Virtual Reality Game Playing in Amblyopia Therapy: A Randomized Clinical Trial

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ABSTRACT

Purpose: To compare the visual outcome of occlusion therapy with virtual reality game playing as a new therapy for children with amblyopia.

Methods: This randomized clinical trial was performed on 50 children between 4 and 10 years old who had unilateral amblyopia. They were randomly divided into virtual reality and patching groups (n = 25 in each). The virtual reality group was trained binocularly using the virtual reality games through a head set for 1 hour per day 5 days a week for 4 weeks. Patients in the patching group occluded their non-amblyopic eyes 2, 4, and 6 hours for mild (best corrected visual acuity [BCVA] 0.2 to 0.3 logarithm of the minimum angle of resolution [logMAR]), moderate (0.3 to 0.6 logMAR), and severe (worse than 0.6 logMAR) amblyopia, respectively.

Results: The mean BCVA based on logMAR units improved significantly in both groups ($P < .0001$), but the difference between the two groups was not significant ($P = .59$). BCVA based on the responded letters improved in both groups (virtual reality: $P = .0001$, patching: $P = .001$), and change in BCVA in the virtual reality group was higher than in the patching group ($P = .002$).

Conclusions: Virtual reality game playing was equal or superior to patching in an analysis of linear and letter BCVA, respectively. Therefore, applying this new amblyopia therapy is recommended.

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INTRODUCTION

Although the traditional definition of amblyopia is the unilateral or, rarely, bilateral decreasing of visual acuity with no structural abnormalities of the eye or visual pathways, a new definition states that "amblyopia is a neurodevelopmental disorder with deficit in both monocular and binocular functions and it extends even beyond the primary visual integration centers"; therefore, amblyopia is not a "lazy eye," but it is a "lazy brain."[1,2] The standard methods of amblyopia therapy are optical correction, occlusion, and penalization.[3,4] New modalities are needed because not all patients respond to the traditional methods and even the patients who respond often show residual amblyopia at 10 years old. Approximately 25% of successfully treated children will suffer from amblyopia recurrence. Thus, long-term efforts of the child and their family are needed and there are many challenges for treating amblyopia in adults.[5]

The current theory is that suppression plays a causal role in amblyopia and its reduction would in-

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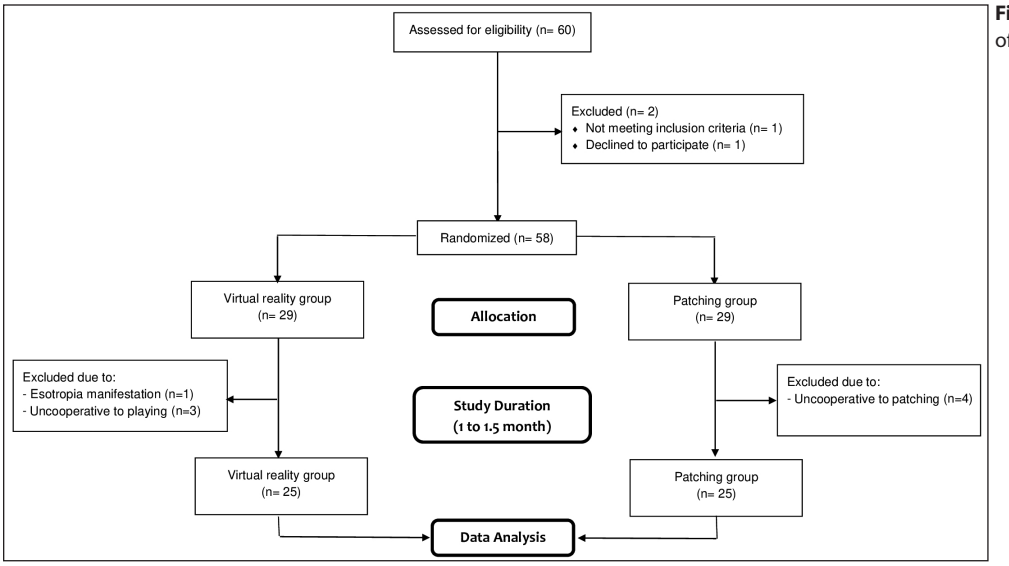

