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A Prospective Trial to Assess the Efficacy of Eye-Tracking-Based Binocular Treatment versus Patching for Children's Amblyopia: A Pilot Study

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ABSTRACT

Purpose: To assess visual acuity (VA) and stereoacuity (SA) improvements in children with amblyopia treated with either binocular dichoptic treatment or patching treatment.

Methods: In this pilot prospective coherent study, 34 participants between 4 and 9 years of age with unilateral anisometropic amblyopia and without history of prior amblyopia treatment were enrolled into three groups. Full treatment group (FTG; $n = 12$): participants were prescribed the binocular dichoptic treatment to watch for 90 minutes per day, 5 days a week. Part-time treatment group (PTTG; $n = 8$): participants were prescribed the same binocular treatment as FTG, 90 minutes per day, 3 days per week. Patching treatment group (PTG; $n = 14$): participants wore an adhesive patch over the dominant eye for 2 hours per day, 7 days per week. Amblyopic-eye distance visual acuity (DVA), near visual acuity (NVA) and SA were evaluated at baseline, 4, 8, and 12 weeks.

Results: At 12 weeks, mean amblyopic-eye DVA improved 1.8 lines (95% CI, 1.1–2.5) in FTG, 1.5 lines (95% CI, 0.4–2.7) in PTTG and 3.0 lines (95% CI, 2.0–4.0) in PTG. The amblyopic-eye NVA improved 2.9 lines (95% CI, 2.4–3.5) in FTG, 1.7 lines (95% CI, 0.5–3.0) in PTTG and 2.8 lines (95% CI, 1.8–3.9) in PTG. The SA improved 0.38 log-arcseconds (95% CI, 0.24–0.53) in FTG, 0.59 log-arcseconds (95% CI, 0.36–0.82) in PTTG and 0.40 log-arcseconds (95% CI, 0.13–0.67) in PTG. No significant differences were found in DVA, NVA or SA improvement between FTG and PTG at 12 weeks.

Conclusions: VA and SA after binocular dichoptic treatment produced a similar therapeutic outcome to patching, suggesting a potential value for binocular therapy when treating anisometropic moderate degree of Children's amblyopia.

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Amblyopia; Binocular treatment; Patching; Stereoacuity; Visual acuity

INTRODUCTION

Amblyopia is the most common cause of visual impairment in children, with prevalence estimated at 1% to 5%.[1–3] The most common associated amblyopia risk factors are uncorrected refractive error, anisometropia, strabismus, form-deprivation or any combination of those. In addition to visual impairment, amblyopia may also lead to dysfunction with accommodation, fixation, binocularity, vergence, reading fluency, and/or contrast sensitivity.[4–6] The commonly practiced modality for management of amblyopia is refractive correction followed by either part-time patching or atropine penalization of the dominant eye.[7–11] These have varied rates of success; unsuccessful part-time patching treatment can be attributed to poor compliance with the prescribed treatment regimens,[12] and that the results fail to achieve binocular function.[13] There remains a need for novel amblyopia treatments, and ideally these should be both visually unobtrusive and non-interfering with the dominant eye's vision.

Studies have suggested that binocular cortical mechanisms remain intact with unilateral amblyopia and a binocular approach to treating amblyopia is feasible.[14–17] Dichoptic therapies are a specific type of binocular treatment that use adjusted dichoptic stimuli for both eyes simultaneously in order to reduce the interocular suppression and transfer the images to the brain simultaneously. CureSight™ (NovaSight, Israel) is an eye-tracking-based, dichoptic system designed to treat amblyopia under dichoptic conditions. The system allows for online content to be tailored individually per eye and then presented simultaneously to both eyes. The aim of this prospective pilot study was to determine whether this binocular therapy could improve visual acuity (VA) and stereoacuity (SA) in patients with unilateral amblyopia.

