Review of the Literature • Binocular Treatment of Amblyopia

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ABSTRACT

Amblyopia, which has been discussed and treated as early as the 18th century, is a visual problem in which the brain fails to process input signals equally between the eyes, causing the patient to favor one eye. The causes can be refractive, strabismic, or via deprivation of visual stimulation. Amblyopia is a diagnosis of exclusion; thus, ocular pathology must be ruled out. Clinically, it is defined as a decreased best-corrected visual acuity (BCVA) in one or both eyes. Organizations such as the Pediatric Eye Disease Investigator Group (PEDIG) have produced much groundwork when discussing the standard of care for treating amblyopic patients. Numerous studies have shown that treatment efficacy decreases significantly after a certain age, and about a quarter of all patients successfully treated will regress. Over the last two decades, a variety of treatment protocols have been tested, including spectacle correction, part-time occlusion, full-time occlusion, and pharmaceuticals such as atropine. The mainstay of amblyopic management is penalizing the better-seeing eye, leading to better vision development in the amblyopic eye. Amblyopia, however, is a binocular problem, and recent studies have tried to address this concern. Those studies, as mentioned above, had problems with both patient numbers and compliance with study protocols. These issues could be casting a shadow of doubt on the possibility of a more efficacious treatment that also helps with lingering binocular vision issues. Currently, no studies performed have shown greater efficacy when treating amblyopia long-term than sequential patching after optimal correction.

A Randomized Trial of a Binocular iPad Game Versus Part-Time Patching in Children 5 to 12 Years of Age with Amblyopia

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The current standard of care for amblyopia is part-time occlusion of the better-seeing eye to stimulate appropriate visual development in the amblyopic eye. Patches can be adhesive ones that stick to the child's face or one that slides on over the glasses if warranted. The latter of the two options is less preferred due to the child's ability to look around the patch and not use the amblyopic eye. It has been shown that there is an equivalent visual acuity improvement between moderate and severe amblyopia with either patching or weekend atropine use. For most new treatment studies, patching will be at least one arm of the study because of its now well-known effect on increasing visual acuity in the amblyopic eye.

There have been significant changes to medicine in the last 20 years; the fields of optometry and ophthalmology are no exception. While the eye patch is a simple tool that has been used for hundreds of years, sophisticated technology has improved our treatment protocols; temperature gauges can assess whether the patch is placed on the eye, thus allowing for more precise dose-monitoring. Dichoptic training on computer monitors is starting to become as well known as standard red/green anaglyphic glasses. The way amblyopia treatment is viewed is ever-changing in this more digitized world. This first study emphasized the use of technology when treating amblyopia compared to the standard of care.

This study was a randomized, two-arm, non-inferiority clinical trial. (One of the arms of the study was tested to see whether it was not inferior to the other.) This was determined by a pre-set value that still would make one arm better than optical correction alone. Patients were seen at various full-scope multidisciplinary centers by members of a large cohort of physicians who volunteer for the PEDIG group. This study included a robust sample size of 385 children, ages 5-12, with large ranges in visual acuity and cause of amblyopia. Most PEDIG

clinical studies serve to answer a specific question. In this study, the question was whether binocular training via an iPad game was not inferior to part-time patching when treating amblyopia.

The 385 participants were split between the two arms of the study randomly. Baseline visual acuity was taken on each subject, with follow-up visits at 4, 8, 12, and 16 weeks. For standardization purposes, single-surround HOTV letters were used for children 5-7 years of age, and E-ETDRS letters were used for the older age group of 7- to 12-year-olds. Also, stereoacuity was tested using the randot butterfly or randot preschool stereoacuity test. Lastly, a standard cover test was performed to mark any changes in alignment throughout the testing period. To reduce bias, the examiners were masked as to who was in each group.

In the binocular group, there were 190 subjects. Each subject was given an iPad with a pre-programmed "falling blocks" game. This game requires the subjects to clear rows of blocks by alignment into straight rows. Red/green anaglyphic glasses were used, with the green lens over the amblyopic eye. The amblyopic eye was given full contrast compared to the non-amblyopic eye, with contrast decreasing in that eye until it achieved 10%. Subjects could set the levels for easy, medium, or hard with complete discretion. Subjects in this arm of the study were asked to play 1 hour per day, seven days per week, for 16 weeks. If subjects could not participate in the game every day, they shoudld attempt at least four days per week. The patching arm of the study had 195 subjects. These subjects were given normal patches and were instructed to complete two hours of continuous patching seven days per week with no minimum-day standard.

