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NEIVATECH pilot study: immersive virtual reality training in older amblyopic children with non-compliance or non-response to patching

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Immersive virtual reality (VR) is recently being explored as a therapeutic alternative for the treatment of amblyopia. This pilot study aimed to evaluate the preliminary efficacy, safety, usability and satisfaction obtained with the use of a novel VR system (NEIVATECH) to provide binocular vision training in previously treated older amblyopic children with non-compliance or non-response to patching. A prospective, multicentre, open-label, single-arm, pilot study was conducted in which the intervention under study was 9 h of therapy with the NEIVATECH system, distributed in 18 half-hour sessions spread over 1 month. A comprehensive visual assessment was conducted before and after the intervention, and at the end of the intervention the safety and usability of the system and patient satisfaction were evaluated. After therapy, statistically significant differences were observed in the near best-corrected visual acuity (BCVA) of the dominant ($p = 0.022$) and non-dominant ($p = 0.022$) eye, in stereopsis based on the Binocular Function Score ($p = 0.045$) and in the break ($p = 0.012$) and recovery ($p = 0.009$) points of negative fusional vergence for distance vision. The safety and usability of the system and patient satisfaction with the therapy were adequate. These findings support further investigation of this treatment option in future studies incorporating a control group with which to compare the results obtained. Trial registration: NCT04819386.

Keywords Amblyopia, Virtual reality, Perceptual learning, Dichoptic training, Gamification

Amblyopia is defined as a decrease in the best-corrected visual acuity (BCVA) of one or, less commonly, both eyes, attributable to abnormal binocular experience in early life[1]. This abnormal binocular experience may be caused to the existence of a different refractive error in each eye (anisometropia), the presence of abnormal binocular interaction (strabismus), or visual deprivation due to congenital cataract or ptosis[2–6]. Currently, the pooled overall prevalence of amblyopia is estimated to be 1.75% (95% CI: 1.62–1.88), and while approximately 100 million people were affected in 2019[7], these numbers are expected to increase to 175.2 million people affected in 2030 and 221.9 million people affected in 2040, respectively[8].

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Clinically, amblyopia is characterised by deficits in several aspects of spatial vision, such as visual acuity (VA), Vernier acuity and contrast sensitivity (CS), accompanied by a total or partial loss of binocular vision. In addition to these deficits, it has been observed that higher functions of visual processing such as global shape[9], position[10], orientation[11] or motion[12] may also be affected, suggesting that neural deficits first found in primary visual cortex (V1) may amplify to extrastriate visual areas (V2, V3, V4 and V5/MT+). These deficits have a significant impact on the child's physical, social and scholastic competence[13], as they can compromise a wide range of skills such as reading rate[14], visual attention and visual search[15], eye-hand coordination movements[16], fine motor skills[17], reaching[18,19] or balance and gait control[20,21].

The initial phases of amblyopia treatment consist of correcting any factors that may degrade the quality of visual input received by the non-dominant eye and providing the necessary refractive correction to maximise the quality of the visual stimulus. If visual deficits persist after applying these measures, occlusion or penalisation therapies are prescribed, which aim to force the use of the non-dominant eye to stimulate the formation of functional neural connections at V1[22]. These treatments have been shown to be effective in improving BCVA in the non-dominant eye, but have important limitations.

One of these limitations is that the BCVA gains they produce occur very slowly. It has been estimated that about 170 h of patching are required to achieve a 2 logarithm of the minimum angle of resolution (logMAR) line improvement in amblyopic children aged 4 years and > 200 h to achieve a similar improvement in amblyopic children aged 6 years[23], while up to 400 h may be required to achieve this improvement in amblyopic children aged 7 years and older[24]. Another important limitation of these methods is that prolonged treatment periods may not result in normal VA in a considerable proportion of patients (15–50%)[25–28]. In addition, monocular treatment methods themselves can lead to reduced binocular vision and stereopsis and, in the case of occlusion therapy, also cause psychosocial problems that hinder therapeutic adherence[29,30].

