A Flicker Therapy for the Treatment of Amblyopia

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ABSTRACT

Background: Standard clinical treatment methods for amblyopia penalize the non-amblyopic eye, with subsequent compliance problems, and do not address the associated binocular vision abnormality. The purpose of this study is to evaluate a novel approach to amblyopia treatment that uses rapid alternating occlusion and flicker and aims to improve monocular and binocular vision.

Methods: A pre-post (12 weeks) interventional study with historical data control. Children with anisometropic amblyopia (ages 5 to 17 years, n=23) were enrolled by consecutive sample. Subjects wore Eyetronix Flicker Glass, shutter glasses with liquid crystal lenses that rapidly alternated occlusion at a programmable frequency, for 1-2 hours daily while performing a near task of their choice, e.g., homework, computer. Outcome measures were: (1) best-corrected LogMAR visual acuity (BCVA) and (2) Random Dot 2 stereopsis.

Results: After 12 weeks of therapy, 96% (n=22) of the children treated improved BCVA in the amblyopic eye (p<0.001) - over 26% (n=6) improved 2 LogMAR lines or more (fellow eye BCVA did not change) - and 89% of the children with reliable data (n=18) improved global stereopsis.

Conclusions: This relatively passive therapy has shown encouraging results as a potential treatment for amblyopia. The improvement in BCVA is comparable to previous studies that used traditional amblyopia therapies. The improvement in stereopsis suggests that the therapy promotes binocular vision. Notably, BCVA and stereopsis improved across all ages and in subjects who had previously plateaued with conventional therapies. Randomized masked and controlled studies are the next step to further quantify the clinical efficacy of this therapy.

BACKGROUND

Amblyopia is a leading cause of permanent monocular vision impairment[1], the fourth most prevalent disability among children in the US, and a significant public health problem. Failure to identify children with amblyopia at young ages, when treatment is most successful,

leaves clinicians with limited options to treat amblyopia. Compliance problems[2-4] and reduced neuroplasticity[5,6] in older children and adults further reduce treatment success rates[7].

Amblyopia is a neurological developmental disorder that presents with deficits in spatiotemporal vision processing[8-18] and abnormal binocular vision[19-22]. In spite of being recognized as a binocular vision disorder, the standard clinical therapy for amblyopia is still monocular penalization of the non-amblyopic eye, using patching or atropine[23]. With good compliance, penalization often improves visual acuity in the amblyopic eye of young children[2,4,23]. However, these methods do not address binocular vision deficits other than those due to improvement in monocular acuity[24-26].

These challenges drive clinicians and scientists to find more effective treatment methods for treating amblyopia. Successful therapies should not simply improve visual acuity in the amblyopic eye, but should also promote binocular vision, broadly defined as the images perceived by each eye combined into one percept[27]. Binocular amblyopia therapies more closely approximate "natural" two-eyed sight, and may treat a fundamental defect in amblyopia: lack of binocularity[19,20,22,28]. Promoting binocular vision and avoiding penalization of the better-seeing fellow eye should also improve compliance[2,4,29,30].

Previous literature suggests that rapid square-wave alternation of visual stimuli between eyes, i.e., flicker, may improve vision in amblyopic eyes[31], presumably by decreasing the depth of suppression. The suggested mechanisms for the effect of flicker in amblyopia include: (1) an apparent increase in transmission to the cortex[32]; (2) reduced masking and contour interaction from the non-amblyopic eye[31]; and (3) strong visual motion stimulus (flicker)[33,34]. As lack of visual motion is known to decrease visibility[35], the use of a flicker may promote visibility. Promoting

central vision with repetitive flicker may also cause neural learning at the synaptic level[36]. Schor et al[31] found that a 7 Hz alternation rate was most effective in temporarily improving visual acuity in a sample of 5 amblyopic subjects. The temporal phase relationship found suggested that this was due to a masking mechanism. Later, Hussey[33,37] found that alternating occlusion with liquid crystal lenses programmed at 5 Hz may shorten suppression and increase binocular periods.

These reports suggest visual alternating flicker may decrease suppression while promoting binocularity, both valuable in treating amblyopia. However, it was only recently that advances in technology have allowed rapid alternation to be tested as a feasible and practical alternative to penalization methods for amblyopia treatment. The purpose of this study was to conduct an initial pilot evaluation of a new amblyopia treatment method that is based on alternating flicker.