Each arm of this study had 96% of its subjects complete all study 5 visits. Compliance was deemed "good" if treatment was adhered to 75% of the time. Subjectively, the parents in the binocular group and the patching group noted good compliance with protocol in 67% (122) and 92% (158) of the subjects, respectively. However, the iPad device indicated that only 22% (40 subjects) completed at least 75% of the treatment. Mild crossover treatment was needed for 4 subjects in the binocular group (3 patching, one low-dose atropine), and no patching subject received binocular training post-study. No egregious side effects were present on either arm of the study after the treatment period.

After 16 weeks of treatment, visual acuity was measured. Using a 95% confidence interval and conversion to a standardized logMAR vision unit, the patching and binocular groups increased from the baseline visual acuity by 1.32 lines and 1.08 lines, respectively. With the upper limit of the values exceeding the pre-determined non-inferiority limit of 0.5 lines, there was a failure to reject the null hypothesis. This failure to reject was the main reason this study was indeterminate. Post-hoc analysis of the data would favor the patching over the binocular group in this study. Another finding after analysis of the data was that the younger age group (5-7 years) showed greater improvement in both arms (2.5 +/-1.5 lines for binocular and 2.5 +/-0.8 lines for patching) than the 7- to 12-year age group.

Lastly, the study found that the visual acuity change in the binocular group was not directly associated with the number of hours playing the game. For subjects who completed >50% of the game (51 subjects), visual acuity gains at 16 weeks were similar to those in subjects who completed <50% (125 subjects).

This study gives readers the required information needed to understand where physicians are in treating amblyopia. The study indicates that current binocular treatment protocols are seemingly inferior to the current standard-of-care patching treatment. The researchers were able to obtain a robust sample size and an appropriate range of ages to treat. They were unable to reject the null hypothesis, yet for the sake of well-rounded data, performed a posthoc analysis. The major limitation in this study was compliance. Only 22% of the subjects who completed the binocular group's treatment could be marked as having "good" compliance. There could be many factors contributing to this number, but the most probable answer is the lack of exciting gameplay for the children. With the sophisticated videogames out in today's world, it would be difficult to keep children engaged in a block-stacking game. The authors noted that more vigorous games should be on the horizon to promote compliance. The post-hoc analysis showed that the number of hours played was not directly related to the amount of visual acuity gained, but most data had to be extrapolated from the few patients who completed minimum requirements. Compliance will always be a hindrance on a quality study because it is entirely out of the physician or examiner's control.

Compliance on the patching arm was purely measured through subjective parent response. A large percentage of parents (92%) reported "good" compliance with patching two hours every day; however, this number could also greatly be inflated. The difference in visual acuity gains may have been

even more statistically significant, providing greater support for the failure to reject the null hypothesis.

Binocular iPad Game vs. Patching for Treatment of Amblyopia in Children

Kelly KR, Jost RM, Dao L, Beauchamp CL, Leffler JN, Birch EE. JAMA Ophthalmol 2016;134(12):1402-8.

This study involves a single-crossover treatment protocol. This is used to alleviate patient variation and compare a single patient's response to two different study arms. In amblyopia, a crossover treatment provides an insight as to which of two treatment arms has the potential for higher rates of gain in visual acuity. In this study, the main question to be answered was whether there was a difference between binocular treatment, the current standard of care, and patching for amblyopia treatment in children.

The authors designed this study primarily to test a new adventure game on the iPad as a binocular treatment in amblyopia and to compare its results to patching. The secondary goal was to test possible gains in stereoacuity along with changes in depth of suppression. This is important because amblyopia treatment success is usually measured only by the BCVA of the amblyopic eye; the closer to 20/20, the better. Until recently, the thought of depth of suppression and true binocularity were afterthoughts in the minds of the investigators. As stated above, amblyopia is a binocular problem, so finding treatment protocols that could enhance binocularity and increase BCVA in the amblyopic eye would be most beneficial to the patient affected.

This study was performed with red/green anaglyphic glasses and the game Dig Rush. This game is a multi-level adventure game that involves the patient navigating their miner (seen by the amblyopic eye) to find gold and avoiding obstacles (seen by the non-affected eye). The amblyopic eye is prompted to dominate the viewing due to higher-contrast miners and lower-contrast gold and obstacles. The incentive for each level is a star-based rewards system. A maximum of three stars can be earned on each level. This game is similar to many of the current iPhone applications that children and teens alike enjoy.

