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Clinical Study

Thin-film optical notch filter spectacle coatings for the treatment of migraine and photophobia

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ABSTRACT

Previous evidence suggests optical treatments hold promise for treating migraine and photophobia. We designed an optical notch filter, centered at 480 nm to reduce direct stimulation of intrinsically photosensitive retinal ganglion cells. We used thin-film technology to integrate the filter into spectacle lenses. Our objective was to determine if an optical notch filter, designed to attenuate activity of intrinsically photosensitive retinal ganglion cells, could reduce headache impact in chronic migraine subjects. For this randomized, double-masked study, our primary endpoint was the Headache Impact Test (HIT-6; GlaxoSmithKline, Brentford, Middlesex, UK). We developed two filters: the therapeutic filter blocked visible light at 480 nm; a 620 nm filter was designed as a sham. Participants were asked to wear lenses with one of the filters for 2 weeks; after 2 weeks when no lenses were worn, they wore lenses with the other filter for 2 weeks. Of 48 subjects, 37 completed the study. Wearing either the 480 or 620 nm lenses resulted in clinically and statistically significant HIT-6 reductions. However, there was no significant difference when comparing overall effect of the 480 and 620 nm lenses. Although the 620 nm filter was designed as a sham intervention, research published following the trial indicated that melanopsin, the photopigment in intrinsically photosensitive retinal ganglion cells, is bi-stable. This molecular property may explain the unexpected efficacy of the 620 nm filter. These preliminary findings indicate that lenses outfitted with a thin-film optical notch filter may be useful in treating chronic migraine.

1. Background

Over 90% of migraine sufferers report photophobia, an abnormal sensitivity to light, during an attack; many report that light can trigger a migraine attack, and some are chronically light sensitive [1,2]. Patients with chronic headache are particularly prone to visual symptoms and eye strain [3], and non-incandescent artificial indoor light can provoke headaches. [4]. To this point FL-41, a special tint, has been the only migraine-specific optical treatment. Originally developed to reduce light sensitivity attributed to fluorescent lighting, the FL-41 tint blocks blue-green light. In 1991 Good et al. found that FL-41 tinted spectacle lenses reduced migraine frequency from 6.2 to 1.6 per month in a cohort of children with migraines [5]. Despite demonstrated benefit in migraine, this tint has not gained widespread use. FL-41 also has been shown to reduce photophobia and blinking in benign essential blepharospasm, another condition associated with light sensitivity [6].

A fMRI study demonstrated that precision optical tints could reduce cortical hyper-excitation in migraine [7]. This study did not attempt to determine if use of these tints could reduce headache frequency or severity. Nevertheless, there appears to be evidence that optical treatments hold promise for treating migraine and photophobia.

The pathway that mediates photophobia begins with intrinsically photosensitive retinal ganglion cells (IPRGC) and trigeminal afferents [8,9]. These retinal cells do not require input from photoreceptors and have been shown to be responsible for circadian rhythm entrainment and the pupillary light reflex. These cells constitute a pathway separate from that of the visual pathway [10]. IPRGC contain the chromophore melanopsin [11]. Melanopsin has an action potential spectrum that peaks at 480 nm, in the

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blue-green region of the visible spectrum [12]. It is conceivable that the effectiveness of FL-41 may be attributed to its attenuation of those light wavelengths that activate IPRGC.

Despite its effectiveness, FL-41 was developed before the discovery of IPRGC and has drawbacks. FL-41 cannot be made dark enough to obtain maximal blocking at 480 nm without making the tint too dark for indoor use. For this reason, we designed an optical notch filter based on "thin-film" technology that minimizes light transmission at 480 nm. Our objective was to determine if this filter could reduce headache impact in a cohort of study subjects with chronic migraine.

2. Methods

The University of Utah Institutional Review Board approved this study and all study procedures were performed in compliance with prevailing USA Health Insurance Portability and Accountability Act standards and the Declaration of Helsinki. Study subjects provided informed consent before participation.

Study subjects with chronic migraine were recruited from the authors' clinics. Subjects were included if they had a diagnosis of chronic migraine according to International Headache Society criteria (second edition of the International Classification of Headache Disorders; http://ihs-classification.org/en/). Subjects already using tinted lenses were excluded. Subjects taking medications with ocular side effects (for example, ethambutol, hydroxychloroquine, amiodarone) were excluded. Subjects were excluded if they had best-corrected visual acuity less than 20/40 or retinal diseases. Subjects who met the criteria for medication overuse were excluded.

2.1. Spectacle lenses

Conventional spectacle tints found in prescription and non-prescription eyewear consist of organic dyes. By contrast, thin-film coatings consist of very thin optically transparent layers deposited on the lens surface.