METHODS
1. Subjects:
Criteria for inclusion were: (1) 5 to 17 years of age; (2) Mild to moderate anisometropic amblyopia defined as best-corrected visual acuity (BCVA) in the amblyopic eye between +0.20 to +0.70 logMAR (20/32 to 20/100 Snellen equivalent), BCVA in the fellow eye +0.20 logMAR (20/32 Snellen equivalent) or better, a difference in BCVA between the two eyes of +0.20 logMAR (two lines) or more, and anisometropia greater than 1.00D of spherical refractive error or 1.50D of astigmatism; (3) No strabismus detectable with cover test; (4) Full-time wear of glasses with best-correction for a minimum of eight weeks prior to the study; (5) No amblyopia treatment one month prior to the study; and (6) No personal or family history of epilepsy.

Twenty-three children (10.6 ± 4 years; age range 5 to 17 years) with anisometropic amblyopia met all inclusion criteria (Table 1). All enrolled children completed the

Table 1. Subjects' information at baseline: age in years; best-correction as spherical equivalent (SE, rounded to the nearest 0.25D) and best-corrected visual acuity (BCVA) in logMAR units for right (OD) and left (OS) eyes. The amblyopic eye is indicated with[†]. Baseline global stereopsis measured with the Random Dot 2 test is reported in arc sec. Most subjects had undergone previous penalization treatment that was not successful or not fully successful.

Subject #	Age (years)	Best Rx OD (SE, D)	BCVA (logMAR) OD	Best Rx OS (SE, D)	BCVA (logMAR) OS	Stereopsis (arc sec)	Previous Penalization Treatment?
101	13	+1.50	0.00	+3.25	0.36[†]	>500	Yes
102	7	+3.75	0.04	+5.50	0.37[†]	>500	Yes
105	17	+0.25	-0.08	+4.50	0.42[†]	500	Yes
106	17	0.00	-0.12	+3.50	0.54[†]	>500	Yes
112	6	+1.00	0.02	+4.00	0.32[†]	500	Yes
113	6	-0.25	-0.02	+4.25	0.42[†]	>500	Yes
116	14	+4.25	0.54[†]	+0.25	-0.06	>500	Yes
201	16	0.00	-0.18	+6.75	0.60[†]	>500	No
202	15	+4.75	-0.02	+6.25	0.81[†]	>500	Yes
203	13	-0.25	0.04	+1.50	0.30[†]	>500	Yes
204	9	+3.50	0.48[†]	+1.50	-0.02	>500	Yes
301	5	0.00	0.16	+1.25	0.46[†]	N/A	Yes
302	6	+3.75	0.28[†]	+1.25	-0.06	500	Yes
304	7	+3.25	0.00	+5.00	0.68	>500	Yes
305	17	+1.25	-0.04	+5.00	0.56[†]	500	Yes
306	10	+3.00	0.00	+4.25	0.24[†]	500	Yes
307	6	+5.00	0.43[†]	+4.00	0.12	500	No
308	10	0.00	-0.04	+3.75	0.70[†]	500	No
309	11	+4.00	0.14	+4.75	0.44[†]	250	Yes
310	9	+0.25	-0.06	+5.00	0.70[†]	500	Yes
312	9	+1.00	0.16	+2.50	0.66[†]	>500	Yes
313	8	+2.75	0.34[†]	+0.75	-0.04	250	No
314	12	+0.25	-0.06	+2.75	0.20[†]	125	No

study. The study was approved by the New England College of Optometry (NECO) IRB and conformed to the requirements of the United States Health Insurance Portability and Accountability Act.