Figure 1. The workflow of the current study.

duce a greater level of plasticity of the brain followed by increased visual acuity, stereopsis, and contrast sensitivity.[1,6] On this basis, new amblyopia therapy should be purely binocular through perceptual learning and dichoptic training.[6,7] Unlike perceptual learning, where a single visual task is presented to both eyes simultaneously or under monocular viewing condition, dichoptic treatment presents separate stimuli to each eye, simultaneously, through equal background and different foreground, showing part of the image to each eye, or displaying the same images with small disparity. Therefore, stimulation of the amblyopic eye and inhibition of the non-amblyopic eye is possible coincidently.[8,9] In addition, this theory needs to balance binocular viewing in terms of clarity, contrast sensitivity, and color and motivation of the patient through interactive games, videos, scores, and rewards to encourage the child's compliance.[10] The evolution of dichoptic training begins with displaying lenticular (eg, holographic images), anaglyphic dichoptic with red and green glasses,[8,9] and then virtual reality game technique.[11] The image appears larger and at a greater distance with stereoscopic sense by virtual reality headsets.[11]

In the literature, randomized clinical trial studies comparing Interactive Binocular Treatment (I-BiT) games with occlusion were either short term (2 weeks),[12] in adults,[13,14] or compared with sham games.[15] Some studies were in children.[8,9,16] No study reported statistically significant differences between patching and virtual reality (I-BiT).

The purpose of this study was to compare the visual outcomes of occlusion with game playing through a virtual reality system in children with unilateral amblyopia at Negah Eye Hospital.

PATIENTS AND METHODS

This randomized clinical trial was performed on 50 children with unilateral amblyopia who were referred to Negah Eye Hospital between March 2019 and February 2020 (**Figure 1**).

Children with unilateral amblyopia, central fixation, an alignment within 8 prism diopters (PD), and who were between 4 and 10 years old were included. Children with bilateral amblyopia, eccentric fixation, an eye deviation of more than 8 PD, ocular pathologies, physiologic or mental disorders, and penalization within 2 weeks before the study, and non-compliant children were excluded.

The study was approved by the Ethics Committee of the Ophthalmic Epidemiology Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran (IR.SBMU.ORC.REC.1398.024), and was registered on the website of www.clinicaltrial.gov via the approval number of NCT04261868. All study procedures adhered to the tenets of the Declaration of Helsinki and a signed consent form was obtained from all participants before study allocation.

At least 3 months after wearing glasses following cyclorefraction and prescription for appropriate glasses, the children were randomly divided into virtual reality (n = 25) and patching (n = 25) groups. Children in the virtual reality group were trained binocularly using the virtual reality games through a headset for 1 hour a day 5 days a week for 4 weeks (total of 20 to 30 hours). Patients in the patching

group occluded their non-amblyopic eyes for 2, 4, and 6 hours for mild (0.2 to 0.3 logarithm of the minimum angle of resolution [logMAR]), moderate (0.3 to 0.6 logMAR), and severe (worse than 0.6 logMAR) amblyopia, respectively. Compliance with amblyopia therapy was defined as whether the child could fulfill at least 75% of the recommended time for amblyopia treatment in both groups.

Initially, the game instructions were explained to the child or their parents and they were asked to play in the office for 30 minutes under supervision to evaluate their abilities. Then, the software and headset were given to them to continue the training at home, and the playing time was controlled by online monitoring.

Randomization

The permuted-block randomization method was used, and the block length varied between 2 and 6 m. It was generated by a computer program, and the sequence of randomization was concealed from the investigators.

Sample Size

To have a power of 80% to detect a 0.20 logMAR difference between the two groups when the standard deviation of best corrected visual acuity (BCVA) between them was assumed to be 0.25 logMAR, a sample size of 25 in each group was calculated.[17]

Clinical Examinations

The presenting visual acuity was measured and recorded in the virtual reality and patching groups. Cyclorefraction was performed 45 minutes after instillation of one drop of cyclopentolate 1% and tropicamide 1% with an interval of 5 minutes.