To overcome these limitations, several attempts have been made in recent years to develop more effective treatment approaches for amblyopia, mainly through perceptual learning[31–35] and dichoptic training[36–40] techniques. During perceptual learning tasks, the patient is provided with an active visual experience that requires attention and action. However, this can lead to boredom, as the patient is exposed to the same visual stimuli repeatedly, which limits adherence and makes its application in daily clinical practice unfeasible. To overcome this drawback, different authors have combined perceptual learning tasks with game elements and dynamics to involve young children in their performance and motivate them to progress. This, coupled with the presentation of different elements of the same visual scene to each eye in a way that favors the non-dominant eye (i.e. dichoptic training), is a promising treatment modality that has been the subject of extensive research over the last years[41–45].

More recently, immersive virtual reality (VR) has emerged as a useful complementary tool for this line of research, due to the possibility of head-mounted displays (HMDs) to provide different visual content to each eye simultaneously[46]. These systems are mostly well tolerated by patients for short time exposures and do not produce significant long-term adverse effects, although their use has been associated with cyber-sickness and some visual complications[47,48]. The use of these systems can be attractive to children and also avoids the social stigma of patching, the side effects of atropine and the risk of reduced binocular vision of monocular treatment approaches, as the vision of the dominant eye is not occluded or degraded during therapy. In this context, this study aimed to evaluate the preliminary efficacy of a novel VR system (NEIVATECH) designed to provide binocular vision training in previously treated older amblyopic children with non-compliance or non-response to patching, as well as to determine the safety and usability of the system and patient satisfaction with the therapy.

Methods

Study design

A prospective, multicentre, open-label, single-arm pilot study was conducted in which 9 h of therapy with the NEIVATECH system (TRC, Madrid, Spain), distributed in 18 sessions of 30 min each, spread over 1 month, were provided to previously treated older amblyopic children with non-compliance or non-response to patching. For practical reasons, all therapy sessions with the NEIVATECH system took place on weekdays, excluding weekends and public holidays, and as a minimum necessary requirement, attendance at least 3 times per week was required.

Study setting

Patient recruitment and comprehensive visual assessments were performed in the Ophthalmology Departments of the University Clinical Hospital of Valladolid, the Río Hortega University Hospital of Valladolid and the Optometric Clinic of the University of Alicante, while the therapy sessions with the NEIVATECH system took place at the Faculty of Medicine of the University of Valladolid and at the Optometric Clinic of the University of Alicante.

Study population

Children older than 7 years, with an established diagnosis of amblyopia and non-compliance or non-response to patching at the discretion of the physician were selected for this study. Specifically, the following eligibility criteria were established:

Inclusion criteria

- BCVA in the non-dominant eye ≤ 0,1 logMAR.
- Interocular difference of BCVA ≥ 1 logMAR line.

- Interocular difference of spherical equivalent ≥ 1 D or astigmatism difference between the corresponding meridians of both eyes ≥ 1.5 D.
- Intermittent strabismus or microstrabismus (angle of deviation < 10 PD) with some degree of fusion.
- Use of best refractive correction for at least 2 months prior to inclusion.

Exclusion criteria

- Active eye disease.
- History of ocular surgery.
- Interpupillary distance (IPD) < 56 mm.
- Persistent strabismus or strabismus with an angle of deviation ≥ 10 PD.
- History of photosensitive epilepsy or neurodevelopmental disorders.
- History of previous treatment for amblyopia for at least 2 months prior to inclusion.

