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ORIGINAL ARTICLE

Supervised dichoptic gaming versus monitored occlusion therapy for childhood amblyopia: Effectiveness and efficiency

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Abstract

Purpose: To compare the effectiveness and efficiency of supervised dichoptic action-videogame play to occlusion therapy in children with amblyopia.

Methods: Newly diagnosed children with amblyopia aged 4–12 years were recruited, excluding strabismus >30PD. After 16 weeks of refractive adaptation children were randomized to gaming 1 h/week supervised by the researcher, or electronically monitored occlusion 2 h/day. The gaming group played a dichoptic action-videogame using virtual reality goggles, which included the task of catching a snowflake presented intermittently to the amblyopic eye. Contrast for the fellow eye was self-adjusted until 2 identical images were perceived. The primary outcome was visual acuity (VA) change from baseline to 24 weeks.

Results: We recruited 96 children, 29 declined and 2 were excluded for language or legal issues. After refractive adaptation, 24 of the remaining 65 no longer met the inclusion criteria for amblyopia, and 8 dropped out. Of 16 children treated with gaming, 7 (6.7 years) completed treatment, whereas 9 younger children (5.3 years) did not. Of 17 treated with occlusion, 14 (5.1 years) completed treatment and 3 (4.5 years) did not. Of 5 children with small-angle strabismus, 3 treated with occlusion completed treatment and 2 treated with gaming did not. Median VA improved by 0.30 logMAR (IQR 0.20–0.40) after gaming, 0.20 logMAR (0.00–0.30) after occlusion ($p=0.823$). Treatment efficiency was 1.25 logMAR/100 h (range 0.42–2.08) with gaming, 0.08 (−0.19–0.68) with occlusion ($p<0.001$).

Conclusion: Dichoptic gaming seems a viable alternative for older children with refractive amblyopia after glasses adaptation. Treatment efficiency with gaming under continuous supervision was 15 times higher than with occlusion at home.

KEYWORDS
amblyopia, dichoptic treatment, occlusion therapy, treatment efficiency

1 | INTRODUCTION

Amblyopia is the main cause of unilateral visual acuity loss in children, with a prevalence of 2%–4% of the population (Attebo et al., 1998; Brown et al., 2000; Friedman et al., 2009). The long-established treatment has been occlusion of the better eye for several hours per day (Stewart et al., 2004). Occlusion therapy has proven to be a successful treatment, even over the long term, with 74% having stable or improved visual acuity 12–15 years post-treatment (Kadhum, Simonsz-Toth, et al., 2021). However, its success is hampered by poor compliance, on average 50%–60% (Loudon et al., 2006; Stewart et al., 2004). Compliance has been shown to be associated with parental fluency in the national language, country of origin, level of education and initial visual acuity of the child. Using an educational program aimed at the child explaining the rationale for treatment significantly improved compliance (Loudon et al., 2006). Primarily, compliance is highly dependent on the level of understanding of the rationale of therapy.

The dose–response of occlusion therapy has been investigated using the occlusion dose monitor. The number of occlusion hours required to achieve 1 logMAR line in visual acuity gain was 120 h (Stewart et al., 2004). Occlusion therapy has been shown to result in up to 7

Trial registration: NCT03767985.

logMAR lines of visual acuity improvement. It is most effective within the first few weeks of treatment with on average 58 h of required occlusion to achieve 1 logMAR line in visual acuity gain after 1 month; after 4 months, this is on average 169 h (Fronius et al., 2014). In addition, the age of the child plays a significant role in the efficiency of treatment: the number of required occlusion hours for younger children is less than for older children to achieve the same visual acuity gain (Loudon et al., 2006; Stewart et al., 2004). The recently introduced measure 'treatment efficiency' (Fronius et al., 2014) is not based on the dose–response calculation and, hence, permits the inclusion of patients with no change in visual acuity in the calculation (no division by zero). This reduces bias in comparisons where patients with a poor compliance or older children are included in study samples (Fronius et al., 2014).