2. Device:

Eyetronix Flicker Glass (http://eyetronix.com/) is a wearable lightweight spectacle frame (Figure 1) with liquid crystal lenses, similar to those used to watch 3D TV, but with electronic control to produce accurate, rapid, direct square-wave alternating occlusion at specific frequencies. For this study, the

Figure 1. Eyetronix Flicker Glass.

device was pre-programmed to a 50/50 flicker alternation rate between the two eyes at 7 Hz. These parameters were chosen based on the previous findings of improved acuity and binocularity at this frequency[31].
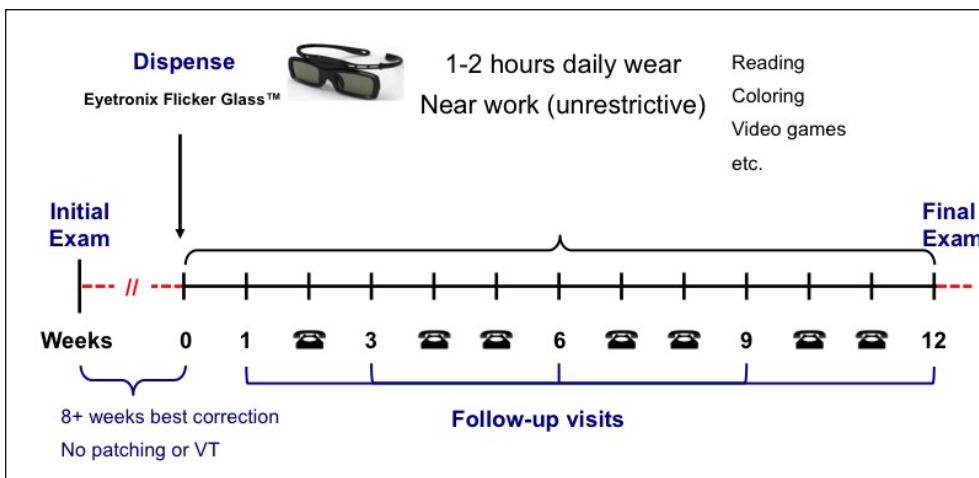
Figure 2: Visit Schedule. The week # indicates the time between visits.

3. Study protocol and procedures:

For this open-label interventional study, outcome measures were compared to historical controls, a large sample of clinical trials with validated data on the treatment effect of current clinical gold standard therapies for amblyopia[24,38]. The study was conducted in four locations: two clinics affiliated with NECO, in Boston, MA, a private practice office in Spokane, WA, and a private practice office in Fort Worth, TX. Each investigator was trained on site on the specific protocol of the study. Study investigators were not masked to the purpose of the study or the subject's condition.

The treatment period lasted 12 weeks from the dispensing visit (Figure 2). A total of seven visits were scheduled as follows:

I. Initial Visit.

A comprehensive eye examination with cyclopegia was performed unless the investigator had access to the patient's records and a cyclopegic exam that complied with the study protocol had been performed within one month of this visit. The investigator (licensed optometrist) determined the optimal ophthalmic prescription for the subject following standard clinical procedures that were uniform across the sites. If the

child was already wearing best ophthalmic correction, a dispensing visit was scheduled; if not, the subject was given an updated eyeglass prescription and asked to wear the new glasses full-time for a minimum of eight weeks[39] (Figure 2).

II. Dispensing Visit.

The dispensing visit occurred after the subject had been wearing the optimal correction for at least 8 weeks. Eligibility, based on subjects meeting all inclusion criteria, was confirmed at this visit.

BCVA was measured with LogMAR charts viewed at 4 meters. Stereopsis was evaluated with the Random Dot 2, a clinical test that measures 3 levels of global stereopsis (500, 250 and 125 arc seconds) and 12 levels of local stereopsis (from 400 to 12.5 arc seconds). Subjects were also given a logbook calendar and asked to record daily device wear time.

The therapy regimen was 1 to 2 hours of daily Eyetronix Flicker Glass wear at least 5 days a week, analogous to other current amblyopia treatment protocols[40]. Subjects were instructed to use the flicker glasses over their regular eyeglasses while doing near-tasks[41] of their choice, such as reading, writing, drawing or playing video games. Near tasks were chosen for safety reasons. There were no restrictions on the type of near tasks that subjects could perform.

III. Follow-Up Visits.

Follow up visits were scheduled at week #1 (±3 days), #3 (±3 days), #6 (±5 days) and #9 (±5 days) following dispensing. At each follow-up visit, BCVA, stereopsis and ocular health evaluations were performed

and use of the device was discussed. For intervening weeks without a visit, investigators called parents to monitor compliance with treatment and provide an opportunity for parents to discuss the treatment.

IV. Final/Exit Visit.

At the final visit at week 12 (±5 days), a comprehensive eye exam with cyclopegia was conducted in addition to the typical follow-up visit tests.