Study intervention

The NEIVATECH system has been developed collaboratively by the Applied Clinical Neurosciences Research Group of the University of Valladolid, the Optics and Visual Perception Group of the University of Alicante and the company TRC (Madrid, Spain) as a Serious Game (SG) to provide binocular vision training to amblyopic children in an interactive and immersive VR environment. This system consists of several mini-games combining the concepts of perceptual learning and dichoptic training with different game elements and dynamics. The perceptual learning task integrated in the system consists of discriminating the orientation of Gabor patches that were only presented to the non-dominant eye in a binocular background, the main novelty of this system being the real-time modification of its contrast through the Best PEST (Parameter Estimation by Sequential Testing) psychophysical method[49]. This method is based on the procedure described by Taylor and Creelman[50], and monitors the user's performance on a given task by dividing the number of trials to which he/she responds correctly by the total number of trials to obtain a numerical score between 0 (all wrong) and 1 (all correct). This score is then compared to a target accuracy to modify the difficulty level of the task, so that if the user's performance is too high, the task becomes more difficult (the contrast of the Gabor patches decreases), and vice versa. Each time the difficulty of the task is modified, the accuracy is reset and the test is restarted. Considering this, the maximum contrast of the stimuli presented was 100%, while the minimum contrast corresponded to the patient's contrast threshold, determined in an initial test performed before accessing each mini-game. In each mini-game, the patient had to aim (using the HMD controller) and "shoot" (by pressing the trigger of the HMD controller) at those Gabor patches whose stripes matched those of a reference Gabor patch located in the centre of the screen. The diameter of the presented Gabor patches was 3.5 cm, subtending an angle of 3° at a distance of 40 cm, and their spatial frequency could vary between 0.5, 1, 1.5 and 3 cpg. The mean luminance of the stimulus and background was set at 50 cd/m^2, and the orientation of the Gabor patch stripes was set randomly, varying with each response provided by the patient. The mini-games that made up the system were developed with the Godot game engine and run through SteamVR software on a PC with an Intel® CoreTM i5-12400 F processor, an NVIDIA GeForce RTX 3060 graphics card, a Windows 10 OS and 16 GB RAM. The HMD used for the therapy was the HTC VIVE Pro Eye 2 (HTC Corporation, New Taipei, Taiwan). Screenshots of each mini-game have been previously published[51,52]. Importantly, prior to its use in amblyopic children, the safety and acceptability of exposure to the system was tested in healthy individuals, with preliminary results supporting the conduct of this pilot study[53].

Study outcome measures

Primary outcome measures

As primary outcome measures, the following visual parameters were assessed before and after therapy: monocular BCVA for both near (40 cm) and distance (4 m) vision (assessed with a logarithmic Landolt "C" eye chart), monocular CS (assessed with the CSV-1000E test), stereopsis (assessed with the TNO stereo test), monocular accommodative facility (assessed with the ± 2D flipper test), near point of convergence break and recovery points (assessed with an optotype of 2 logMAR lines larger than the BCVA of the non-dominant eye) and positive and negative fusional vergence break and recovery points for both near (40 cm) and distance (4 m) vision (assessed with a prism bar). Cycloplegic refraction was another study measure but was determined as part of the ophthalmological assessment and not at the study visits themselves.

Secondary outcome measures

As secondary outcome measures, the safety and usability of the system and patient satisfaction with the therapy were assessed after therapy. Specifically, the Simulator Sickness Questionnaire (SSQ)[54] was used to assess system safety, the System Usability Scale (SUS)[55] was used to assess system usability, and the User Satisfaction Evaluation Questionnaire (USEQ)[56] was used to assess patient satisfaction with therapy. These assessment methods were selected because they were standardised, but it should be noted that some of their items incorporated sophisticated language, so their meaning had to be conveyed by the research staff into clear and simple terms, understandable to the children (e.g. 'integrated' = 'mixed', 'complex' = 'difficult', 'rehabilitation' = 'healing', 'cumbersome' = 'uncomfortable', etc.).

Ethical considerations

This study has been conducted in accordance with the ethical principles for medical research involving human subjects of the Declaration of Helsinki and has been approved by the Drug Research Ethics Committee of the Valladolid East Health Area (Ref.: CASVE-NM-21-516). Prior to any testing and after explaining the possible

consequences of the study, written informed consent was obtained from the parents or legal guardians of each child participating in the study.

Statistical analysis

The distribution of the data was described with means and their variability with standard deviations. To test the normality of the data, the Shapiro-Wilk test was used. To compare the means of the visual parameters assessed before and after therapy, the paired T-test was used for variables following a normal distribution and the Wilcoxon signed-rank test for variables following a non-normal distribution. To include those patients with complete suppression and no measurable stereopsis before the start of the therapy in the analysis of the TNO stereo test scores, the Binocular Function Score (BFS)[57] was applied, which is a validated scale based on common clinical tests that provides a more complete analysis of binocular outcomes. The frequency of responses to the different questionnaires administered after therapy was studied by means of graphs. Statistical significance was set at a p-value < 0.05 and all analyses were performed with the statistical package R 4.3.2.