In the past decade, there has been a particular interest in behavioural training therapies for amblyopia. These include perceptual learning, video gaming or movie watching. Viewing conditions are either monocular, using only the amblyopic eye, or dichoptic, using two eyes. Perceptual learning is the ability to improve performance on sensory tasks as a result of repeated practice (Bavelier et al., 2010). Playing video games with the amblyopic eye has been shown to generate similar changes as perceptual learning: a reduction of noise and an increase in sampling efficiency (Tsirlin et al., 2015). Dichoptic gaming or movie watching is based on the idea that amblyopia is a binocular disorder and is caused by suppression. With dichoptic viewing conditions, different information is presented to the two eyes, with the amblyopic eye receiving a more intense stimulus than the fellow eye, by reducing the contrast of the image presented to the fellow eye. The goal is to reduce suppression and/or improve fusion (Pineles et al., 2020; Tsirlin et al., 2015). Most of these studies have reported a positive effect on visual acuity in children as well as in adults (Pineles et al., 2020; Tsirlin et al., 2015).

The results of behavioural training therapies such as perceptual learning, video gaming and dichoptic therapies are on average 1–2 logMAR lines of improvement in visual acuity in children as well as in adults (Pineles et al., 2020; Tsirlin et al., 2015). The number of treatment hours varies across studies from 10 to 112 h. No clear dose–response relationship has been demonstrated, however, the number of required treatment hours seems to be less as compared to occlusion therapy (Pineles et al., 2020; Tsirlin et al., 2015).

Previous studies comparing gaming with occlusion therapy in children have not monitored compliance electronically (Holmes et al., 2016; Jost et al., 2022; Kelly et al., 2016; Manh et al., 2018; Rajavi et al., 2021). Some studies have investigated only the effectiveness of gaming or dichoptic movie watching and did not compare with occlusion therapy (Barollo et al., 2017; Birch et al., 2015; Bossi et al., 2017; Gambacorta et al., 2018; Gao et al., 2018; Herbison et al., 2016; Huang et al., 2022; Kelly et al., 2018; Li et al., 2015a; Mansouri et al., 2014; Mezad-Koursh et al., 2018; Portela-Camino et al., 2018). Other studies compared a combination of treatments, making it difficult to identify the contribution of gaming therapy (Birch et al., 2020; Dadeya & Dangda, 2016; Rajavi et al., 2016; Singh et al., 2017) (Hsieh et al., 2022; Pediatric Eye Disease Investigator G et al., 2019; Xiao et al., 2022). Furthermore, many of these studies included children who were previously occluded, whereby treatment was either incomplete or ineffective (Barollo et al., 2017; Gambacorta et al., 2018; Gao et al., 2018; Herbison et al., 2016; Holmes et al., 2016; Huang et al., 2022; Li et al., 2015a; Manh et al., 2018; Mansouri et al., 2014; Mezad-Koursh et al., 2018; Portela-Camino et al., 2018; Rajavi et al., 2021). It is unclear whether previous occlusion therapy acts as a barrier to improvements from subsequent dichoptic gaming therapy or actually makes it more likely to be successful.

Therefore, we designed this randomized clinical trial to compare for the first time the effectiveness of supervised dichoptic video gaming using Virtual Reality (VR) goggles with electronically monitored occlusion therapy for children with newly diagnosed amblyopia.

2 | MATERIALS AND METHODS

The study was conducted at 5 clinics in the Netherlands: Haaglanden Medical Center (The Hague), Tergooi Hospital (Hilversum, Blaricum), IJsselland Hospital, HU Clinics University of Applied Science Utrecht and ErasmusMC University Medical Center Rotterdam. From December 2017 until June 2020, 10 treating orthoptists referred eligible children to the research centre. The Ethics Committee of the ErasmusMC University Medical Center Rotterdam and the Boards of the participating clinics approved the protocol and informed consent forms. Written informed consent was obtained from each subject's parents/legal guardians. The study adhered to the tenets of the Declaration of Helsinki. The study is listed on www.clinicaltrials.gov under the identifier NCT03767985.