4. Outcome Measures and Data Analyses:

The primary outcome measure, change in BCVA in the amblyopic eye compared to the change in the fellow eye, was analysed using paired t-test statistics. Potential associated factors such as age and initial BCVA were analysed using Spearman ρ correlation statistics. The change in global stereopsis was a secondary outcome measure.

RESULTS

Following 12 weeks of treatment, the group mean improvement in BCVA in the amblyopic eye (week #1 compared to week #12) was significantly greater than the change in BCVA in the fellow eye (paired t-test t(21) = 3.66, p=0.001) (Figure 3). Most subjects (96%, n=22)

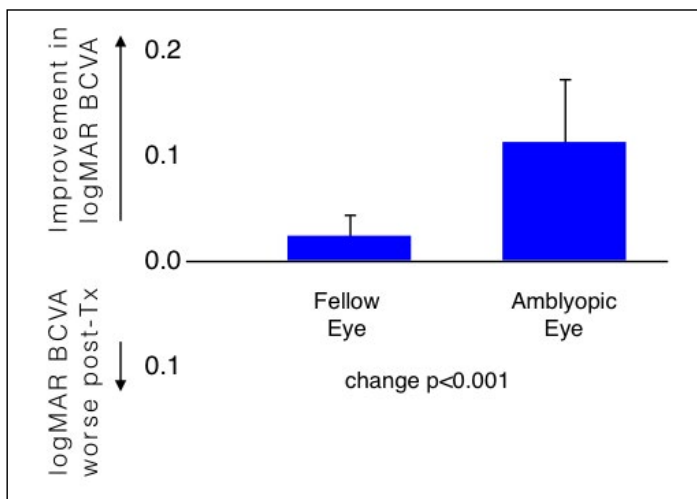**Figure 3:** Mean change in BCVA in amblyopic eye and fellow eyes from baseline (Week #1) to the end of the therapy (Week #12). Error bars represent ±1SD.
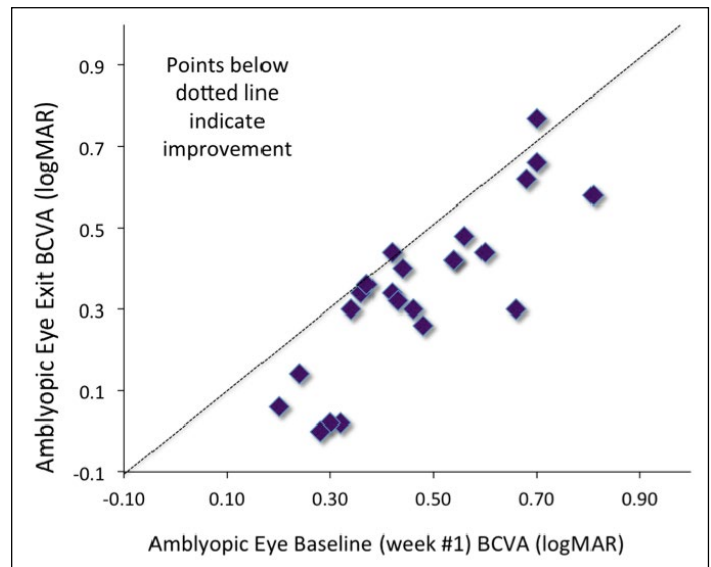
Figure 4: Individual BCVA (logMAR) in amblyopic eye at baseline (week #1) (x-axis) plotted against BCVA (logMAR) in amblyopic eye at exit visit (week #12) (y-axis).

showed 1 to 4 lines of improvement in BCVA in the amblyopic eye, with mean improvement -0.124 ± 0.111 logMAR. Additionally, 26% of the subjects (n=6) showed improvement of two lines or more, similar to previously published data in this age group[38,42] (Figure 4). Importantly, the fellow eye BCVA did not change. The mean change in the fellow eye was -0.02 ± 0.07 logMAR (paired t-test t(21) = 1.34, p=0.19), contrary to certain previous reports of studies that showed worsening of BCVA in patched fellow eyes[43]. No change in BCVA was found with optical correction alone for one subject (#313) who was given a new optical correction after the initial visit[44].

