course along the peripheral aspects of the optic nerve. These fibers link to the visual cortex as well as the mid-brain and thalamus. Central fibers originate from the macula, mostly from cone cells, and are not myelinated at birth. This absence of myelination accounts in part for the observation that infants lack clarity of vision in early life. The macula fibers course along the central aspect of the optic nerve and link to central areas of the visual cortex (Padula, Munitz, Magrun, 2012).

Unlike central vision, peripheral visual processing is largely a preconscious activity (Schneider, 1967). Lower vertebrates such as amphibians and reptiles have visual systems that are primarily peripheral in nature and respond almost solely to movement. Often sited research studies have demonstrated that a frog placed in a box with stationary dead flies will starve; whereas the same frog presented with a dead fly placed on a moving string will instantly detect and consume the fly (Lettyin, 1959). The complex coordination of preconscious peripheral visual processing and more conscious and object-oriented central vision is a hallmark of the more highly evolved visual systems of primates. Preconscious awareness of movement elicits almost instantaneous redirection of the eyes and localization of the object of regard. As Padula has stated, the coordination of the two visual systems "becomes the grounding or background relationship for the higher visual processes of perception and cognitive function. Without the ambient (i.e. peripheral) visual process, the visual world would become fragmented and isolated in detail" (2012, p.7). Aside from detection of movement of objects, the peripheral system links to the mid-brain to provide a sensorimotor feed back loop to many areas of higher cortical functions (Nelson, 2007). Coordination with the mid-brain provides for stabilization of visual images not only during the movement of the objects but also with movement of the head (Padula, 2012).

The more primitive, preconscious peripheral visual system helps us to detect danger, coordinate motor function, and understand our position in three-dimensional space. It is also fundamental to our ability to track moving objects and direct our central vision to objects of interest or concern. The central system helps us to bring attention and concentration to specific objects and provides us with the ability to derive additional information relating to the details and patterns of objects.

SACCADIC AND SMOOTH PURSUIT EYE MOVEMENTS AND THEIR RELATIONSHIP TO PERIPHERAL AND CENTRAL VISUAL PROCESSING.

The visual system is constantly faced with two conflicting demands. The first is the need to move objects of interest from the peripheral retina to the central retina in order to bring images into sharper focus. The second is the need to hold objects still, so they can be better visualized (Godlove, 2013).

Image movement on the retina results in visual blur. As a visual image moves across the retinal surface, the time needed to convert light energy into a high quality neural impulse is reduced. Primates in general have been shown to be relatively slow in transducing light information at the retinal level (Carpenter).

Saccadic eye movements provide extremely quick readjustments of eye position. The primary function of saccadic movements is to shift objects of concern from peripheral retina to the area of central vision. Smooth pursuit eye movements then take over. The primary function of smooth pursuit movements is to stabilize images in order to provide greater clarity.

Smooth pursuit eye movements track more slowly and compensate for motion of the visualized object, thereby reducing blur (Krauzlis, 2004). Smooth pursuit movements, therefore, are more of a "gaze holding" than a "gaze moving "eye movement (Godlove).

The coordination and synchronization of the saccadic and smooth pursuit eye movements, therefore, would appear to be critical, if the eye is to provide both an effortless transfer of images from the peripheral to central vision, and the stabilization of images centrally.

TRIGEMINAL NERVE MEDIATED EXTRAOCULAR MUSCLE PROPRIOCEPTION

The existence of proprioceptive fibers exiting extraocular muscles and carrying information to the trigeminal nerve is well established (Ruskell, 1983; Atasaver, 1992; Weir, 2006). Retrograde tracer studies, using horseradish peroxidase, have demonstrated that afferent fibers from the oculomotor nerve course through the ophthalmic branch of the trigeminal nerve and enter the trigeminal ganglion (Atasever). Clinical observations, moreover, confirm the proprioceptive functions of the trigeminal nerve as it relates to extraocular eye movements (Weir). Patients who have undergone trigeminal nerve ablation either surgically or with thermo-coagulation as treatment for trigeminal neuralgia have been shown to exhibit difficulty with visually guided eye movements (Steinbach, 1986) Patients suffering from active herpes zoster ophthalmicus also have been reported to demonstrate problems with visual spatial localization (Campos, 1986).

PROPOSED RELATIONSHIP BETWEEN PERIPHERAL AND CENTRAL VISUAL TRACKING, TRIGEMINAL NERVE MEDIATED EXTRAOCULAR MUSCLE PROPRIOCEPTION AND TRIGEMINAL DYSPHORIA

It is widely believed that chronic daily headaches occur when activated trigeminal nerve fibers trigger a dilation of blood vessels located on or near the surface of the brain. Activation of the trigeminal nerve is believed to occur from a host of causative factors, including an alteration of sleep-wake cycle; missing or delaying a meal; medications that cause a swelling of the blood vessels; daily or near daily use of medications designed for relieving headache attacks; bright lights, sunlight, fluores-

cent lights, TV and movie viewing; certain foods; and excessive noise (NHF).

The authors of this study believe that a subset of chronic daily headache patients, particularly those who have proven to be unresponsive to traditional therapeutic modalities, suffer from imbalances of ocular motility including misalignment of the peripheral visual tracking, and central vision fixation. Our hypothesis is that this lack of coordination results in an over stimulation of the trigeminal nerve. The proprioceptive fibers of the extraocular muscles have afferent nerve branches to the trigeminal nerve. These proprioceptive fibers are activated by constant attempts to rectify an imbalance of alignment of binocular peripheral and central tracking. This activity is believed to cause an overstimulation of the trigeminal nerve, which over activates the trigeminal nucleus caudalis. The trigeminovascular system links the trigeminal nerve and the upper cervical region via the trigeminal nucleus caudalis, causing trigeminal dysphoria with pain referred to the head and neck.

CONCLUSION

Participants in this study were a highly selected group of patients who suffered from CDH. They represent a group of individuals who had failed to receive relief of their symptoms after trying most, if not all, other therapeutic modalities. All patients were evaluated, using a new proprietary device, called the neurolens measurement device. This device is designed to measure the contoured prismatic correction needed to create total binocular alignment and guides the manufacture of glasses with contoured prisms, designed to correct the measured imbalance. Patients found to have an imbalance based on evaluation with this instrument were entered into the study and where given spectacles with the recommended contoured prismatic correction. A unique proprietary manufacturing technique allows the power of the contoured prismatic correction to vary from distance to near vision.

Self reported efficacy, utilizing a validated metric for gauging severity of headache symptoms (HIT6), indicated that 146 of the 179 patients (81.6%) had a positive response to the treatment. The two-sided p-value against the hypothesis of no-effect was highly statistically significant with a P-value < 0.0001. The data further show that those patients who suffered from the most severe headache symptoms upon entering the study reported the greatest benefit in terms of symptom relief. Based on the findings of this study, we believe that this new therapeutic approach for the treatment of severe CDH that involves no drugs, injections or medications of any kind should be more widely considered.

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