2.1 | Orthoptic examinations

The treating orthoptist referred all newly diagnosed amblyopic children aged 4 to 12 years; that is no previous treatment for amblopia. Amblyopia was associated with a refractive error, strabismus or a combination of the two, with an interocular visual acuity difference of at least 0.2 logMAR. Exclusion criteria were non-comitant or large angle strabismus >30 prism diopters (PD), a neurological disorder, nystagmus, other eye disorders and diminished visual acuity due to medication, brain damage or trauma. Cycloplegic refraction was performed by the treating orthoptist using retinoscopy, 30 min after cyclopentolate 1% in both eyes. Spectacles were prescribed in those with anisometropia ≥1.00 D difference between the eyes in spherical equivalent, astigmatism ≥1.50 D difference between the eyes in any meridian and/or a hypermetropia (spherical equivalent) ≥1.50 D. Children were prescribed 0.5 D undercorrection from the full cycloplegic refraction. Whenever possible, the cycloplegic refraction was subjectively confirmed. Prior to randomization, a refractive adaptation period of 16 weeks

was incorporated. Eligible children were referred to the research orthoptist (ET) who performed a baseline standard orthoptic examination. This included: (1) best corrected visual acuity using the crowded tumbling E chart (Precision Vision®), (2) stereo acuity using the circles Randot Stereotest at 40 cm, (3) contrast sensitivity using the Pelli-Robson chart in older subjects and CSV-1000 in the younger children, (4) ocular motility and (5) alignment with the cover-uncover and alternating cover test at 30 cm and 5 m distance.

2.2 | Randomization and treatment

Children in whom amblyopia persisted after refractive adaptation were randomized to either the occlusion group: 2 h/day or the gaming group: dichoptic action video game using the Oculus Rift VR goggles once a week for 1 h at the outpatient clinic. The randomize R package version 1.3 was used for generating the randomization list using a permuted block design with R version 3.3.2. Treatment was prescribed for 24 weeks. Compliance in the children in the occlusion group was monitored using the Occlusion Dose Monitor (ODM) for 1 week every 6 weeks (Loudon et al., 2006; Simonsz et al., 1999), that is 4 measurements. Parents were instructed to attach the ODM to the front of the patch with double-sided Scotch tape. It thus measured the temperature difference between the front and the back every 3 min, enabling exact determination of when and for how long the patch was worn. Parents were asked to use the ODM the week following the visit to the clinic. Compliance (%) was calculated by dividing the number of *monitored* occlusion hours by the *prescribed* occlusion hours, multiplied by 100.

The principles of the game have been reported in detail elsewhere (Kadhum, Tan, et al., 2021). In short, it was a dichoptic action video game using the Oculus Rift VR goggles, custom-made and based on the previously reported games described elsewhere (Vedamurthy et al., 2015). Snowmen appeared and the child was instructed to throw snowballs at them to gain points. A red snowflake appeared every 30 s for 10 s solely to the amblyopic eye; the child was instructed to catch the snowflakes to gain extra points. This was to ensure that the amblyopic eye was still engaged during gameplay. The software included settings for perceptually balancing the images seen by the two eyes by attenuating the contrast of the image seen by the fellow eye. Contrast setting began by presenting the image with full contrast to the amblyopic eye and a black screen to the fellow eye. The image (Figure 1a) for the fellow eye was gradually increased in contrast by steps of 10% until the child perceived two equally balanced images. This procedure was repeated four times and the average of these outcomes was used to play the game. The game also included settings to correct for misalignment. Two nonius lines were presented dichoptically, which had to be aligned until a full cross was perceived. Both the perceptual balance and alignment tasks were adjusted at the start of each game session and they were based on the input of the child. In the gaming group compliance was registered by the researcher, who supervised the gaming session and used a stopwatch to determine the exact game duration. Figure 1b shows a 6-year-old boy playing the game in the clinic.