MATERIALS AND METHODS

Participants

A pilot prospective coherent study was conducted at Eye and ENT Hospital of Fudan University in Shanghai, China and the Sheba Medical Center, Tel-Hashomer, Israel. A total of 34 participants were enrolled into three groups from December 2018 to March 2020:

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Group 1: Full treatment group (FTG; $n = 12$), where participants used the CureSight device to watch videos for 90 minutes per day, 5 days a week for 12 weeks (totaling 120 hours). Parents of participants were instructed that the 90 minutes of daily treatment should be completed in a single 90-minute session, but if this is not possible for whatever reason, the treatment may be divided into two shorter sessions totaling 90 minutes per day, 5 days per week for 12 weeks.

Group 2: Part-time treatment group (PTTG; $n = 8$) where participants were prescribed the same binocular online content watching as FTG, 90 minutes per day, 3 days per week for 12 weeks.

Group 3: Patching treatment group (PTG; $n = 14$) where participants wore an adhesive patch over the dominant eye for 2 hours per day, 7 days per week for 12 weeks. Parents of subjects will be instructed that the 2 hours of daily patching should be completed in a single 2-hour session.

The major inclusion criteria of the study were as followed: (1) age ≤9 years; (2) amblyopia associated with anisometropia; spectacles (if required) worn for at least 16 weeks; (3) VA in the amblyopic eye 20/32 (0.2 LogMAR) to 20/100 (0.7 LogMAR) inclusive (4) best-corrected dominant-eye VA [20/40 (0.3 LogMAR) or better for age 4 to 5 years; 20/32 (0.2 LogMAR) or better for age 5 years or older]; (5) interocular difference ≥ 2 logMAR lines (≥10 letters). Major exclusion criteria included (1) myopia greater than −6.00 D spherical equivalent in either eye; (2) known skin reactions to patch or bandage adhesives; (3) any other condition which could be a potential cause for reduced best-corrected VA according to the investigator; (4) severe developmental delay that would interfere with treatment or evaluation; (5) subjects that do not wear their spectacles; (6) history of light-induced seizures; (7) wearing rigid gas permeable contact lenses; (8) any reported anatomic ocular anomaly; (9) previous intraocular or refractive surgery.

The study was approved by the ethics committee of Eye and ENT Hospital of Fudan University and was conducted according to the tenets of the Declaration of Helsinki for the use of human subjects in biomedical research. Informed consent was obtained from all individual participants included in the study.

Binocular curesight treatment

CureSight is an eye-tracking-based, dichoptic system designed to treat amblyopia under dichoptic conditions that incorporates eye gaze tracking and separation of streamed visual stimuli presented on a monitor into two separate digital channels, one for each eye. The technology is based on real-time eye tracking and separation of the visual stimuli presented on a monitor into two separate digital channels, one for each eye. Using this dichoptic method, online content can be tailored individually per eye and then presented simultaneously to both eyes. Subjects were instructed to wear the CureSight dichoptic anaglyph glasses over habitual spectacle correction. A second component of the CureSight system is a computer with 11.6-inch monitor used for stimuli presentation and an eye-tracker that allows continuous tracking of each eye. The proprietary software blurs the non-amblyopic eye's central image area (i.e., the fovea), thereby forcing the visual system to use the information from the amblyopic eye's fovea (Figure 1).

Participants in the treatment group will be asked to watch digital content presented on CureSight system while wearing red/blue (anaglyph) glasses over current spectacle correction, if applicable. The participant should be instructed to sit in front of the system at the distance of ~60 cm. Positioning algorithm will automatically guide the participant to the optimal position. Each participant is supplied a pair of anaglyph glasses according to his/her amblyopic eye, with a red filter positioned in front of the non-amblyopic eye and a blue filter positioned in the amblyopic eye; the latter eye will have a higher intensity compared to the red filtered image as a consequence of the channel separation. Diameter and magnitude of the blur are adjusted during the treatment as the VA in the amblyopic eye improves.

