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Research Article

4 Week's Report for Virtual Reality on Children Amblyopia Therapy

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Abstract

Purpose: To compare safety and Visual Acuity (VA) improvement in children with amblyopia treated with Virtual Reality (VR) plus spectacle correction and patching versus. spectacle correction and patching only.

Design: Multicenter randomized clinical trial.

Subjects: Twenty-eight subjects aged 4 to 12 years with amblyopia (20/400 to 20/25) from strabismus, refractive amblyopia, and visual deprivation amblyopia or combined types according to "Consensus of experts in the diagnosis of Amblyopia" in 2011 by Chinese Ophthalmology Society. Subjects were required to have never been treated or stopped treatment of patching over 4 weeks prior to enrollment. Subjects were randomly assigned to either VR games for 0.5 hour a day with patching and spectacles correction (12 subjects; VR group) or patching and spectacles correction (18 subjects; control group). Study follow-up visits were scheduled at 4, 8, and 13 weeks. This paper was only for 4 weeks.

Methods: Eligible subjects (mean baseline corrected logMarVA was 0.54±0.28) were randomly assigned to treatment for 4 weeks with the VR binocular therapy (prescribed for 30min per day 3 days per week) plus spectacle correction and patching if needed (n=12) or spectacle correction with patching if needed (n=16). Main outcome measures: Advent event in VR group and change in amblyopic-eye VA from baseline to 4 weeks, assessed by a masked examiner.

Results: Safety: All 28 children reported no severe adverse event or device failure rate during 4 weeks of treatment; There was no significant difference between the dropping BCVA of fellow eye between VR group and control group. There were 12 and 16 experimental groups and control groups in baseline group, respectively, 8 and 6 completed complete 4-week treatment and follow-up.

Effective: At Week 4, the VR group had a significant improvement in BCVA (logMarVA=0.4±0.35) compared to baseline BCVA (logMarVA=0.575±0.34) (P=0.029, t-test); The BCVA of the relatively good eyes in the experimental group improved but was not significant (logMarVA increased from baseline 0.169 to 0.115); At the baseline, there was no significant difference between the baseline and the control group, with the average BCVA of 0.575 to 0.34, 0.588 to 0.26 (P=0.914), and after 4 weeks of treatment, the VR group had an average BCVA (0.40±0.35, n=6), higher than the control group's average BCVA (0.525 ± 0.26, n=8), but the difference was not significant (P=0.458).

Conclusions: Caterna Virtual Reality was safe with a viable treatment option for the children amblyopia. Combining therapy of VR, spectacles and patching at baseline significantly improved the BCVA at 4 weeks.

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Introductions

The standard amblyopia treatment in the recent decades included refractive correction at first, followed necessary patching or atropine penalization to the sound eye [1].

A challenge of amblyopia treatment was that some amblyope after many years' standard therapies, still ended in residual amblyopia. And the rate was approximately 15–50%, who failed to achieve normal vision even after extended periods of treatment [2].

Besides baseline treatment ages, initiate severity, and combined pathology such as nystagmus, congenital cataract, or albinismus, another alternative explanation for failure to achieve normal vision was that standard treatments of recent years took too long and too boring to keep compliance with standard prescription. While compliance was significant related with the treatment results [3].

Moreover, standard amblyopia treatment had significant heterogeneity [4] no matter refraction adaptation period or occlusion periods. Following the standard treatment would also get other side effects, such as delay emmetropization. A Randomized Control Trial (RCT) study by Ingram et al. (n=287) [5], showed that those who were prescribed full correction from the age of 6 months and had good adherence to glasses wear, the effect on emmetropization was significantly delayed in comparison to those who were poor compliers or were not prescribed any refractive correction.

Amblyopia, a unilateral, less often bilateral condition with abnormal Best-Corrected Visual Acuity (BCVA) due to a mismatch between the images perceived with each eye, caused by early life abnormal visual experience such as visual deprivation, unequal refractive errors, or strabismus. Besides reduced BCVA, amblyopia had a plethora of visual deficits, including time delay of vision [6], reduced contrast sensitivity [7], and suppression [8]. And unilateral amblyopia affects two eyes [9].