During the 24 weeks of occlusion therapy or gaming therapy, all children were examined every 6 weeks by the same research orthoptist (ET) using the same strict protocol to prevent any bias. During these orthoptic examinations at the clinic, the ODM was given to the parents in the occlusion group with instructions on how to attach the ODM to the patch. Treatment was completed if equal visual acuity was measured on two consecutive visits. If no further treatment was required (i.e. no standard occlusion therapy necessary) VA was measured 3 months after completion of the study trial. After 24 weeks children were referred back to their treating orthoptist for further treatment if necessary.

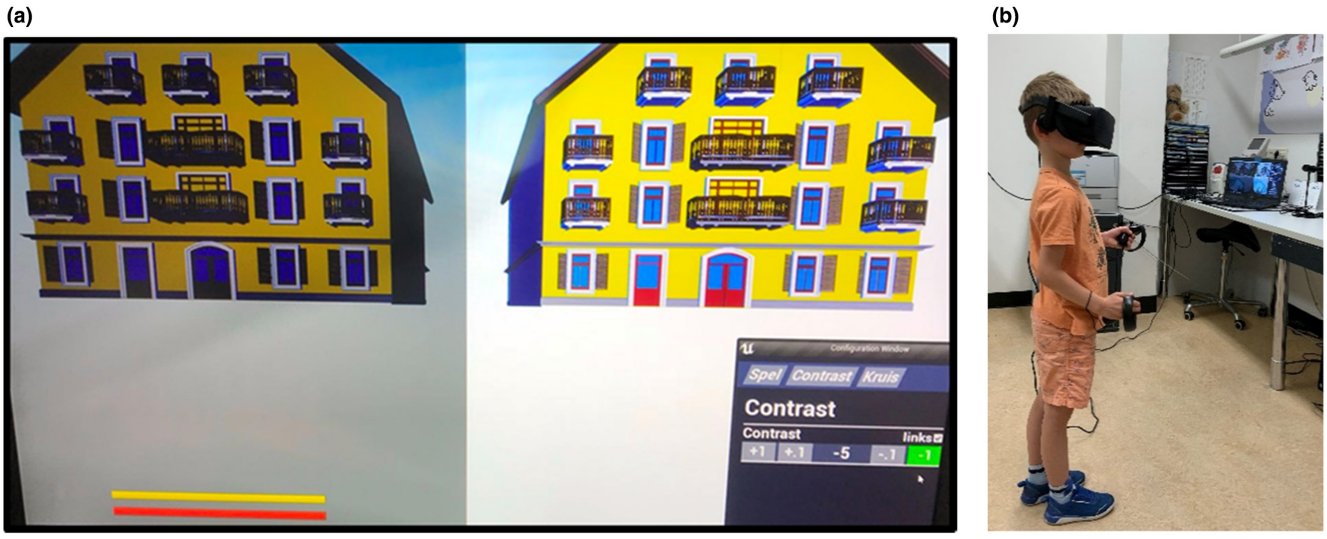

FIGURE 1 (a) An image with attenuated contrast for the fellow eye (left eye) in order to match the image perceived by the amblyopic eye (right eye). (b) A child playing the dichoptic action video game using Virtual Reality goggles at the outpatient clinic. On the right side of the figure, you can see the laptop displaying the image the child sees in the headset.

2.3 | Statistical analysis

We hypothesized that there would be no significant difference in visual acuity improvement after 24 weeks of treatment between the gaming group and the occlusion group. We performed an equivalence trial.

Based on the literature, the number of required treatment hours for gaming seems to be less, as compared to occlusion therapy: 10–20 h of gaming seems comparable to 100–120 h of occlusion (Stewart et al., 2004; Tsirlin et al., 2015). Hence, we compared 2 h of prescribed occlusion per day, 7 days per week (336 total hours) to 1 h of gaming per week (24 total hours).

Differences in clinical characteristics between the gaming group and occlusion group were investigated using Mann–Whitney U tests for the following continuous variables: age at the start of therapy, visual acuity at the start of therapy, stereo acuity, spherical equivalent of both eyes and anisometropia. The chi-square test was used to investigate the categorical variable sex.