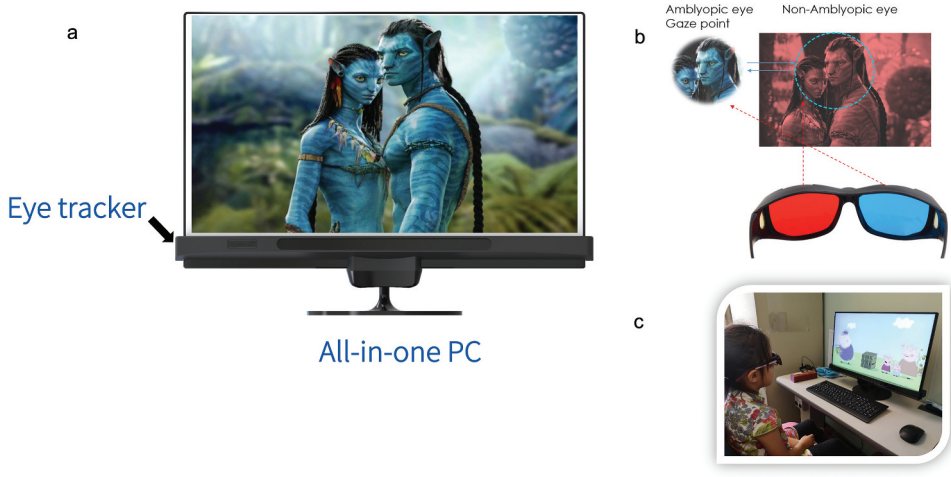


Figure 1. CureSight system and treatment principle. a. The component of the CureSight system is a computer with 11.6-inch monitor used for stimuli presentation and an eye-tracker that allows continuous tracking of each eye. b. The proprietary software blurs the non-amblyopic eye's central image area, thereby forcing the visual system to use the information from the amblyopic eye's fovea c. Participants are asked to watch digital content presented on CureSight system while wearing red/blue glasses over current spectacle correction.

Study schedule

Subjects were randomly assigned to one of the three treatment groups. Outcome assessments were performed at weeks 4, 8, and 12.

The primary outcome results in this study were distance visual acuity (DVA), near visual acuity (NVA) and stereoacuity (SA). DVA testing was performed in current refractive correction (if required) in each eye using the Electronic Early Treatment Diabetic Retinopathy Study (E-ETDRS) protocol on a study-certified acuity tester displaying single surrounded optotypes.[18] DVA was tested before NVA for all participants. NVA testing was performed in current refractive correction (if required) in each eye by a certified examiner assessed at 40 cm using the Pediatric Eye Disease Investigator Group (PEDIG) Amblyopia Treatment Study (ATS) near acuity test comprise of a series of flip cards with single-surrounded LEA symbol charts.[9] SA testing was assessed at near in current spectacle correction (if required) by examiner using the Titmus stereoacuity tests.

Statistical analysis

All analyses were performed in SPSS software, version 25.0 (IBM, Chicago, IL, USA). Continuous variables were presented as mean ± standard deviation, while categorical variables were presented as frequency and percentage. Stereopsis was converted to natural log scale for statistical calculations. Demographic and baseline measures were compared among the three groups using Pearson's chi-squared test. The primary outcome measure was the difference in amblyopic-eye DVA, NVA and SA from baseline to the 4, 8, and 12-week follow-up visits within and among the three groups. The improvements of DVA, NVA and SA from baseline to 12 weeks were compared using paired *t*-test, respectively. Multivariable analyses of DVA, NVA, and SA improvements were performed at 4, 8, and 12 weeks, adjusting for age and the baseline values. All *p* values were two-sided and were considered statistically significant when the values were < 0.05.