In nature history, amblyopia, was a permanent visual impairment with a risk factor for 1.2% blindness [10]. For this reason, the early and sufficient treatment of this condition was crucial.

However, the mainstream standard therapies resulted with commonly mild residual amblyopia [11] with only 50%–85% achieving normal vision [12–15]. Moreover, clinical studies had elucidated that the time constant for successful patching was long: About 26% improvement for each 120h patching, as well as only 48% average concordance [14]. On the contrary, active therapy such as perceptual learning, and video games, would be more efficient to get the same improvement [16].

Binocular therapy had been used to treat amblyopia in children with some binocularity [17,18]. Images were presented dichoptically; high-contrast images were presented to the amblyopic eye and low-contrast images were presented to the fellow eye. However, the results were complicated with difference such as promising studies [19-22] or not as good as patching [23]. However, all those binocular therapies were compared to patching after sufficient optical correction time. And each study had different games and different adherence. To our best knowledge, there's no RCT study on Virtual Reality (VR) for children amblyopia with combining VR plus patching and optical correction at baseline.

VR was an innovative binocular approach to treating amblyopia with two screens on either eye. It could do the patching or dichoptic therapy by changing either screen's illumination, contrast, as well as speed of displaying sequence for the same or different image. And there was some adult amblyopia treatment study using VR with significant improving results [24]. And we wondered if the VR would facilitate patching and optical treatment to children amblyopia.

The purpose of the present randomized clinical trial was to establish whether treatment of amblyopia with VR dichoptic games (prescribed 0.5 hour per day for 13 weeks) plus spectacles wear (if needed) combined with patching was clinically safe and effective in BCVA of children amblyopia; As well as whether VR group would be superior than treatment only with spectacle wear (if needed) and patching of the sound eye in children age 4 to 12 years, with 20/25 to 20/200 BCVA of amblyopia eyes. And this paper focused the results on BCVA at 4 weeks for the above purpose.

Table 1: Study Inclusion and Exclusion Criteria.

ELIGIBILITY CRITERIA
The following criteria must be met for the patient to be enrolled in the study:
1. Age 4 to ≤12 years (including 4 years or 12 years old)
2. According to the Chinese Medical Association Ophthalmology Branch: Strabismus and Pediatric Ophthalmology Experts "Consensus of Amblyopia Diagnosis " (2011) as the standard to be diagnosed as amblyopia with abnormal vision than that of age-based norms, that is, caused by abnormal visual development due to strabismus, uncorrected refractive error or form deprivation, the BCVA of single eye or both eyes below age-based norms (Previously treated or untreated), or 2 eyes' vision acuity difference larger than 2 lines or more.
The normal minimum limit of vision acuity for children of different ages are as the followings:
• The normal minimum limit of vision acuity for children aged 4 to 5 years is 0.5(decimal vision acuity); • And the normal minimum limit of vision acuity for children aged 6 and over is 0.7(decimal vision acuity).
3. The subject's supervisor fully understood the purpose of the trial and sign an informed consent form; And the subject can cooperate with the whole treatment and related eye examinations.
EXCLUSION CRITERIA
1. Subjects suffered from tumors, heart disease, hypertension (blood pressure top limitation of children aged 4 to 6 years: 110/70 mmHg, blood pressure top limitation of children aged 7 to 12 years: 120/80mmHg), or epilepsy. 2. The subject had implanted electronic device, such as pacemaker. 3. The subject had or ever had a mental illness. 4. Any eye of the subject due to keratitis, conjunctivitis, internal turning eyelashes and other diseases leading to photophobia or continuing tears. 5. Subject suffered from vertigo, acrophobia or traumatic brain lesions. 6. The subject had congenital glaucoma, congenital ptosis, dacryocystitis, eye trauma history and other significant vision related lesions. 7. Subject received a masking therapy or a treatment instrument for amblyopia treatment before joining this study. 8. The subject participated in other clinical trials before joining this study. 9. For safety reason or patient benefit, the researchers forecast that the patient should not participate because of other conditions, such as suffering from a certain severe heart, liver or kidney disease.