Results

During the 18-month recruitment period of the study (September 2022 to February 2024), a total of 12 previously treated older amblyopic children with non-compliance or non-response to patching (6 boys, 6 girls, 11.25 ± 2.45 years) were enrolled. Of these, 8 were recruited in Valladolid and 4 in Alicante. All patients had a history of previous treatment for amblyopia with at least patching for several years, but it is difficult to attribute the lack of response to treatment to non-compliance or treatment failure per se. Importantly, all included patients complied with the study protocol and the established visiting regimen and none dropped out of the study during its course. Descriptive data for the sample are provided in Table 1.

Primary outcome measures

The visual parameters assessed before and after therapy are shown in Table 2.

After therapy, statistically significant differences were observed in the near BCVA of the dominant ($p = 0.022$) and non-dominant eye ($p = 0.022$), in stereopsis based on the BFS[57] ($p = 0.045$), and in the break ($p = 0.012$) and recovery points ($p = 0.009$) of negative fusional vergence for distance vision. In other visual parameters of importance, such as distance BCVA of the dominant and non-dominant eye, there was a trend towards improvement, but it did not reach statistical significance. Specifically, using the method described by Stewart et al.[58], which allows the calculation of the proportion of the change in vision obtained after therapy, an average improvement of 24% in near BCVA and 15% in distance BCVA was observed in this study. It is also noteworthy that, of three participants in whom stereopsis could not be measured before therapy, this only occurred in one individual after therapy.

Age (y/o)	Sex	Refraction (D)	Cover test (PD)	Worth	TNO
12	M	RE + 0.00 LE + 2.75	Near 0 Distance 0	Near 4 Distance 4	120”
12	M	RE + 5.50 -3.00 180º LE + 0.75–0.75 180º	Near RE 2XT’ Distance RE 16 F/T; RE/LE 4 HT	Near 4 Distance 3	No stereo
10	F	RE + 0.50 LE + 6.00–1.00 180º	Near LE 6ET’ Distance LE 6ET	Near 4 Distance 4	No stereo
12	F	RE + 2.25–0.75 180º LE + 5.75–1.75 180º	Near 2XF’ Distance 0	Near 4 Distance 4	60”
8	F	RE SRx (-7.00): +0.00–2.00 15º LE + 0.75–1.25 10º	Near 12EF’ Distance 4EF	Near 4 Distance 3	1980”
15	M	RE + 5.25–1.50 5º LE + 8.00 -1.75 180º	Near LE 30 F/T’ Distance LE 14 F/T	Near 4/2 Distance 2	No stereo
10	M	RE + 4.50–0.75 180º LE + 0.50 − 0.25 180º	Near 2EF’ Distance 0	Near 4 Distance 3	240”
12	M	RE + 2.00 -0.75 155º LE + 0.50	Near 10EF’ Distance 4EF	Near 4 Distance 3	120”
14	F	RE + 0.75 − 0.50 180º LE + 4.25 -1.00 180º	Near 8XF’ Distance 2XF	Near 4 Distance 4	120”
8	F	RE + 4.50–1.50 180º LE + 1.50–0.75 110º	Near 4XF’ Distance 2ET	Near 4 Distance 4	480”
8	F	RE + 3.25 LE + 0.00	Near 4XF’ Distance 0	Near 4 Distance 4	120”
14	M	RE + 5.25 LE + 8.00 -1.25 160º	Near 2XF’ Distance 0	Near 4 Distance 4	240”

Table 1. Characteristics of the study sample. *D* Diopters, *EF* Esophoria, *ET* Esotropia, *F* Female, *F/T* Phoria/Tropia, *HT* Hypertropia, *LE* Left eye, *M* Male, *OR* Over-Refraction, *PD* Prismatic diopters, *RE* Right eye, *XF* Exophoria, *XT* Exotropia, *y/o* Years old.