BCVA was measured 48 hours after cycloplegia using the crowded E chart at a distance of 6 m based on responded line and letter number in both groups. Line BCVA was based on the patients' response of 50% or more of letters in each line of the chart, whereas with the letter counting method, it was based on the exact number of letters that the patients could respond to. Amblyopia was considered when the BCVA was 0.2 logMAR or worse in one eye or if the difference of at least two BCVA lines was detected between the two eyes. Extraocular function was also evaluated through duction and version and recorded based on a scoring system of -4 to +4. Ocular alignment was measured with the alternate prism cover test at far (6 m) and near (33 cm) distances. Furthermore, the anterior and posterior ocular segments were examined by slit lamp and indirect ophthalmoscope.

Follow-up Visits

The follow-up examination was performed 4 weeks after virtual reality game playing in the virtual reality group and patching in the patching group. BCVA was measured similar to measurement performed in the baseline examination. If the amblyopic eye achieved optimal BCVA (0.1 logMAR) or BCVA was equal to the fellow eye, the patient could either cease the therapy or continue with fewer hours of playing or patching.

If the BCVA of the amblyopic eye was improved but was worse than the fellow eye, it was recommended to continue the same method of therapy. If the BCVA was unchanged or worse, it was suggested to change the method of therapy (patching therapy for the virtual reality group and virtual reality technique for the patching group).

At the last follow-up visit, all patients who continued their same method of therapy were reexamined at the eighth week.

Main Outcomes

The main outcome of this study was the change in BCVA of the amblyopic eye in the two groups in the compliant children. The results of the noncompliant children in the two groups were considered as secondary outcomes of this study.

Software Designing

The virtual reality games were designed according to the binocular strategy in which the amblyopic eyes saw both background and foreground details, moving objects and more balanced color, clarity, and contrast sensitivity, and quality of image, whereas the non-amblyopic eye saw only background details, fixed objects, and less background color, clarity, and contrast sensitivity, and quality of image.

An application was designed with the Android Studio IDE and Java programming language to be used as a centralizing hub for games. The application can be used to download, install, and open the games. Each game was designed and built with the Unity game engine, and its three-dimensional models were created with Maya modeling software (Autodesk). The games run on Android version 5.1

TABLE 1

Baseline Characteristics of Participants in the Virtual Reality and Patching Groups

Parameters	Total	Virtual Reality (n = 25)	Patching (n = 25)	*P*
Sex, no. (%)				.57[a]
Male	25 (50.0)	14 (56.0)	11 (44.0)	
Female	25 (50.0)	11 (44.0)	14 (56.0)	
Age (y), mean ± SD, median (range)	7.1 ± 1.8 7 (4 to 11)	6.7 ± 1.9 7 (4 to 10)	7.6 ± 1.7 7 (5 to 11)	.08[b]
Sphere (D), mean ± SD, median (range)	3.52 ± 2.42 3.25 (-4.00 to 8.00)	3.60 ± 1.81 3.00 (0.00 to 7.00)	3.44 ± 2.94 3.50 (-4.00 to 8.00)	.81[b]
Cylinder (D), mean ± SD, median (range)	-1.52 ± 1.13 -1.50 (-4.00 to 0.00)	-1.59 ± 1.23 -1.50 (-4.00 to 0.00)	-1.44 ± 1.03 -1.50 (-4.00 to 0.00)	.64[b]
Amblyopic eye SE (D), mean ± SD, median (range)	2.77 ± 2.61 2.88 (-6.00 to 7.00)	2.84 ± 1.85 2.75 (-2.00 to 6.50)	2.71 ± 3.23 3.00 (-6.00 to 7.00)	.86[b]
Non-amblyopic eye SE (D), mean ± SD, median (range)	2.04 ± 2.36 1.75 (-2.75 to 8.00)	2.00 ± 2.13 2.00 (-2.75 to 6.25)	2.07 ± 2.59 3 (-6.00 to 7.00)	.934[b]
Anisometropia (SE difference ≥ 1.00 D), no. (%)				.52[a]
No	37 (75.5)	20 (80.0)	17 (70.8)	
Yes	12 (24.5)	5 (20.0)	7 (29.2)	
Strabismus (deviation < 10 PD), no. (%)				.87[a]
Orthophoria	32 (64.0)	17 (68.0)	15 (60.0)	
Exophoria	2 (4.0)	1 (4.0)	1 (4.0)	
Esophoria	16 (32.0)	7 (28.0)	9 (36.0)	

SD = standard deviation; D = diopters; SE = spherical equivalent; PD = prism diopters
[a]Based on chi-square and Fisher exact tests.
[b]Based on a *t* test.