Methods

The study was conducted at 3 clinical sites and approved by the Institutional Review Boards (IRB) of Jiangsu Province Hospital. All patients or guardians were informed about the study protocol and provided a written informed consent following the tenets of the Declaration of Helsinki. And each participant assented to subject as required. The study protocol was approved by the Ethics Committe of Jiangsu Province Hospital on January 8th, 2019. The study was registered on www.clinicaltrials.gov, under identifier NCT04238065. Eligibility criteria was listed in Table 1.

Study Visits and Testing Procedures

Visual acuity was measured in each eye with optimal refractive correction, and with cycloplegia at baseline by masked examiners. We used a consistent method throughout the study for each subject either VR protocol or the patching time (if applicable): 2 hours per day for both mild and moderate amblyopia while 6 hours per day for the severe amblyopia. Visual acuity was converted to the logarithm of the minimum angle of resolution (logMAR) scale. Additional testing at all study visits included measurement of adverse events related to the VR(Virtual Reality, Caterna, DOBOSO, item code: SJ-VRS2018) and defective medical device, as well as stereoacuity using Titmus Stereo Test/Wirt Circles and contrast vision using CSV-1000E. Follow-up visits occurred at 4, 8, and 13 weeks (±1 week) after randomization (±1 week), with the primary outcome visit at 13 weeks and secondary outcome at 4 and 8 weeks, respectively. At each visit, two groups were administered to subjects and their parents to assess any adverse event. And this paper only focused on vision acuity at baseline and 4 weeks.

Randomization and Treatment

Subjects were randomly assigned via the envelope random method with equal probability, using a permutated block design stratified by treatments and sites, to receive either Group of VR with patching and spectacles treatment or Group of patching with spectacles (subsequently referred to as the "VR" or "control" group, respectively).

Both groups were prescribed 2 hours or 6 hours of daily patching for BCVA >0.1 (decimal BCVA) or for BCVA ≤0.1 (decimal BCVA), respectively. The VR group was prescribed the VR games for 0.5 hour a day (divided into 2 sessions with 5 min interval each day), 3 days a week for continue 13 weeks.

There were 12 different video games were played with 12 Milli Second(ms) time delay setting to the fellow eye, that is to say, 12ms faster display to the amblyopia eye from the VR screen output. Subjects played the games by sequence and repeat the sequence within 12 games with the level of difficulty set at the subject's discretion. While the contrast of all games for the amblyopic eye was 100%, the contrast for the fellow eye was based on the interocular difference of logMAR BCVA and the BCVA of amblyopia eyes at baseline and automatically increased/decreased by 5-10% increments (with a lowest level of 10%), or left unchanged from the last contrast level, based on logMar BCVA from the latest BCVA record. The VR device automatically recorded the duration of game play, contrast and performance.

Statistical Analyses

Fisher's Exact test was analyzed to the adverse events of two groups in 4 weeks, as well as listed some special cases from VR.

A sample size of 28 subjects was selected to have 90% power with a 2-sided type I error of 5% to detect a treatment group difference at 4 weeks if the true difference in mean LogMar BCVA change, The primary outcome measure was the change in amblyopic-eye BCVA from baseline to that of 4 weeks. Only BCVA and Unaided Corrected Visual Acuity (UCVA) of amblyopia eyes and fellow eyes were compared, respectively; Independent t-test was performed to the 4 weeks' BCVA and UCVA to the VR group and control group, respectively. Also, the difference between 2 groups was compared in mean change in BCVA at 4 weeks from baseline VA. Analyses were conducted using SPSS version 22.0 (IBM Inc., Cary, USA). All P values were 2-sided.

Results

There were no severe adverse event or device failure (device failure was defined as VR hardware and software cannot be normally used or broken in the use period or study periods) rate reported of all 28 subjects (both groups) during the total 4 weeks. No 2 lines or worse BCVA reported in either group.