A mixed model with time as a factor and interaction with treatment was used to compare visual acuity in the amblyopic eye at the start and after 24 weeks within the dichoptic game and occlusion groups and to compare the improvement in visual acuity between the two groups. Random effects for patients and time were included to account for the clustered structure of the data within patients. Within the mixed model, we used an intention-to-treat analysis for all included children to correct for any dropout during the study. In addition, a per-protocol analysis was conducted including only the children who completed the therapy. A p value of <0.05 was considered statistically significant. Visual acuity was log-transformed to meet the criteria of normally distributed values for the mixed model.

As mentioned, children in the occlusion group were prescribed 2 h of occlusion per day. Compliance was electronically monitored for 1 week every 6 weeks. The number of occlusion hours was calculated by prescribed occlusion hours multiplied by the monitored percentage of compliance. Treatment efficiency was calculated by dividing VA improvement by occlusion hours. In the gaming group, children came once a week to the outpatient clinic to play the dichoptic video game for 1 h. Treatment efficiency was calculated by dividing VA improvement by the number of supervised gaming hours at the outpatient clinic.

To calculate treatment efficiency (expressed as acuity gain in logMAR per 100 h of treatment), the measured visual acuity gains were divided by the hours of treatment and multiplied by 100 (Fronius et al., 2014). We used the following formula (Fronius et al., 2014):

$$\frac{\textit{visual acuity gain } (\textit{logMAR}) * 100}{\textit{number of treatment hours}}$$

The difference in treatment efficiency between the treatment groups was investigated using the Mann–Whitney U test.

Stereo acuity was converted to the logarithm (base 10) of the stereo acuity values and participants who failed the stereo acuity test were arbitrarily assigned a value of 800 arcsec (2.90 logarcsec), similar to Gambacorta, which corresponds to double the maximum testable disparity in the circles Randot Stereotest (Gambacorta et al., 2018). A mixed model was used to compare stereo acuity at the start of therapy and after 24 weeks within the dichoptic game and occlusion groups and to compare the improvement in stereo acuity between the two groups. Stereo acuity was log-transformed to meet the criteria of normally distributed values for the mixed model.

To investigate any correlation between the change in the contrast balance setting and change in visual acuity in the amblyopic eye and change in stereo acuity, we used Spearman rank correlation.

3 | RESULTS

Ninety-six newly diagnosed amblyopic children were recruited; two were excluded due to language problems or legal issues. Participation in the study was offered to 94 families. Twenty-nine refused participation. Reasons for not participating in the game therapy are listed in a previous publication (Kadhum, Tan, et al., 2021). Mostly, these were for reasons directly related to the game therapy because they were either unwilling or unable to comply with the weekly game sessions (Kadhum, Tan, et al., 2021). Sixty-five were eligible for the study. Children were first prescribed glasses when necessary. After the refractive adaptation period, amblyopia was sufficiently treated in 24 children and these, therefore, did not meet the inclusion criteria. Another eight participants dropped out: due to the time-consuming nature of the weekly visits to the clinic, three refused further participation, three due to the inclusion-stop caused by the COVID-19 pandemic and two withdrew their participation. Thirty-three children were randomized: 17 to the occlusion group and 16 to the gaming group (Figure 2). During the study, three (18%) children dropped out of the occlusion group and nine (56%) out of the gaming group. Reasons for dropout are listed in a previous publication (Kadhum, Tan, et al., 2021). Twenty-one completed the full 24-week study period: 14 in the occlusion group and 7 in the gaming group.