Visual parameter	Before therapy	After therapy	*p* value
SE NE (D)	3.16 ± 3.87	3.28 ± 3.93	0.335
SE DE (D)	1.53 ± 0.50	1.56 ± 0.75	0.714
Near BCVA NE (logMAR)	0.46 ± 0.37	0.34 ± 0.26	0.022*
Near BCVA DE (logMAR)	0.06 ± 0.06	-0.03 ± -0.04	0.022*
Distance BCVA NE (logMAR)	0.43 ± 0.29	0.36 ± 0.29	0.308
Distance BCVA DE (logMAR)	-0.03 ± -0.08	-0.05 ± -0.07	0.397
CS NE (3 cpd)	1.69 ± 1.63	1.77 ± 1.85	0.315
CS NE (6 cpd)	1.75 ± 1.70	1.90 ± 1.91	0.067
CS NE (12 cpd)	1.40 ± 1.47	1.50 ± 1.54	0.154
CS NE (18 cpd)	1.03 ± 1.03	1.02 ± 0.96	0.866
CS DE (3 cpd)	1.80 ± 1.78	1.91 ± 1.93	0.133
CS DE (6 cpd)	2.02 ± 1.99	2.11 ± 2.14	0.055
CS DE (12 cpd)	1.67 ± 1.69	1.75 ± 1.76	0.183
CS DE (18 cpd)	1.18 ± 1.25	1.33 ± 1.25	0.083
BFS (log arcsec)	2.81 ± 2.38	2.41 ± 2.23	0.045*
AF NE (cpd)	7.29 ± 7.75	7.95 ± 11.00	0.475
AF DE (cpd)	12.58 ± 13.50	13.68 ± 16.00	0.556
NPC break point (cm)	5.58 ± 4.00	4.36 ± 3.00	0.310
NPC recovery point (cm)	7.71 ± 6.00	8.33 ± 6.50	0.575
Near PFV break point (PD)	16.70 ± 14.00	12.90 ± 12.00	0.101
Near PFV recovery point (PD)	11.80 ± 9.00	8.54 ± 6.00	0.247
Distance PFV break point (PD)	11.45 ± 12.00	11.63 ± 12.00	0.918
Distance PFV recovery point (PD)	8.30 ± 9.00	6.72 ± 8.00	0.617
Near NFV break point (PD)	19.27 ± 16.00	12.20 ± 10.00	0.087
Near NFV recovery point (PD)	12.80 ± 13.00	7.60 ± 8.00	0.075
Distance NFV break point (PD)	12.63 ± 8.00	6.40 ± 6.00	0.012*
Distance NFV recovery point (PD)	5.00 ± 4.00	3.60 ± 4.00	0.009*

Table 2. Comparison of visual parameters assessed before and after therapy. *AF* Accommodative facility, *BCVA* Best-corrected visual acuity, *BFS* Binocular Function Score, *cm* centimeters, *cpd* cycles per degree, *CS* Contrast sensitivity, *D* Diopters, *DE* Dominant eye, *log arsec* logarithm of arcseconds, *logMAR* logarithm of the minimum angle of resolution, *NE* Non-dominant eye, *PD* Prismatic diopters, *PFV* Positive fusional vergence; *NPC* Near point of convergence, *NFV* Negative fusional vergence, *SE* Spherical equivalent. * $p < 0.05$.

Secondary outcome measures

System safety

In the SSQ administered after therapy to assess system safety, three patients reported severe symptoms (difficulty in focusing, difficulty in concentrating and burping) and seven moderate symptoms, including headache ($n = 1$), "fullness" of the head ($n = 3$), fatigue ($n = 1$), sweating ($n = 2$) and eyestrain ($n = 2$). The remaining symptoms reported by patients were mild and comprised most of those included in the SSQ (Table 3).

System usability

Patients' perceptions of system usability on the SUS scale were generally good, with the exception of item 1, where only 25% of patients agreed or strongly agreed that they would like to use the system frequently. However, all found it easy to use, with over 80% considering that its functions were well integrated, that most people would learn to use it very quickly and that they felt very confident using it. Similarly, most patients disagreed or strongly disagreed that the system was unnecessarily complex, that they needed to learn a lot of things to use it and that they needed expert support to use it. Lastly, more than 40% of patients strongly disagreed or disagreed that the system was too inconsistent or very cumbersome to use (Fig. 1).