1 subject (16.67%) in the VR group and 3(37.5%) subjects in the control group tested 1 logMAR line worse in the sound eye at 4 weeks' follow-up compared with that at baseline (Fisher's Exact test, P=0.79) While no further follow-up was available in those 4 subjects (1 in the VR group and 3 in the control group).

And there were some uncomfortable issues happened in VR group from, such as complaining of heavy helmet (1 child), requiring cleaning and replacing touching sponge before wearing helmet (1 child) in the VR group while the control group had reported 2 uncomfortable of spectacles with patching issues (It was no significant difference, P=0.47). Neither diplopia, headache, eye fatique, tumble (fall), skin irritation, or blur was reported in both groups during all 4 weeks' follow-ups.

At Week 4th, the VR group had a significant improvement of almost 2 lines in BCVA compared to the baseline BCVA (logMarVA from 0.58±0.34 into 0.40±0.35, P=0.029, paired t-test), as shown in Table 2. BCVA of amblyopia from both groups significant improved at 4 weeks (P<0.0001); While the sound eyes of two groups significant worse BCVA for 4 weeks compared that of baseline (P=0.004). Among those sound eyes, BCVA of the fellow eyes in the VR group actually slightly improved but was not significant (LogMarVA from baseline 0.169 to 0.115 at 4th week, P=0.402); While BCVA from the fellow eyes in the control group worse but also no significant (LogMarVA from baseline 0.13±0.09 to 0.24±0.11 at 4th week, P=0.254).

Table 2: LogMar BCVA at 4 Weeks vs. Baseline from two therapy.

Groups	Number	Va (Mean±SD)	P (T-TEST)
BCVA Baseline vs.	27 vs. 14	0.55±0.29	<0.00001
BCVA at 4 weeks		0.40±0.28	
BCVA of AE VR group at Baseline vs.	12 vs. 6	0.58±0.34	0.029
BCVA of AE VR group at 4 weeks		0.40±0.35	
BCVA of NAE at Baseline vs.	27 vs. 14	0.10±0.10	0.004
BCVA of NAE at 4 weeks		0.16±0.17	
Baseline BCVA of AE from VR group vs.	16 vs. 12	0.58 ± 0.34	0.914
Baseline BCVA of AE from control group		0.59 ± 0.26	
BCVA at 4th week of AE from VR Group Vs.	8 vs. 6	0.40 ± 0.35	0.458
BCVA at 4th week of AE from Control Group		0.53 ±0.26	

Note: AE: Amblyopia Eyes; NAE: None-Amblyopia Eyes; VA: Visual Acuity; SD: Standard Deviation

At the baseline, there was no significant difference between the VR and the control group, with the average BCVA of 0.58±0.34, 0.59±0.26 (P=0.914), respectively; And after 4 weeks of treatment, the VR group had an average BCVA (0.40±0.35, n=6), better than that of control group's average BCVA (0.53±0.26, n=8), but the difference was not significant (P=0.458).

Baseline Characteristics

Between September 2019 and Feb 2020, 28 participants were randomly assigned to the VR group (n=12) or to the control group (n=16). Baseline characteristics were similar in the two groups (Table 3).

Table 3: Baseline Characteristics of Randomized Participants.

	VR Group	Control Group
	(n=11)	(n=16)
	N(%)	N(%)
Age at Enrollment: Mean(SD)	4~12(masked)	4~12(masked)
Distance Amblyopic-Eye Best Corrected Visual Acuity(Decimal Vision Acuity)		
0.1	2(18.18%)	3(18.75%)
0.12	0	0
0.15	1(9.09%)	0
0.2	1(9.09%)	1(6.25%)
0.25	0	0
0.3	0	5(31.25%)
0.4	3(27.27%)	4(25.00%)
0.5	1(9.09%)	3(18.75%)
0.6	2(18.18%)	0
0.8	1(9.09%)	0
Mean (SD) LogMAR Mean± SD	0.50±0.32	0.59±0.26
Mean Decimal Equivalent	0.3	0.2
Distance Fellow-Eye Visual Acuity Mean (SD) ± SD	0.05±0.08	0.13±0.11
Mean Decimal Equivalent	0.8	0.8
Interocular Difference		
Mean±SD (Lines)	5.18±2.30	4.53±2.30
Baseline Stereoacuity (Seconds of Arc)		
No Stereoacuity	7(58.33%)	10(62.5%)
900	0	1(8.3%)
100	1(8.3%)	0
40	1(8.3%)	0
Median (Range)	No Stereoacuity	No Stereoacuity
Amblyopia cause		
Strabismus	4(33.33%)	9(56.25%)
Anisometropia	1(8.33%)	1(6.25%)
Refractive error	3(25%)	1(6.25%)
Visual-deprivation	0	1(6.25%)