(Google) or higher without any need to use a third-party software, so it is easy to install on any smartphone with the aforementioned requirements.

Statistical Analysis

To assess the normal distribution of data, the Kolmogorov-Smirnov test and Q-Q plot were used. The data were presented as mean, standard deviation, median and range, frequency, and percent. Baseline characteristics of the participants were compared with the *t* test, Mann-Whitney test, chi-square test, and Fisher's exact test. To assess the improvement within the groups, the linear mixed model was used, and multiple comparisons were considered by the Bonferroni method. The differences between the groups were evaluated by analysis of covariance and adjusted for the baseline values. All statistical analysis was performed with SPSS Statistics for Windows software (version 22.0; IBM Corporation). A *P* value less than .05 was considered statistically significant.

RESULTS

The epidemiologic characteristics of children in the virtual reality and patching groups were not different based on age, sex, spherical equivalent (SE), and anisometropia (SE difference ≥ 1.00 diopters [D]) (**Table 1**). Ocular alignment was orthophoria in most patients (64%), 28% of patients were esophoric (< 8 PD), and 4% of patients were exophoric (< 8 PD). Two patients were twins.

BCVA before and after treatment is presented in **Table 2**. Although the mean BCVA improved significantly in both groups (*P* = .0001), the difference between the two groups was not significant. The difference in BCVA was significant before (*P* = .02) and after (*P* = .04) amblyopia therapy between the virtual reality and patching groups. After baseline adjustment, the virtual reality group was 10% better, which was not significant. There was no significant change in BCVA in the non-amblyopic eyes within each group or between the two groups.

TABLE 2

BCVA of the Amblyopic and Non-amblyopic Eyes in the Virtual Reality and Patching Groups Before and After Treatment[a]

Parameter	Virtual Reality (Mean ± SD)	Virtual Reality (Median [Range])	Patching (Mean ± SD)	Patching (Median [Range])	*P*[a]
Amblyopic eye					
BCVA (logMAR)					
Before	0.300 ± 0.027	0.25 (0.2 to 0.6)	0.404 ± 0.033	0.4 (0.2 to 0.7)	.020
After	0.229 ± 0.030	0.20 (0.1 to 0.6)	0.320 ± 0.032	0.30 (0.1 to 0.7)	.046
Change	-0.070 ± 0.015	-0.10 (-0.2 to 0)	-0.084 ± 0.014	-0.10 (-0.2 to 0)	.525
P[b] within group	.0001		.0001		
BCVA (letters)					
Before	29.28 ± 1.87	30 (19 to 45)	36.13 ± 1.65	42 (19 to 45)	.0001
After	34.64 ± 1.70	36 (17 to 46)	36.67 ± 1.72	42 (21 to 48)	.021
Change	5.36 ± 0.68	5 (0 to 14)	3.54 ± 0.89	3.5 (-4 to 12)	.009
P[b] within group	.0001		.001		
Non-amblyopic eye					
BCVA (logMAR)					
Before	0.146 ± 0.02	0.10 (0.1 to 0.4)	0.168 ± 0.02	0.10 (0.1 to 0.5)	.045
After	0.162 ± 0.018	0.10 (0.1 to 0.4)	0.152 ± 0.02	0.10 (0.1 to 0.4)	.670
Change	0.071 ± 0.020	0 (-0.2 to 0.3)	-0.016 ± 0.03	0 (-0.3 to 0.4)	.393
P[b] within group	.491		.590		
BCVA (letters)					
Before	46.4 ± 0.95	48 (30 to 48)	43.56 ± 130	48 (24 to 43)	.133
After	45.7 ± 1.09	48 (29 to 48)	44.44 ± 1.25	48 (23 to 48)	.449
Change	-0.34 ± 0.31	0 (-7 to 2)	0.88 ± 0.89	0 (-13 to 10)	.208
P[b] within group	.295		.332		

BCVA = best corrected visual acuity; SD = standard deviation; logMAR = logarithm of the minimum angle of resolution
[a]Based on a *t* test.
[b]Based on a paired *t* test.