RESULTS

There were 36 participants enrolled in the study; of these, two subjects were excluded due to inadequate follow-up time, leaving 34 cases (18 male and 16 female, 4 ~ 9 years) for final analysis. There were no statistically significant differences in age, gender, or amblyopic eye among the three groups ($P > .05$). Moreover, there were no significant differences among the three groups in the baseline values for DVA, NVA, or SA ($P > .05$). Baseline demographic and clinical characteristics are summarized in Table 1.

In the FTG group, the amblyopic eye DVA improved significantly to 0.48 ± 0.21 logMAR at 4 weeks, 0.39 ± 0.18 logMAR at 8 weeks, and 0.37 ± 0.19 logMAR at 12 weeks ($P < .001$). In the PTTG group, the DVA improved significantly to 0.54 ± 0.22 logMAR at 4 weeks, 0.50 ± 0.23 logMAR at 8 weeks, and 0.46 ± 0.31 logMAR at 12 weeks ($P = .016$). In the PTG group, the DVA improved significantly to 0.36 ± 0.15 logMAR at 4 weeks, 0.28 ± 0.14 logMAR at 8 weeks, and 0.26 ± 0.15 logMAR at 12 weeks ($P < .001$). This correlates to a 1.8 line improvement in the FTG group (0.18 logMAR; 95% CI, 1.1–2.5 lines), a 1.5 lines improvement in the PTTG group (0.15 logMAR; 95% CI, 0.4–2.7 lines), and a 3.0 lines improvement in the PTG group (0.30 logMAR; 95% CI, 2.0–4.0 lines) at 12 weeks. After adjusting for the baseline DVA and the age, statistically significant differences were found in DVA improvement between FTG and PTG at 4 weeks ($P = .009$) and at 8 weeks ($P = .028$), between PTTG and PTG at all follow-up time points: 4 weeks ($P = .016$), 8 weeks ($P = .001$), and 12 weeks ($P = .019$) (see Figure 2). Table 2 further delineates these differences.

All groups showed a statistically significant improvement from baseline for the amblyopic eye NVA at all timepoints. The FTG group improved to 0.38 ± 0.17 logMAR at 4 weeks, 0.27 ± 0.10 logMAR at 8 weeks, and 0.26 ± 0.14 logMAR at 12 weeks ($P < .001$); the PTTG group improved to 0.48 ± 0.27 logMAR at 4 weeks, 0.44 ± 0.27 logMAR at 8 weeks, and 0.41 ± 0.27 logMAR at 12 weeks ($P = .013$); and the PTG group improved to 0.37 ± 0.15 logMAR at 4 weeks, 0.28 ± 0.12 logMAR at 8 weeks, and 0.25 ± 0.11 logMAR at 12 weeks ($P < .001$). This correlates to a 2.9 line gain in the FTG group, a 1.7 line gain in the PTTG group and a 2.8 line gain in the PTG group at week 12 (see Figure 3). Table 3 shows the statistically significant differences between groups after adjusting for baseline NVA and age.

A statistically significant difference from baseline SA was noted in all groups beginning at week 4. In the FTG group, SA improved to 2.22 ± 0.46 at 4 weeks, 2.09 ± 0.46 at

Table 1. Baseline demographics and characteristics.

	Full treatment ($n = 12$)	Part-time treatment ($n = 8$)	Patching treatment ($n = 14$)	*P* value
Age (range), years	6.42 ± 1.44 (4, 9)	5.63 ± 1.69 (4, 9)	5.71 ± 1.33 (4, 8)	0.380[a]
Sex (no., %)				
Male	6 (50)	3 (37.5)	9 (64.3)	0.465[b]
Female	6 (50)	5 (62.5)	5 (35.7)	
Amblyopic eye (no., %)				
Right	5 (41.7)	5 (62.5)	7 (50)	0.659[b]
Left	7 (58.3)	3 (37.5)	7 (50)	
Baseline vision				
LogMAR (range)				
Distance visual acuity	0.55 ± 0.19 (0.30, 1.02)	0.61 ± 0.23 (0.30, 0.98)	0.56 ± 0.18 (0.32, 0.92)	0.802[a]
Near visual acuity	0.55 ± 0.16 (0.32, 0.94)	0.58 ± 0.26 (0.22, 0.92)	0.53 ± 0.17 (0.28, 0.74)	0.827[a]
Stereoacuity, arcsec	2.39 ± 0.42 (1.78, 2.90)	2.44 ± 0.42 (1.78, 2.90)	2.26 ± 0.35 (1.60, 2.90)	0.530[a]