LogMAR: Logarithm of the Minimum Angle of Resolution; SD: Standard Deviation

Table 4: Comparing 2 eyes' logMar BCVA Difference between VR group and control group.

	Group	number	Mean	SD	P value
Base difference 79	VR	11	5.182	3.2502	0.579
	Control	16	4.531	2.4046	
4w Difference	VR	6	1.83	2.137	0.411
	Control	8	2.88	2.416	

Table 5: Distribution of Amblyopic-eye Visual Acuity at 4 Week.

	VR Group (N=6)		Control Group (N=8)	
	N	%	N	%
Distribution of Amblyopic-eye Visual Acuity (Decimal Vision Acuity)				
0.1	0	0	1	12.50%
0.2	0	0	2	25%
0.25	1	16.67%	0	0
0.3	0	0	1	12.50%
0.4	1	16.67%	1	12.50%
0.5	0	0	1	12.50%
0.6	1	16.67%	2	25%
0.8	2	33.33%	0	0
1	1			
1	1	16.67%	0	0
Mean LogMar BCVA±SD (P=0.045)	0.23±0.23		0.53±0.26	
Distribution of Amblyopic-eye Visual Acuity Change				
≥3 lines better	3	50.01%	3	37.50%
2 lines (10–14 letters) better	0	0	2	25%
1 line (5–9 letters) better	0	0	1	12.50%
0 line (within 4 letters)	2	33.33%	1	12.50%
1 line (5–9 letters) worse	1	16.67%	1	12.50%
2 lines (10–14 letters) worse	0	0	0	0
≥ 3 lines (≥ 15 letters) worse	0	0	0	0
Mean±SD (P=0.490)	3.57±4.58		1.75±1.67	
Participants with Amblyopic-eye Improvement of ≥2 Lines from Baseline	3	42.86%	4	44.44%
Participants with Amblyopia Resolution	1	16.67%	0	0

SD: Standard Deviation; CI: Confidence Interval; Amblyopia resolution was defined as having an amblyopic-eye visual acuity of 20/25 or better and an interocular difference within 1 line.

Visit Completion

The 4-week primary outcome was completed by 6(50%) in the VR group and 8(50%) in the control group. M asking of the visual acuity testers was maintained at 100% and 100% of visits for the VR group and control groups, respectively.

Amblyopic Eye Visual Acuity

At 4 weeks, after adjusting for baseline VA, mean amblyopic eye VA improved from baseline by 3.35 lines in the VR group and only 1.65 lines in the control group. The difference between VR and control group was 1.05 and 0.65 lines (p=0.411) at 4 weeks and at baseline, respectively; favoring VR group (Table 4). But neither baseline difference nor 4 weeks' difference was statistically different between two groups. (P=0.579, P=0.411, respectively).

At 4 weeks, amblyopic eye VA improved ≥2 lines from baseline for 3(50.01%) and 3(37.50%) participants in the VR and control groups, respectively. One amblyopia eye in VR group achieved amblyopia resolution (VA of 20/25 or better and within 1 logMAR line of the fellow eye) while no subject achieved amblyopia resolution in the control group.

Discussion

VR therapy was as same safe as the treatment of control group with spectacles and patching from the adverse events form the 4 weeks' records.