3.1 | Study population

Median age was 5.4 (IQR 4.5–6.7) years; 16 were girls (49%) for the two groups together. There was no significant difference in baseline characteristics between the two groups (Table 1). Median age of the children in the gaming group was 0.9 years older than the occlusion group (not statistically significant). Twenty-eight children had amblyopia associated with anisometropia. Three children had strabismus amblyopia with mean age of 5.8 (SD 0.8) years, mean strabismus angle was 10 (SD 7) PD, mean visual acuity at start was 0.47 (SD 0.31) logMAR and stereo acuity was 2.25 (SD 0.57) logarcsec. Visual acuity at the end was 0.20 logMAR in the amblyopic eye in one child; the other two children dropped out after 1 game session. There were two children with combined mechanism

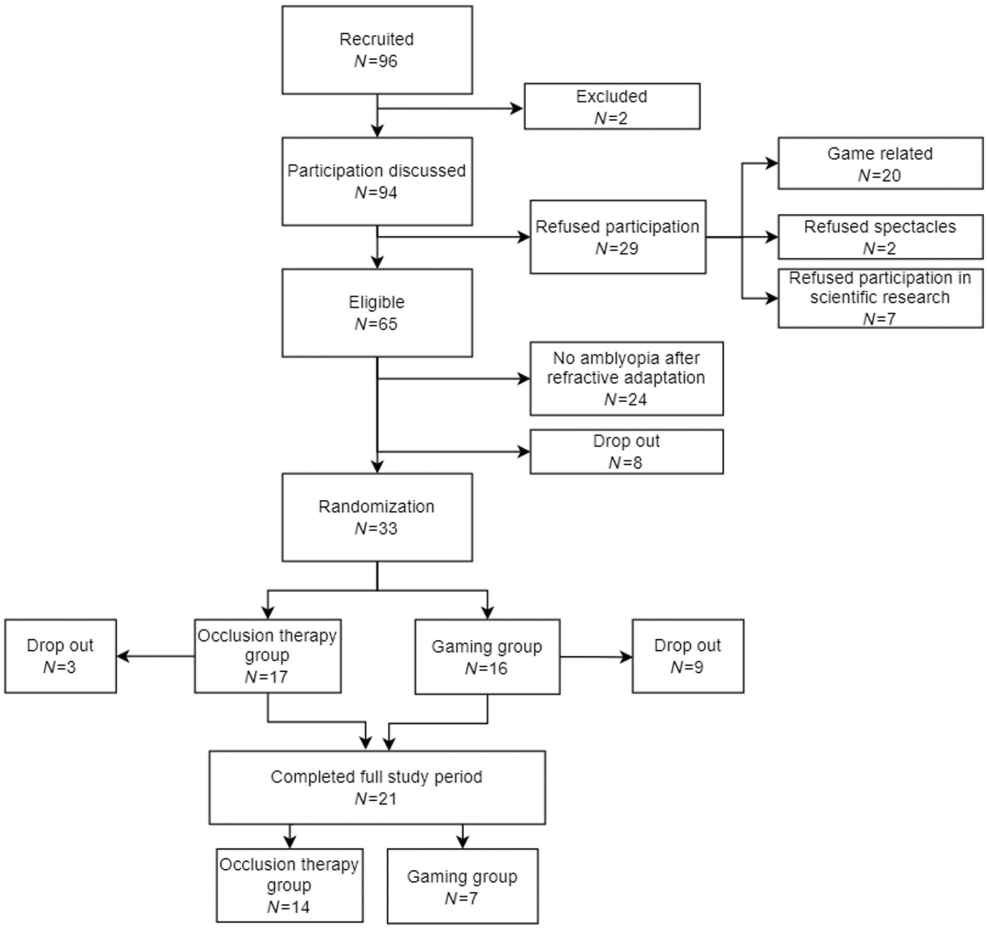

FIGURE 2 Study flowchart with the number of participants.

TABLE 1 Baseline characteristics for all randomized participants ($N=33$). Differences between the two groups are analysed with Mann–Whitney U test (continuous variables) or Chi-square test (categorical variables).