LogMAR, logarithm of the minimum angle of resolution.
[a]One-way Analysis of Variance.
[b]Pearson's chi-squared test.

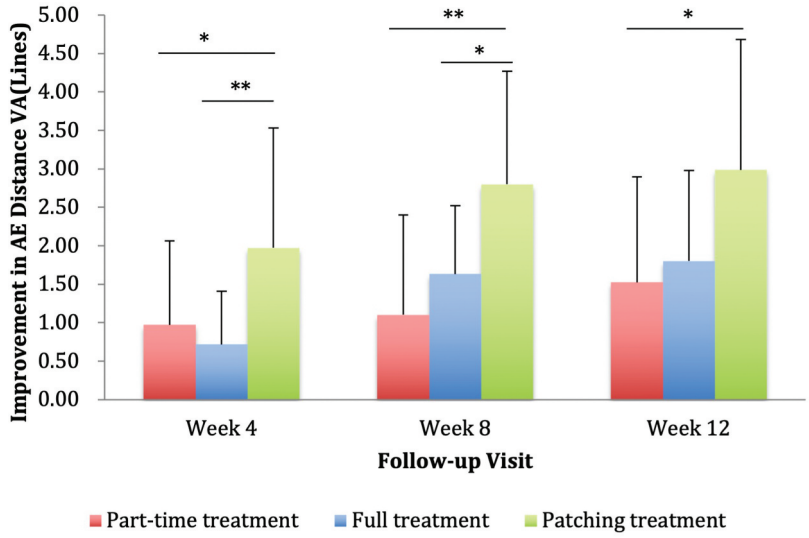


Figure 2. Improvement in distance visual acuity for the three groups over the duration of the study. The DVA of amblyopic eye improved 1.8 lines for the FTG group, 1.5 lines in PTTG and 3.0 lines in PTG at 12 weeks. * stands for *p* value less than 0.05. ** stands for *p* value less than 0.01.

Table 2. Multivariable analysis of improvement in distance visual acuity for amblyopic eye at three follow-up visits.

	4 weeks		8 weeks		12 weeks	
	Coefficient	95% CI	Coefficient	95% CI	Coefficient	95% CI
Baseline	0.77	(0.55, 0.99) **	0.73	(0.51, 0.94) **	0.80	(0.53, 1.57) **
Age	−0.01	(−0.04, 0.02)	0.01	(−0.02, 0.04)	0.02	(−0.02, 0.06)
Group						
PTTG *vs.* FTG	0.00	(−0.11 ~ 0.12)	0.08	(−0.03 ~ 0.19)	0.05	(−0.08 ~ 0.19)
FTG *vs.* PTG	0.13	(0.04 ~ 0.23) **	0.11	(0.01 ~ 0.20) *	0.10	(−0.01 ~ 0.22)
PTTG *vs.* PTG	0.13	(0.03 ~ 0.24) *	0.18	(0.08 ~ 0.29) **	0.17	(0.03 ~ 0.29) *

CI, confidence interval; FTG, Full Treatment Group; PTTG, Part-Time Treatment Group; PTG, Patching Treatment Group
* $P < .05$; ** $P < .01$.