It could be following points to explain the better BCVA and significant better improvement VA lines from VR combing therapy. Firstly, it aimed at initiate amblyopia treatment or those stopped patching more than 4 weeks for any reason before the enrollment. And all the participants were combined spectacles and patching treatment without optical adaptation at baseline. Those who never got optical therapy but with refractive error, would significant improve their BCVA at first several weeks, even for elder children [25]. Secondly, there were 12 different VR games with richly detailed incredibly lifelike to improve compliance especially for children. And compliance was the key to success [26]. And thirdly, we created 12ms time delay for the fellow eyes with individually settings of contrast balance between amblyopia eyes and the fellow eyes. And amblyopia eyes in adults had reported significant time delay [27].

Mean improvement in amblyopic-eye VA with VR treatment over our 4-week study was much better in magnitude (approximately 3.35 logMAR lines) to those previously reported mean visual acuity improvements of 0.15 to 0.20 logMAR (1.5–2 Snellen lines) in amblyopic children in non-randomized studies and RCT [28-31] prescribing total 9-10 hours of binocular treatment for 2~4 weeks [17]. It partly owed to these previous studies of binocular iPad treatment included only the same or a few games [Tetris, Dig Rush] with low compliance. While this Caterna VR included 12 different games. Its difference might be partly due to higher compliance of VR with more choices of VR games besides initiate combing with spectacles adaptation and patching at baseline.

Our total VR therapy time was 30 min *3 time/week *4 weeks=360 min for those children with spectacles and patching. Compared to those adult amblyopia VR therapy study [24] reported 40 min *8 sessions=320 min VR therapy for 17 adults with amblyopia, the total therapy time was similar; And both studies got significant BCVA improvement in about an accumulative 350 min therapy while our study got much more lines improvement at the 4 week from the baseline (3.35 lines); It could be the ages and combing optical adaptation difference.

And our creating VR display was 12 ms difference between amblyopia eyes and the fellow eyes. It was reported that adult amblyopia had average value of about 20 ms time delay from the amblyopia eye to the faster fellow eye [27]. Whether the VR settings of intraocular time difference helped amblyopia treatment, especially for children, or at least, improved the lazy eyes' priority, requiring the further investigation.

In this study, 50% subjects dropped out of the 4 weeks' amblyopia treatment with BCVA records for either group, which was due to the COVID-19 pandemic in 2019 winter and continued to 2020 worldwide. All Chinese hospitals were listed high dangerous to the public to avoid the COVID-19 to participants.

And the reasons why we had not found a superior efficacy of VR treatment were the limited timing and data for the final assessment. Comparing to other amblyopia dichoptic therapy, we took less frequency (3 times per week vs each day; 30 min vs 1 hours; 4 weeks vs 16 weeks), but intense combined therapies to get total subjects significant results.

Active therapy had reported better outcome [25]. One of our amblyopia children in VR group achieved 1.0 decimal vision at 4 weeks (16.67%) while the control had none resolved. We also found there were participants in either group who failed to progress in contrast to the fellow eye; And there was LogMar BCVA drop case in either group suggesting that the contrast starting point was not optimally set for each participant, and that the initial contrast should be based on an individual measurement of suppression rather than the arbitrary 50%.

In the current preliminary study, we have used a protocol of treatment of 39 sessions of treatment during 4 weeks (3 sessions/weekly, each session last 30 minutes with 5 min break in the middle). The reason for the selection of this protocol was based on the consideration of China amblyopia therapy routine in the past 20 years; And combing therapy with better compliance if the treatment was not so long [32]. Moreover, on previous active therapy such as perceptual learning experiments, it demonstrated that the greatest improvement with perceptual training was achieved in the first eight sessions of treatment [33-34].

Our limitation exited in small number, limited times, and high rate of dropout. Other complicated issue was as without refractive adaptation and patching compliance. The former increased the fail rate, while the latter of combing therapy might increase the compliance and effectiveness at baseline, especially with VR.

Future studies must be conducted to investigate the best treatment protocol with VR on efficacy time, contrast settings, time delay design, video details and amblyopia children's feedback.

In conclusion, 4 weeks' combing therapy with Caterna VR, it was safe and effective for 4~12 amblyopia children.

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