We designed two thin-film optical notch filters. The therapeutic filter was designed to block light around 480 nm, while a 620 nm filter was designed to act as a sham lens. We chose the 480 nm filter to attenuate stimulation of IPRGC. Because the human eye is maximally sensitive at 550 nm and our 480 nm filter is 70 nm shorter than 550 nm, we chose the 620 nm filter as a sham lens because it is 70 nm longer than 550 nm (Fig. 1). Coatings were applied to the front surfaces of prescription and non-prescription lenses, according to each subject's requirements (Fig. 2).

2.2. Study design and procedures

We planned a 12 week, prospective, randomized, double-masked crossover study (Fig. 3). Only research team members without conflicts of interest interacted with research subjects and collected data.

Subjects completed the Headache Impact Test (HIT-6; GlaxoSmithKline, Brentford, Middlesex, UK) (Supp. Fig. 1) and a photophobia questionnaire (Supp. Fig. 2) at six time points throughout the study. Subjects maintained daily headache diaries throughout the study (Supp. Fig. 3). Subjects completed the first set of questionnaires upon enrollment. They did not wear study lenses during the first 4 weeks. After 4 weeks, subjects completed a second set of questionnaires and then were assigned by block randomization to wear either the 480 nm therapeutic lenses or the 620 nm sham lenses. Subjects were instructed to wear the lenses during all waking hours for 2 weeks. Subjects then completed the third set of questionnaires and underwent a 2 week washout period during which they did not wear any study-related lenses. At the end of the washout, subjects completed the fourth set of questionnaires and crossed-over to lenses with the opposite coating for 2 weeks. After 2 weeks, subjects completed the fifth set of questionnaires. The final 2 weeks of the study was another washout period during which no study lenses were worn. At the end of the final washout period, the subjects completed the sixth and final set of questionnaires. Although the HIT-6 is designed to assess headache impact over the previous 4 weeks, at time points 2–5 subjects were instructed to answer the questions based on the previous 2 weeks.

Throughout the trial the investigators and the subjects were masked as to which glasses were being worn. Although the investigators did not monitor whether subjects were wearing the study lenses, subjects were asked to inform the investigative team if they were unable to wear the study lenses for at least 50% of their waking hours. Subjects who completed the entire trial either could keep the study lenses of their choice or receive a check for $US50.

2.3. Data analysis

We determined that 30 subjects would be required to achieve an 80% power for detecting a statistically significant change in the HIT-6. We set our target enrollment at 50, anticipating that some subjects would not complete the study.

A biostatistician developed a data analysis plan before having access to any study data. The primary endpoint was the HIT-6 score. Secondary endpoints included: proportion of days with severe headaches; proportion of days with headaches that made activity difficult, caused activity changes, or caused the subjects to go to bed; proportion of days with headaches requiring use of medication; and proportion of days with light sensitivity. Because the study lenses could potentially affect circadian rhythms, we also tracked the number of hours each subject slept throughout the study. Finally, we reviewed how many subjects chose to keep a study lens *versus* the $50. The primary statistical analysis was based on the results of Questionnaires 2 through 5 obtained immediately prior to and following the interventions of the two periods of the cross-over design. The analysis was performed using a mixed effects model with a random effect for patient, and fixed effects for treatment order and for the pre- and post-treatment measurements for each of the two periods. The primary estimate of the treatment effect was based on a comparison of the post-treatment values between the 2 periods in accordance with the cross-over design using each patient as their own control. Additional contrasts were used to estimate the mean changes from the pre-treatment to the post-treatment for the 2 interventions separately for the 2 periods, and to estimate carry-over effects.

To detect carryover effects, the biostatistician performed an analysis of covariance relating the HIT-6 recorded before lens #2 to the HIT-6 recorded at the end of lens #1. Because there were some outliers in the analysis of covariance, a non-parametric rank-sum test was performed for the same comparison.

3. Results

We enrolled 48 subjects. Thirty-seven completed all study procedures. Twenty-nine were women and eight were men, with an average age of 44 years (range 19–75). Baseline HIT-6 score of all 48 subjects was 65.4. Baseline HIT-6 score for the 37 subjects who completed the study was 64.5. Thirty-three of the 37 subjects completing the study (89%) had baseline HIT-6 scores $\geqslant$60. According to the HIT-6 interpretation, patients with scores $\geqslant$60 have headaches that have a "very severe impact" on their life [13].

Table 1 summarizes the HIT-6 data scores analysis, which indicates that wearing either the 480 nm or 620 nm lenses resulted in