8 weeks, and 2.01 ± 0.31 at 12 weeks ($P < .001$). In the PTTG group, SA improved to 1.97 ± 0.26 at 4 weeks, 2.03 ± 0.32 at 8 weeks, and 1.85 ± 0.22 at 12 weeks (<0.001). In the PTG group, SA improved to 1.94 ± 0.18 at 4 weeks, 1.94 ± 0.22 at 8 weeks, and 1.86 ± 0.34 at 12 weeks ($P = .007$). Figure 4 shows the improvement in logMAR over the duration of the study. Table 4 shows the SA between-group differences.

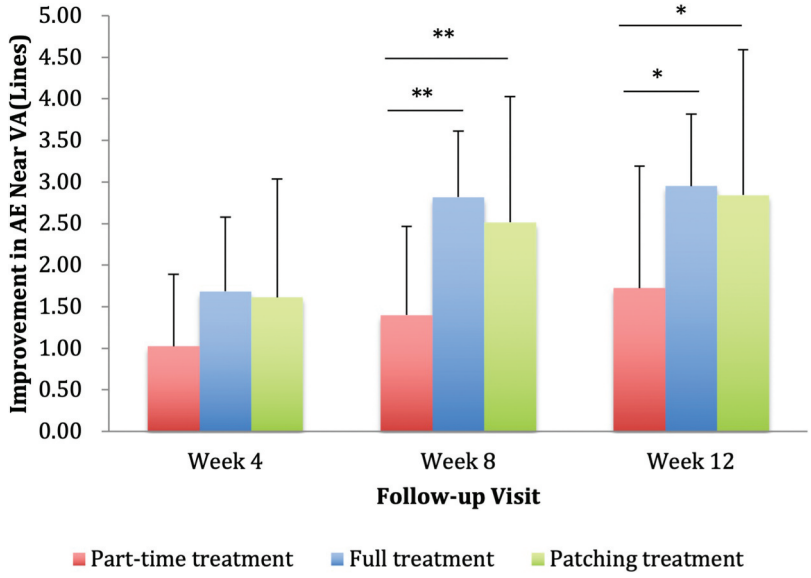


Figure 3. Improvement in near visual acuity for the three groups over the duration of the study. The NVA of amblyopic eye improved 2.9 lines (95% CI, 2.4–3.5 lines) for the FTG group, 1.7 lines (95% CI, 0.5–3.0 lines) in PTTG and 2.8 lines (95% CI, 1.8–3.9 lines) in PTG at 12 weeks. The * stands for *p* value less than 0.05. The ** stands for *p* value less than 0.01.

Table 3. Multivariable analysis of improvement in near visual acuity for amblyopic eye at three follow-up visits.

	4 weeks		8 weeks		12 weeks	
	Coefficient	95% CI	Coefficient	95% CI	Coefficient	95% CI
Baseline	0.80	(0.59, 1.01) **	0.65	(0.47, 0.84) **	0.62	(0.39, 0.86) **
Age	0.01	(−0.02, 0.04)	0.02	(0.00, 0.05)	0.02	(−0.01, 0.05)
Group						
PTTG *vs.* FTG	0.08	(−0.02 ~ 0.19)	0.17	(0.08 ~ 0.26) **	0.15	(0.03 ~ 0.27) *
FTG *vs.* PTG	−0.01	(−0.10 ~ 0.08)	−0.04	(−0.12 ~ 0.04)	−0.02	(−0.12 ~ 0.09)
PTTG *vs.* PTG	0.07	(−0.03 ~ 0.17)	0.13	(0.04 ~ 0.22) **	0.13	(0.02 ~ 0.25) *

CI, confidence interval; FTG, Full Treatment Group; PTTG, Part-Time Treatment Group; PTG, Patching Treatment Group
* $P < .05$; ** $P < .01$.