BCVA improved in older as well as younger subjects, irrespective of prior treatment and depth of baseline amblyopia. BCVA improvement showed no correlation with age (Spearman ρ = 0.12, p=0.58) (Figure 5a), the baseline BCVA of the amblyopic eye (Spearman ρ=0.08, p=0.73) (Figure 5b) or the baseline difference in BCVA between the two eyes (Spearman ρ=0.17, p=0.474). Most subjects (n=18, 78%, Table 1) had undergone some type of clinical amblyopia treatment, patching, atropine and/or vision therapy, beyond optical correction alone prior to this study, but we found no correlation between
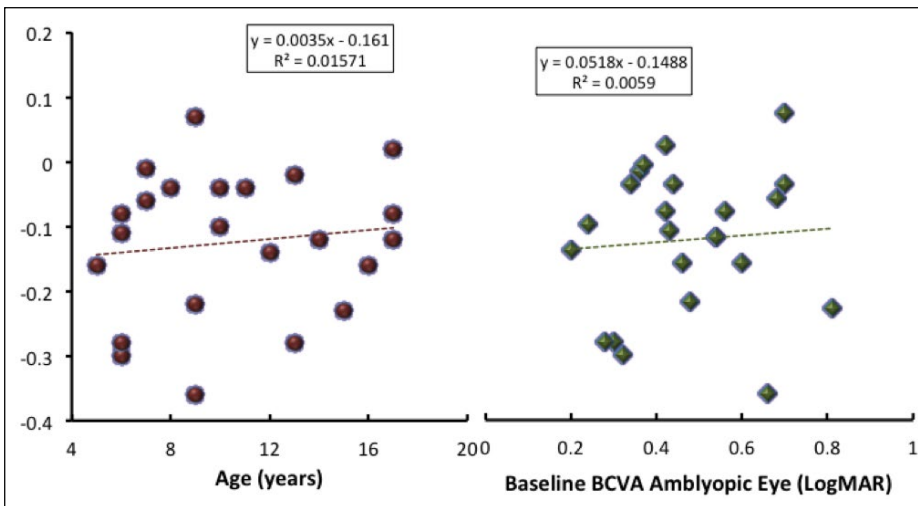
Figures 5a and 5b: Change in BCVA in the amblyopic eye (Y axis) was not correlated with age (figure 5a), or the subject's baseline BCVA in the amblyopic eye (figure 5b).

past treatment and improvement of BCVA in this study (Chi Square -0.13, p=0.57).

Additionally, n=16 of the 18 subjects with reliable stereopsis data (89%) improved global stereopsis following alternating flicker treatment (Figure 6). The mean improvement was 0.43 ± 0.26 Log arc sec, superior to previously reported effects in similar populations when using conventional[25] or experimental amblyopia therapies[19,20,22].

Two subjects (11%) maintained the same level of global stereopsis post-therapy; stereopsis did not worsen in any of the participating subjects. Local stereopsis improved in 83% of subjects (n=15 of the 18 subjects with reliable stereopsis data).

Global stereopsis improved independently of BCVA improvement (Spearman ρ=0.25, p=0.28) and subject age (Spearman ρ=-0.06, p=0.80). The two subjects who did not show improvement in BCVA in the amblyopic eye (#105, #310) did improve in global stereopsis (250 arc seconds improvement each). In addition, the subjects who showed no improvement in stereopsis (n=3) or whose data was not reliable (n=2) did improve BCVA in the amblyopic eye. Therefore, all subjects
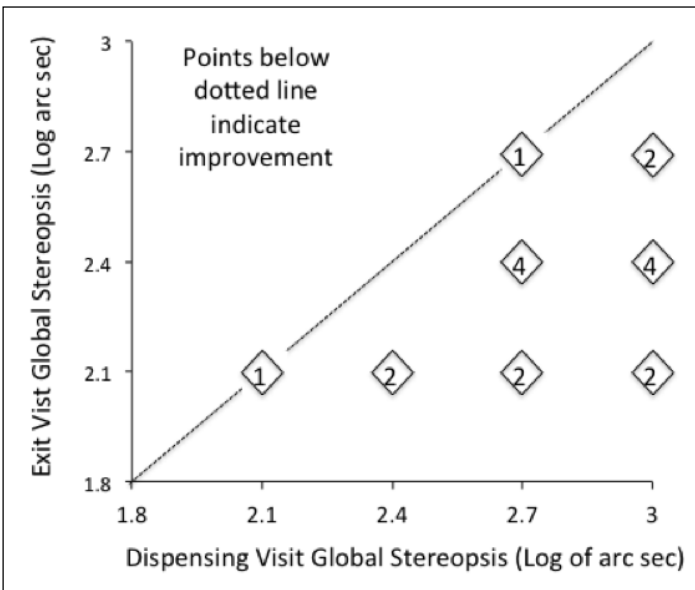