Figures 2-3 show the BCVA of both eyes before and after the amblyopia therapy and at the final follow-up visit in the two groups. BCVA improved during therapy and was stable up to their final visits in both groups. BCVA based on letters before and after treatment is shown in **Table 2**. BCVA improved in both groups (virtual reality: $P = .0001$, patching: $P = .001$), whereas the change in BCVA in the virtual reality group was higher than in the patching group ($P = .009$).

Among the non-compliant patients, the mean BCVA based on the responded line was 0.06 ± 0.04 logMAR (median: 0.05 logMAR; range: 0.00 to 0.10 logMAR) and 0.07 ± 0.03 logMAR (median: 0.05 logMAR; range: 0.05 to 0.10 logMAR) before and after amblyopia therapy, respectively ($P = .621$), and the corresponding values based on the responded letters were 39.8 ± 5.45 (median: 41; range: 33 to 47) and 39 ± 5.65 (median: 42; range: 32 to 45), respectively ($P = .76$).

In the virtual reality group, 2 children (8%) achieved complete recovery (BCVA = 0.1 logMAR) and their therapy was discontinued. Nineteen children (76%) continued their therapy by game playing and 4 children (16%) switched to patching therapy. These results were 2 (8%), 18 (72%), and 5 (20%) patients in the patching group, respectively. All patients were encouraged to continue their follow-up visits.

In the current study, all patients were observed an average of 50.71 ± 19.09 days (median: 45 days; range: 30 to 90 days).

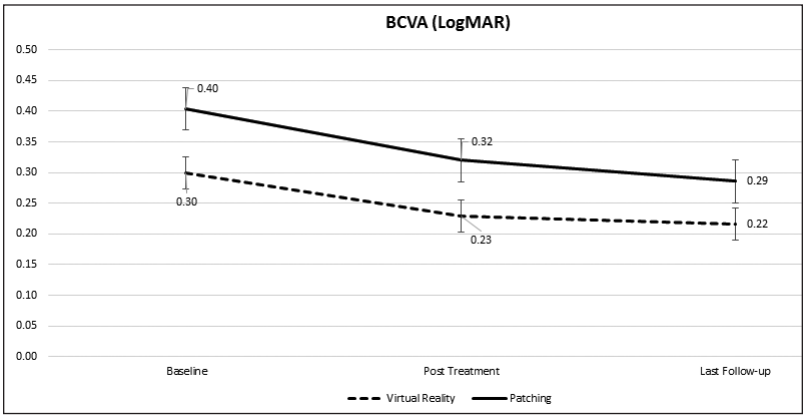

Figure 2. The mean best corrected visual acuity (BCVA) in logarithm of the minimum angle of resolution (logMAR) units of the virtual reality and patching groups at different follow-up visits.

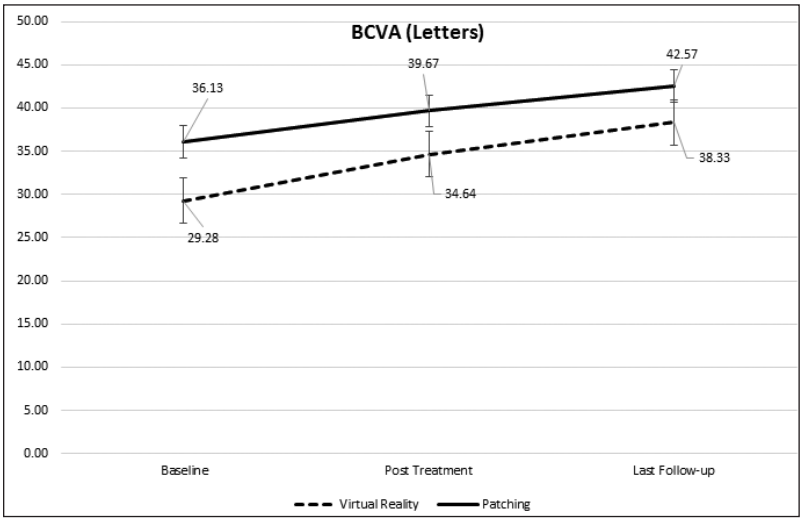

Figure 3. The mean best corrected visual acuity (BCVA) in Early Treatment Diabetic Retinopathy Study (ETDRS) letter of the virtual reality and patching groups at different follow-up visits.