This study consisted of 28 children ranging between the ages of 4 and 10 who were randomized into two treatment groups. Fourteen children were instructed to play the Dig Rush game five days per week for one hour daily. Similar to previous studies, the amblyopic eye was given 100% contrast, and the fellow eye had 20% contrast. An unsuccessful attempt at a level would cause the fellow eye's contrast to drop until stars were earned. After the initial two weeks, the binocular treatment arm was encouraged to continue the game for another two weeks under the same protocol. The patching arm of the study consisted of 14 children who were instructed to start the standard-of-care protocol for patching: 2 hours per day for 14 days. After two weeks, there was a crossover for these subjects, who were then instructed to start the Dig Rush game for the final two weeks of the study.

The study consisted of three visits: baseline testing, 2-week testing, and 4-week testing. Visual acuity was taken with single ETDRS letters for subjects at or above the age of 7. Single HOTV letters were used for any subject under 7. Along with visual acuity, stereoacuity was tested at each visit using the Randot preschool stereoacuity test and the stereo butterfly test. Next, the extent of suppression was tested at 7 distances using the Worth 4-dot. Lastly, the depth of suppression was tested using either a dichoptic eye chart (over age 7) or a dichoptic motion coherence test (under 7). Compliance was measured via subjective parent response (for patching: 99% treatment time reached), and the logs were collected for the binocular game at the 2-week mark (100%) and the 4-week mark with combined groups (82%).

At the end of the testing period, an independent t-test was used to determine whether there was a difference in BCVA for those in the binocular game arm compared to the patching arm at the 2-week evaluation. A paired t-test was used to evaluate whether the BCVA in the binocular group improved significantly. The same protocol was repeated for BCVA at the 4-week mark, and individual t-tests were run to test for significance in extent and depth of suppression.

After the initial two weeks, there was a larger improvement in the binocular game cohort (1.5 lines) as compared to the patching cohort (0.7 lines). This finding was vastly different from previous findings using binocular games such as pong or the falling blocks game in the previously described study. At the 4-week mark, the children who crossed over from the patching group achieved similar visual acuity to the binocular game group. The BCVA gain was 1.7 lines for the binocular game, and the patching crossover group achieved 1.6 lines. Overall, 23 children improved at least one line over the four weeks. Neither group showed improvement in the extent of suppression

at the 2-week mark, but both groups showed a significant improvement in the depth of suppression, although there was no significant difference between the groups.

In their discussion, the authors conclude that there was significant evidence to show that binocular game training improved BCVA better in amblyopic children than the current standard of care of patching two hours daily. The authors also note that double the amount of visual acuity improvment (1.5 logMAR units compared to 0.7 logMAR units) was achieved in less than half of the treatment time (10 hours for the binocular game compared to 28 hours of patching). After two weeks, five children in the binocular group improved to 20/32 or better, which was only achieved in one of the children in the patching group. This led the authors to conclude that binocular game treatment may yield faster BCVA results as compared to standard patching. Previous studies with dichoptic movie training have yielded such results as well: approximately two lines of improvement after four weeks. The authors here attribute better gains with this binocular treatment to the fact that Dig Rush was more interesting than previous games such as pong or falling blocks. The authors also conclude that both groups improved in depth of suppression due to the increase in BCVA of the amblyopic eye.

This study sheds important light on current limitations to the testing of binocular treatment modalities in amblyopia. The first limitation is longevity; while the results of this study were impressive and showed a significant increase in the binocular treatment group compared to the patching group after two weeks, it remians unclear whether this type of treatment is sustainable over time. Can the visual gains seen over a two-week period be extrapolated to multiple months, as most patching protocols require? Also, it has yet to be shown whether regression rates after short-term BCVA increases using binocular treatment are equivalent to those seen with patching. Another limitation to this study noted by the authors is its small sample size. Premier studies require strong sample sizes to enhance the statistical analysis of the data. Studies with larger sample sizes are required if this premise is to become standard of care. Lastly, the authors mention that certain factors such as previous amblyopia treatment or patient age could have affected the data.

In conclusion, these two studies are excellent representations of how medical professionals are ever-evolving in their pursuit for the best possible protocol to treat amblyopia in children. More studies are required to determine whether binocular treatment is truly efficacious compared to the current standard of care. These studies have shown that there must be a large sample size of patients, a better-than-average amount of compliance, and an activity that has the longevity to keep improving visual acuity in our young amblyopic patients.

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