Figure 6: Individual baseline (week #1) global stereopsis data (Log arc sec) plotted against exit (week #12) global stereopsis data. The number indicates the number of subjects represented by the data point. Improvement in stereopsis is represented by a data point below the 1:1 line shown.
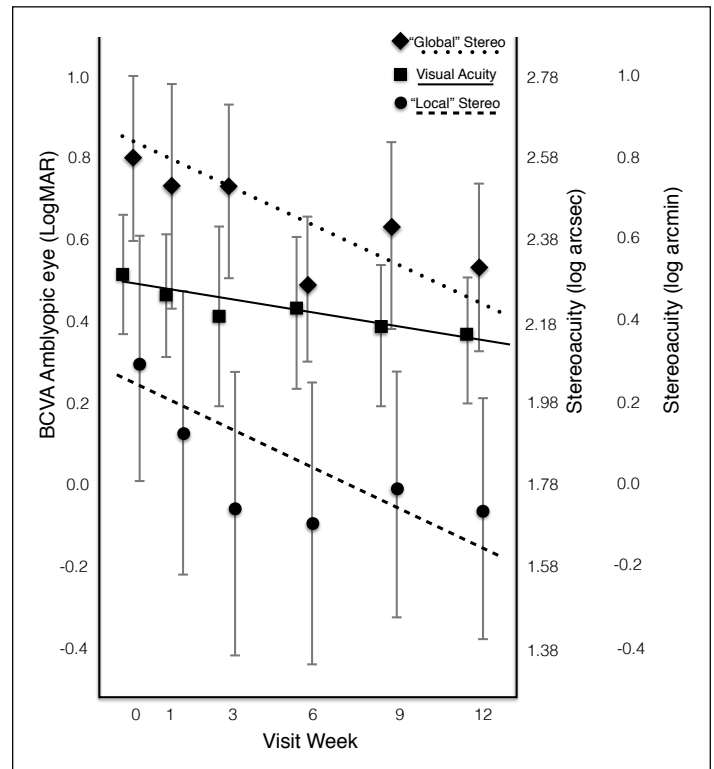

Figure 7: Group mean data on global stereopsis (◆), local stereopsis (●) and BCVA (■) of the amblyopic eye over the 12 weeks treatment period. Note improvement in stereopsis is significantly faster (slope for global stereopsis is -0.08 and for local stereopsis is 0.12 log arc sec) than the improvement in BCVA (slope -0.03 LogMAR).

improved in at least one of these two clinical outcome measures. Although it has been previously reported that as VA improves stereopsis usually improves to a small degree[26], we found that the improvement in stereopsis may precede the change in VA (Figure 7).

Two adverse events not related to the device were reported during the course of the study: (1) a report of blurry vision after the final visit for subject #105, a consequence of the cyclopegic eye drops; (2) hospitalization of subject #116 due to a pre-existing condition. Self reported compliance with the use of the flicker glasses and the strict schedule of visits was very high. Only one subject (#102) missed one follow up visit (#3). For the group of n=23 subjects, some of the visits (24%; n=30 of a total of 126 visits) occurred out of the very narrow time window.

DISCUSSION

Results from this pilot study indicate therapeutic potential of rapid alternating flicker as an amblyopia treatment method. Visual acuity improved across all ages and continued to improve in subjects who had previously plateaued with conventional penalization and/or optical correction therapies (22/23 of our subjects). Stereopsis, as measured with the Random Dot 2 test, also improved across all ages.

Improvements in BCVA, one to four lines, were comparable to those found in previous studies that used penalization treatment methods[38]. This finding was particularly encouraging because the majority of subjects in this study had undergone prior traditional treatment.