Compliance

In this study, 4 children (16%) in the virtual reality group did not continue the study due to the lack of tolerance to the virtual reality headset or incomplete use of it, and 1 child in the patching group developed esotropia after patching. The four children were excluded from the study. Three other children were non-compliant with patching (16%). All children included in the current study completed more than 75% of their prescribed amblyopia treatment.

DISCUSSION

This randomized clinical trial was performed in children with unilateral functional amblyopia who were between 4 and 10 years old, to compare the visual outcome of virtual reality game playing with standard patch therapy.

Although the linear BCVA improvement was significant within each group ($P < .0001$ in both groups), there was no difference between these groups in terms of visual change of amblyopic eyes. BCVA by letter counting showed that it improved more in the virtual reality group than the patching group ($P = .002$).

The authors did not find any study that used letter counting. The current study is possibly is the first one in this regard.

The study of Rajavi et al[9] of 50 children that was based on I-BiT game playing through red/green glasses plus patching in the virtual reality group and only patching in the control group for 1 month reported more visual improvement in the virtual reality group ($P < .001$), even with short-term therapy. The study had the limitation of no sham games in the patching group. Another study by Rajavi et al[8] of 40 children that was based on I-BiT game playing in the virtual reality group and patching in the control group found no difference between the two groups, which is the same result as the current study with virtual reality game playing and patching.

There are few randomized clinical trial studies on children in the literature that compare I-BiT or virtual reality game play with patching.

In 2016, Kelly et al[12] reported the results of their cross-over study on 28 children aged 4 to 10 years by I-BiT game playing in the virtual reality group and patching in the control group both for 2 weeks, then changed the groups for another 2 weeks. Although BCVA improvement was greater in the virtual reality group in the first 2 weeks (P = .02), there was no difference at 4 weeks. The last result of this study is in line with the current study. The different primary findings could be attributed to the small number of patients and short-term amblyopia therapy. In a randomized clinical trial study of 385 children between 5 and 13 years old, Holmes et al[16] compared virtual reality game playing for 1 hour per day for 10 to 16 weeks (n = 190) with patching 2 hours per day (n = 195) for 4 to 16 weeks. Only 22% of the children performed more than 75% of the prescribed virtual reality time. BCVA improvement in the virtual reality game was not as good as patching. This could be due to less compliance in children in this group. Stimulating and motivating games are needed to raise the compliance of children.

BCVA improvement was 0.18, 0.28, and 0.3 logMAR at baseline for game playing, patching, and both, respectively, (P = .03). No superiority of binocular game playing over patching was observed, similar to the study of Rajavi et al.[8]

A randomized clinical trial by Herbison et al[18] of 75 children with strabismic amblyopia who were between 4 and 8 years old found no difference between DVD video clips, I-BiT shooter games, and no I-BiT games. Previous amblyopia therapy and more strabismic amblyopia could be the reason for their similarity.

In 2018, Manh et al[13] conducted a randomized clinical trial on 100 children between 13 and 17 years old who had both strabismic and anisometropic amblyopia. BCVA was compared between iPad I-BiT game playing and 2 hours of patching therapy per day. Only 13% of the patients completed more than 75% of the prescribed treatment. The difference in BCVA was not significant (P = .088) between groups. Low compliance was the main limitation of this study. In the current study, only children who completed more than 75% of the treatment time were included. Virtual reality game playing was controlled by online monitoring and patching was also controlled by the children's parents. In the current study, children who completed at least 75% of the total suggested time for each therapy were included.

Based on our results in the current study, virtual reality game playing was equal or superior to patching in the analysis of linear and letter BCVA, respectively. Therefore, applying this new amblyopia therapy is recommended.

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