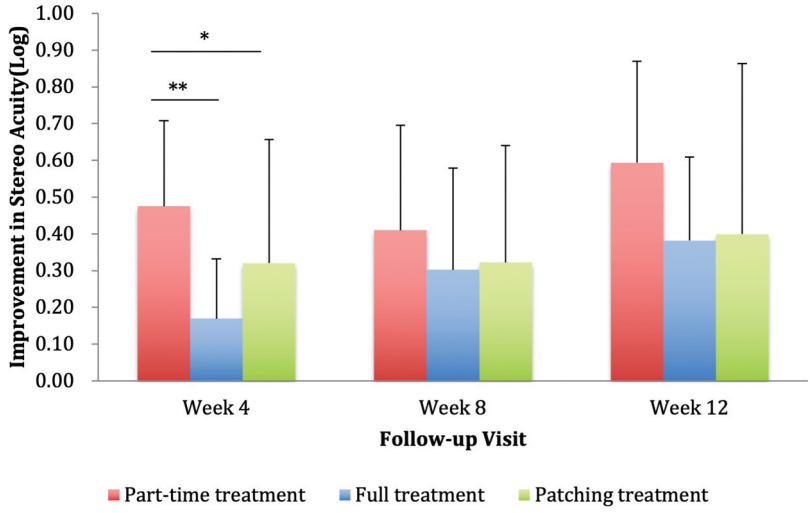


Figure 4. Improvement in stereoacuity for the three groups over the duration of the study. The SA improved 0.38 log-arcseconds (95% CI, 0.24–0.53) in FTG, 0.59 log-arcseconds (95% CI, 0.36–0.82) in PTTG and 0.40 log-arcseconds (95% CI, 0.13–0.67) in PTG at 12 weeks. * stands for *p* value less than 0.05. The ** stands for *p* value less than 0.01.

Table 4. Multivariable analysis of stereoacuity at three follow-up visits.

	4 weeks		8 weeks		12 weeks	
	Coefficient	95% CI	Coefficient	95% CI	Coefficient	95% CI
Baseline	0.63	(0.42, 0.84) **	0.61	(0.36, 0.85) **	0.41	(0.16, 0.67) **
Age	0.03	(−0.09, 0.03)	−0.02	(−0.09, 0.04)	−0.04	(−0.11, 0.03)
Group						
PTTG *vs.* FTG	−0.31	(−0.52~−0.10) **	−0.11	(−0.35~−0.14)	−0.21	(−0.47 ~ 0.04)
FTG *vs.* PTG	0.22	(0.04 ~ 0.40) *	0.09	(−0.13 ~ 0.30)	0.12	(−0.10 ~ 0.34)
PTTG *vs.* PTG	−0.09	(−0.29 ~ 0.11)	−0.02	(−0.26 ~ 0.22)	−0.09	(−0.34 ~ 0.16)

CI, confidence interval; FTG, Full Treatment Group; PTTG, Part-Time Treatment Group; PTG, Patching Treatment Group
* $P < .05$; ** $P < .01$.

No adverse events were noted for the duration of the study. There were no reports of diplopia, asthenopia, ocular misalignment, or worsening of a preexisting condition.

DISCUSSION

This pilot study found VA and SA improved in an amblyopic eye with both binocular and patching treatments in children between 4 and 9 years of age. There were no differences between a full-time binocular approach and patching at 12 weeks, suggesting the two approaches have similar therapeutic effects on amblyopia.

Previous studies of binocular treatment have reported improvements in VA with iPad-based dichoptic video games, with contrast-rebalanced movies, and with shutter glasses for either video watching or interactive activities in children.[19–21] Several studies have demonstrated that small amounts of improvement in VA of amblyopic eyes can also be achieved with binocular treatment in adults.[22–24] The results add to the literature, as we also showed significant improvements in both DVA and NVA in the amblyopic eyes with binocular treatment. However, in Holmes and colleagues[25] study using a binocular iPad game in patients aged 7–12 years, the amblyopic-eye VA letter score improved from baseline by 1.3 with binocular treatment and by 1.7 with continued spectacle correction alone, representing no improvement in VA at 4 or 8 weeks. However, the older population and shorter follow-up time may account for the outcome differences between these two studies. Conversely, in their randomized controlled trial, Xiao and colleagues reported that amblyopic eye VA improved

by 1.8 lines in the digital treatment group but only by 0.8 lines in the comparison group which continued wearing glasses alone at 12 weeks.[26]