Conventional clinical practice assumes that treatment becomes increasingly difficult with age[2]; in this study, older teenagers improved as much as younger children. There is only limited previous evidence that penalization is effective in older, previously treated children. The largest well-designed study in a population of children 7 to 17 years of age (PEDIG, Paediatric Eye Disease Investigator Group) found that only 25% who received both optical treatment and part-time patching responded to treatment[38]. The best results corresponded to subjects who had not been treated previously. PEDIG concluded that teenagers previously treated with patching exhibited little or no benefit from a new treatment[38]. This contrasts with our findings of improvement in BCVA and stereopsis regardless of age and prior treatment.

Almost all subjects (16/18), even those with no measurable stereopsis initially, showed some level of improvement in clinical stereopsis. Few prior studies have evaluated stereopsis as an outcome measure for amblyopia treatment. Tejedor and Ogallar[24] found no measurable improvement in stereopsis when children were treated with either atropine or patching. Wallace et al[25] presented a summary of the changes in stereopsis found in studies conducted by PEDIG where stereopsis was measured, a total of 248 children with anisometropic amblyopia, and found minimal improvement in stereoacuity with 17 to 24 weeks of therapy: only 28% of subjects (n=70) improved, compared to 89% of our subjects. More recently, Hess et al[45] found improvement in stereopsis in about half of the anisometropic amblyopic subjects who were treated with a dichoptic video game. The improvement in stereopsis found in our study, an average of 0.43 Log arc sec, is notably greater than in the PEDIG studies (0.2 Log arc sec)[25] and in other previous reports[22].

Interestingly, the improvement in stereopsis was not correlated with BCVA improvement of the amblyopic eye (unlike previous reports, for a review see[22]), baseline level of stereopsis, nor history of previous treatment. The mechanism behind the stereopsis improvement is unknown, although we hypothesize that it is a function of – and indicates – improved binocularity.

Given the promising improvement attained during the course of the study, a follow-up evaluation 12 weeks after the completion and

discontinuation of therapy was attempted in order to assess whether there was regression in clinical improvements as seen with traditional treatments[43]. With the caveat that this follow-up was done on 10 of the total 23 subjects, 9 of those subjects who did come back actually had slightly improved BCVA in the amblyopic eye relative to BCVA at their exit visit (-0.06 ± 0.09 LogMAR). No changes in BCVA were found in the non-amblyopic eye (Mean ± SD = -0.02 ± 0.06 LogMAR), indicating that this therapy does not affect vision in that eye. Additionally, a small group improvement in global stereopsis was found between the exit visit and the follow-up visits (Mean ± SD = -0.06± 0.21 Log arc sec. We hypothesize that this stability of the benefit may represent a generalized improvement in binocularity.

This study was designed as an initial evaluation of the Eyetronix Flicker Glass Therapy, and as such the study has a number of limitations that include the small number of subjects, the unmasked nature of the study (both examiners and subjects were unmasked), the absence of a control group other than historical data, and the limited stereopsis data range.

The results from this study may support the hypothesis that anisometropic amblyopia involves abnormally strong inhibition by the non-amblyopic eye. It appears that the alternate intermittent flicker frequency used in this study minimized binocular interference of the non-amblyopic eye, therefore improving visual acuity in the amblyopic eye and promoting binocular vision. An alternative – or perhaps an addition – to this hypothesis is that the visual improvements might be caused by the temporal signals created by alternating on-off flicker, which may affect desynchronization of neuronal activities. This would be supported by recent reports that show an effect of coherent and dichoptic motion and alternating flicker in suppression[28,33,46], abnormal critical flicker fusion frequency[47] and temporal neuronal synchronization in amblyopia[48].

For example, Hess' group[28,46] has evaluated monocular motion-stimulus training in a binocular field with dichoptic coherent motion and video games. Future directions include psychophysical investigations to understand the underlying mechanism for improved visual acuity and stereopsis, a large randomized clinical trial with masked study design, and finer measures of stereopsis and suppression to encompass near-threshold values.

CONCLUSIONS

This pilot study shows encouraging results for this relatively passive therapy as a potential treatment for amblyopia, as indicated by the improvement in BCVA and stereopsis across all ages and in subjects who had previously plateaued with conventional therapies. Randomized masked and controlled studies are the next step to further quantify the clinical efficacy of this therapy.

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