Patient satisfaction

Patient satisfaction after therapy was assessed using the USEQ, with equally good results. Among these, all agreed or strongly agreed that they were able to control the system, more than 90% felt that they had been successful in using the system and that the information provided by the system was clear and 75% reported that they had enjoyed their experience with the system. On the other hand, 65% of patients stated that they disagreed or strongly disagreed that they felt discomfort during their experience with the system. Lastly, more than 80% of patients felt that the system would be helpful in their rehabilitation (Fig. 2).

Symptom	None (%)	Mild (%)	Moderate (%)	Severe (%)
General discomfort	83.33	16.66	0.00	0.00
Fatigue	41.66	33.33	25.00	0.00
Headache	58.33	33.33	8.33	0.00
Eyestrain	41.66	41.66	16.66	0.00
Difficulty focusing	66.66	25.00	0.00	8.33
Increased salivation	83.33	16.66	0.00	0.00
Sweating	58.33	25.00	16.66	0.00
Nausea	91.66	8.33	0.00	0.00
Difficulty concentrating	83.33	8.33	0.00	8.33
"Fullness" of the head	33.33	41.66	25.00	0.00
Blurred vision	75.00	25.00	0.00	0.00
Dizzy (eyes open)	83.33	16.66	0.00	0.00
Dizzy (eyes closed)	83.33	16.66	0.00	0.00
Vertigo	100.00	0.00	0.00	0.00
Stomach awareness	83.33	16.66	0.00	0.00
Burping	91.66	0.00	0.00	8.33

Table 3. Proportion of patients reporting mild, moderate, severe or no symptoms on the SSQ after therapy.

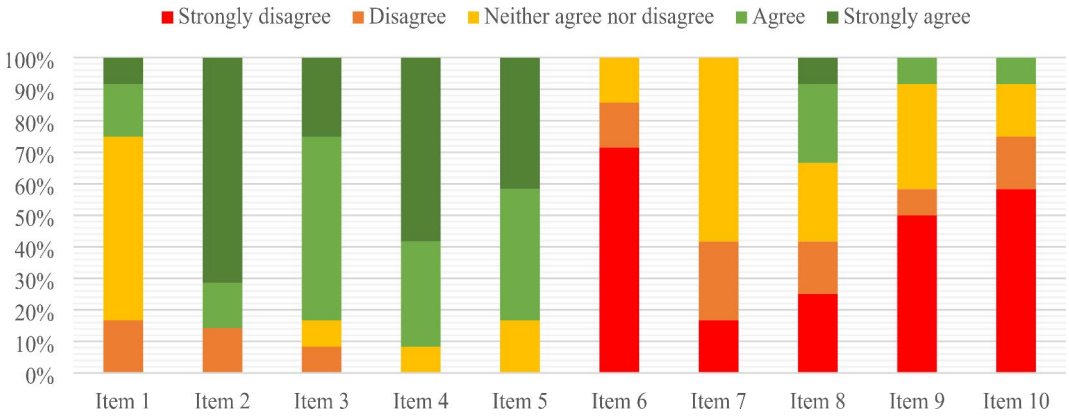

Fig. 1. Proportion of responses given by patients to the SUS after therapy. Item 1 = I think that I would like to use this system frequently; Item 2 = I thought the system was easy to use; Item 3 = I found the various functions in this system were well integrated; Item 4 = I would imagine that most people would learn to use this system very quickly; Item 5 = I felt very confident using the system; Item 6 = I found the system unnecessarily complex; Item 7 = I thought there was too much inconsistency in this system; Item 8 = I found the system very cumbersome to use; Item 9 = I think that I would need the support of a technical person to be able to use this system; Item 10 = I needed to learn a lot of things before I could get going with this system.