In the current study, the DVA was improved by 1.8 lines in the FTG group *vs*. 3 lines in the PTG group at 12 weeks ($P > .05$), but 0.7 lines in the FTG group *vs*. 2 lines in the PTG group at 4 weeks ($P = .009$) and 1.6 lines in the FTG group *vs*. 2.8 lines in the PTG group at 8 weeks ($P = .028$); significant differences were found at weeks 4 and 8 only, suggesting patching may be more effective on DVA than binocular treatment over a short period of time, but that the advantage may dissipate over a longer period of time. In the current study, NVA improvements were similar between the FTG group and the PTG group (1.7 lines *vs*. 1.6 lines at 4 weeks, 2.8 lines *vs*. 2.5 lines at 8 weeks and 2.9 lines *vs*. 2.8 lines at 12 weeks, $P > .05$, respectively). The results differed from other published studies: Holmes and colleagues[27] reported the amblyopic-eye VA improved 1.05 lines in their binocular group and 1.35 lines in their patching group of children aged 5–13, with an adjusted treatment group difference of 0.31 lines favoring patching. Manh and colleagues[28] reported the amblyopic-eye VA improved from baseline by 3.5 letters in their binocular group and by 6.5 letters in their patching group in participants aged 13–17, with an adjusted treatment group difference of – 2.7 letters or 0.5 lines favoring patching. The findings of the current study coupled with these others suggest that age may play a role in vision outcomes with binocular treatment.

Both binocular and patching SA outcomes in other studies are inconclusive, with some studies finding improvements[15,23,24,29] and others reporting no change.[27,30,31] In the current study, the SA improved significantly in both the FTG group and the PTG group, which was not statistically significant between the groups. (0.17 log-arcseconds *vs*. 0.32 log-arcseconds at 4 weeks, 0.30 log-arcseconds *vs*. 0.32 log-arcseconds at 8 weeks and 0.38 log-arcseconds *vs*. 0.40 log-arcseconds at 12 weeks, $P > .05$, respectively). Similarly, Webber and colleagues [32] concluded that SA was highly correlated with depth of suppression, but not with a decrease in VA, and showed significant improvement of stereopsis in amblyopic adults.

The PTTG group was used to analyze the dose schedule of binocular treatment with the CureSight system. The improvement between the FTG group (5 days per week) and PTTG group (3 days per week) at 12 weeks were 1.8 lines vs 1.5 lines for DVA ($P > .05$), 2.9 lines vs 1.7 lines for NVA ($P = .015$), and 0.38 log-arcseconds vs 0.59 log-arcseconds for SA ($P > .05$), respectively. There was significant difference in NVA improvement between these two groups at 12 weeks, but not in DVA and SA improvement, suggesting that binocular treatment for a longer time may be more effective in treating amblyopia. Further studies are warranted to analyze the effect of home-based daily training compared with patching treatment.

This study is not without its limitations, primarily its small sample size and modest follow-up. A larger, multicenter randomized clinical trial using CureSight is necessary to address whether binocular treatment is truly more effective than patching to treat amblyopia. Another limitation with the current study is the requirement that subjects be in the facility to ensure compliance. It is possible that a home environment and/or a longer duration (ie., 7 days) may encourage better treatment adherence and efficacy. However, the outcome of home-based binocular treatment for amblyopia may vary due to different supervision, which needs further studies to confirm the best choice for binocular dichoptic therapy.

In conclusion, both VA and SA in the amblyopic eye improved with binocular treatment in children 4 to 9 years of age. At 12 weeks, no significant differences were found in DVA, NVA or SA between FTG and PTG. The findings support the potential value of binocular therapy for treating anisometropic moderate degree of amblyopia, with the effects similar to patching.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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