Discussion

The NEIVATECH system has been designed as a SG to provide binocular vision training to amblyopic children by complementing the concepts of perceptual learning and dichoptic training with game elements and dynamics in an interactive and immersive VR environment. To our knowledge, this is the first VR vision training system that employs the Best PEST psychophysical method[49] for real-time modification of the contrast of visual stimuli presented to the amblyopic eye during therapy, guiding the patient's responses around their contrast threshold and thus providing a personalised treatment option. In addition, it is also the only system of its kind to use the HTC VIVE Pro Eye 2 HMD for training provision, which is another novel aspect to consider.

For the purpose of this study, previously treated older amblyopic children with non-compliance or non-response to patching were recruited in accordance with other pilot studies[59–62]. These patients have a worse prognosis than those with no history of previous treatment for amblyopia, but were recruited based on the assumption that they were more likely to participate. Although the sample size used in this study may appear small at first glance, it is in line with those used in other pilot studies evaluating the efficacy of other VR-based systems for the treatment of amblyopia[59,60,62–66]. In contrast to other studies, patients with an interocular difference of BCVA ≥ 1 logMAR line were allowed to be included, as this cannot be explained by the test-retest reliability of the assessment method used[67] and therefore remains amblyopia and can be improved. Patients with

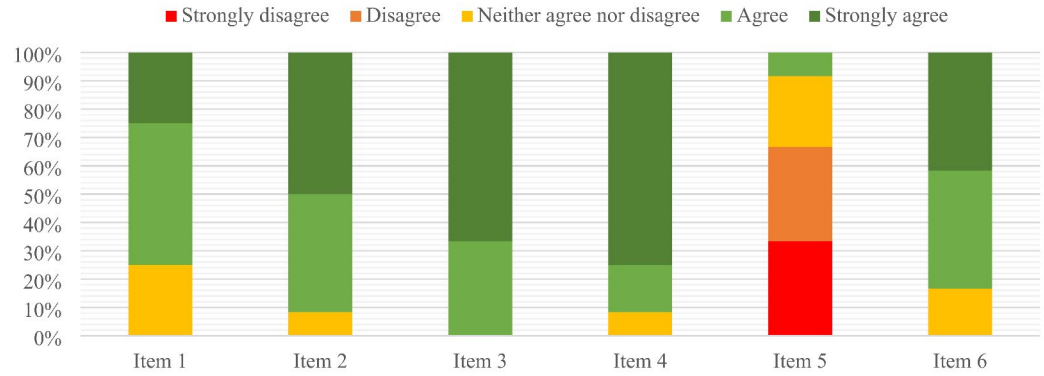

Fig. 2. Proportion of responses given by patients to the USEQ after therapy. Item 1 = Did you enjoy your experience with the system?; Item 2 = Were you successful using the system?; Item 3 = Were you able to control the system?; Item 4 = Is the information provided by the system clear?; Item 5 = Did you feel discomfort during your experience with the system?; Item 6 = Do you think that this system will be helpful for your rehabilitation?

intermittent strabismus or microstrabismus with some degree of fusion were also allowed to be included in the study in order to reinforce their binocular vision.

The BCVA improvements obtained in this study were modest, but it should be noted that they occurred in a group of patients who were outside the optimal period of plasticity of the visual system and in whom conventional occlusion treatment had failed. These results are consistent with those of other studies evaluating the use of other VR systems in amblyopic patients with non-compliance or non-response to patching[60–62], with the exception of the study by Waddingham et al.[59], where the mean age of the participants was 6.25 years. Some reports suggest that a 1–2 line improvement in BCVA is unlikely to make a noticeable difference for patients with severe amblyopia, but may be sufficient to achieve some degree of binocular fusion and even stereopsis in patients with moderate amblyopia[68], which was observed in our study. In this respect, our results are similar to those reported by Elhusseiny et al.[62], which who also found no statistically significant improvement in distance BCVA, but did find a statistically significant improvement in stereoacuity. The observed improvements in stereopsis in our sample also have clinical significance, as the TNO stereo test has been shown to have good reliability[69], although it has been suggested that it may overestimate stereo thresholds compared to other tests. A visual outcome measure that has rarely been considered in studies evaluating VR technologies for the treatment of amblyopia is fusional vergence. In this pilot study, an overall reduction in fusional vergence after therapy was observed, which is in line with other studies evaluating the use of VR technologies in healthy subjects[70–72], including the one assessed here[53]. The fact that this reduction reached statistical significance in negative and not in positive fusional vergence (for distance vision only) may be due to the fact that several patients with esophoria or esotropia were included in the study. Another possible explanation is that, when subjects within the VR environment look at closer targets, the HMD creates a prismatic effect that favours convergence, and could be the reason for the decrease in divergence. In any case, this finding highlights the need to objectively assess fusional vergence as a clinical outcome measure as well as during therapy when evaluating VR systems in amblyopic patients.

System safety was another important outcome measure in this pilot study, despite previous evidence supporting that HMDs are mostly well tolerated by young children[73]. The most frequent symptoms reported by patients in the SSQ after therapy included "fullness" of the head, fatigue and eyestrain (Table 2). However, it should be noted that these symptoms were temporary and did not lead to discontinuation of the sessions or drop-out of the study. Other studies in this line of research have assessed system safety such as the frequency and type of self-reported adverse events[63,74] or the occurrence of diplopia, heterotropia, worsening VA or unexpected adverse events[66,75], but without using an standardised questionnaire. Regarding the usability of the system, the results reported in the SUS after therapy were generally good except for item 1 (willingness to use the system frequently), which could be due to ergonomic factors derived from carrying an HMD or the difficulty of traveling to the centres where the system was installed to carry out the therapy sessions. In terms of satisfaction with the therapy, it should be noted that 75% of participants agreed or strongly agreed that they enjoyed their experience with the system. This satisfaction rate is slightly lower than that observed in similar studies that evaluated this outcome measure[62,66,74], but in these the therapy was administered at home.

This study has a number of strengths and limitations that need to be acknowledged. Among the main strengths of this study are that the sample was evenly distributed in terms of gender, that patients underwent a comprehensive visual assessment (whereas most studies evaluating VR-based systems for the treatment of amblyopia only consider BCVA or stereopsis as visual outcome measures), and that compliance with therapy could be assessed objectively (as therapy sessions were held in person at the centres where the system was installed). On the other hand, the main limitations of this study were the small sample size used (which made analysis of the results by subgroups unfeasible), the absence of follow-up, the lack of a control group and the non-inclusion of neuro-physiological or neuro-imaging tests with which to explain the clinical improvements obtained with the therapy. It is recognized that the absence of a control group may affect the reliability of the

results, but it should be taken into account that these were patients for whom other treatments had failed and that the application of a sham therapy did not seem ethical given that the study required regular travel by the families to the centres where the system was installed.

In turn, important lines of future research emerge from this study, given the preliminary evidence of efficacy, safety, usability and satisfaction observed. A possible first line of future research would be to test whether increasing the intervention time would lead to a statistically significant improvement in distance BCVA or to test different training regimens to determine which may lead to greater visual improvements in a shorter period of time. It would also be interesting to look for the neurological basis of the clinical improvements obtained through neurophysiological or neuroimaging tests, or to study whether these improvements can be transferred to improvements in patients' quality of life or in the performance of activities such as reading. However, the most ambitious line of research would be to conduct a large-scale randomised clinical trial (RCT) with follow-up assessments to determine the true effect size of the intervention compared to a control group and to see if it is sustained over time.

Conclusion

Therapy with the NEIVATECH system appears to be a feasible and effective alternative for previously treated older amblyopic children with non-compliance or non-response to patching. However, these systems should be used with caution and fusional vergence should be monitored during treatment in this population.

Data availability

The datasets generated and/or analysed during the study are available from the corresponding author on reasonable request.

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Declarations

Competing interests

The authors declare no competing interests.

Ethics declarations

This study has been conducted in accordance with the ethical principles for medical research involving human subjects of the Declaration of Helsinki and has been approved by the Drug Research Ethics Committee of the Valladolid East Health Area (Ref.: CASVE-NM-21-516). Prior to any testing and after explaining the possible consequences of the study, written informed consent was obtained from the parents or legal guardians of each child participating in the study.

Additional information

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