	Occlusion therapy group ($N=17$)	Gaming group ($N=16$)	*p* Value
Gender, female	10 (59%)	6 (38%)	0.221
Age at baseline (years, median, IQR)	4.9 (4.3–6.3)	5.8 (4.9–7.2)	0.127
Visual acuity amblyopic eye at baseline (logMAR, median, IQR)	0.40 (0.20–0.45)	0.40 (0.30–0.50)	0.698
Visual acuity fellow eye at baseline (logMAR, median, IQR)	0.00 (0.00–0.18)	0.03 (0.00–0.10)	0.614
Stereoacuity at baseline (log seconds of arc, median, IQR)	2.00 (1.70–2.30)	1.77 (1.35–2.30)	0.163
Amblyopia cause			
Anisometropia	14	14	[a]
Strabismus	1	2	
Combined	2	0	
Spherical equivalent amblyopic eye (diopters, median, IQR)	3.3 (0.7–4.7)	3.5 (1.0–5.3)	0.769
Spherical equivalent fellow eye (diopters, median, IQR)	1.5 (0.5–2.8)	2.1 (0.2–3.4)	0.769
Spherical equivalent anisometropia (diopters, median, IQR)	1.0 (0.4–2.6)	1.1 (0.3–2.1)	0.810

[a]Groups smaller than three were not tested for significance.

amblyopia with mean age of 4.5 (SD 1.3) years, strabismus angle in both children was 8PD, mean visual acuity at the start was 0.65 (SD 0.64) logMAR; stereo acuity was nil in one child, the other child did not have a stereo acuity measurement at the start; mean visual acuity at the end was 0.25 (SD 0.35) logMAR.

3.2 | Occlusion vs dichoptic gaming

3.2.1 | Visual acuity

Median visual acuity in the amblyopic eye improved by 0.30 logMAR (IQR 0.20–0.40) in the gaming group and

0.20 logMAR (IQR 0.00–0.30) in the occlusion group after 24 weeks of treatment (see Figure 3).

An intention-to-treat analysis using a mixed model with time as a factor was conducted with all included children ($N=33$). This analysis showed that visual acuity in the amblyopic eye improved significantly after 24 weeks in both the gaming as well as in occlusion group ($p<0.001$). There was no statistically significant difference in improvement between the two groups after 24 weeks ($p=0.823$). On all measurements, there was no significant difference between the two groups: at 6 weeks ($p=0.115$), at 12 weeks ($p=0.453$) and at 18 weeks ($p=0.719$).

A per-protocol analysis was conducted including only the children who completed the full study ($N=21$), this showed comparable results with the intention-to-treat analysis: a significant improvement after 24 weeks for both groups ($p<0.001$), and no significant difference in visual acuity improvement between the two groups after 24 weeks ($p=0.837$). On all measurements, there was no significant difference: at 6 weeks ($p=0.131$), 12 weeks ($p=0.461$) and at 18 weeks ($p=0.710$).

The intention-to-treat analysis was repeated without the five children with strabismus/combined cause of amblyopia. This analysis also showed no significant difference between the two groups after 24 weeks ($p=0.511$). There was no significant difference on all measurements: at 6 weeks ($p=0.211$), at 12 weeks ($p=0.965$) and at 18 weeks ($p=0.977$).

3.2.2 | Compliance with therapy

Of the 17 children in the occlusion group, two had unknown measurements as they dropped out prior to the 6-week appointment. Mean compliance with occlusion therapy for the remaining 15 children was 81% (min 13, max 100, SD 42%), that is the mean daily dose rate was 1.62±0.84 h/day.

Compliance with gaming was observed by the researcher during each game session ensuring each child completed the full treatment. If a child could not attend the scheduled appointment for whatever reason, or if there was a no-show, a new appointment was made as soon as possible to make up for the missed treatment hours. All children who completed the study achieved 24 h of required game time.

3.2.3 | Treatment efficiency

Treatment efficiency was calculated for both treatment groups using the following formula: (acuity gain (logMAR) × 100 h)/cumulated measured treatment hours. For the occlusion group, we calculated this based on the monitored occlusion hours (Table 2).

Treatment efficiency after 6 weeks ($p=0.001$) and 24 weeks ($p<0.001$) was significantly higher for gaming compared to occlusion therapy.

There was a decrease in treatment efficiency with both gaming and occlusion therapy over time, with the most rapid decrease occurring during the first 12 weeks.

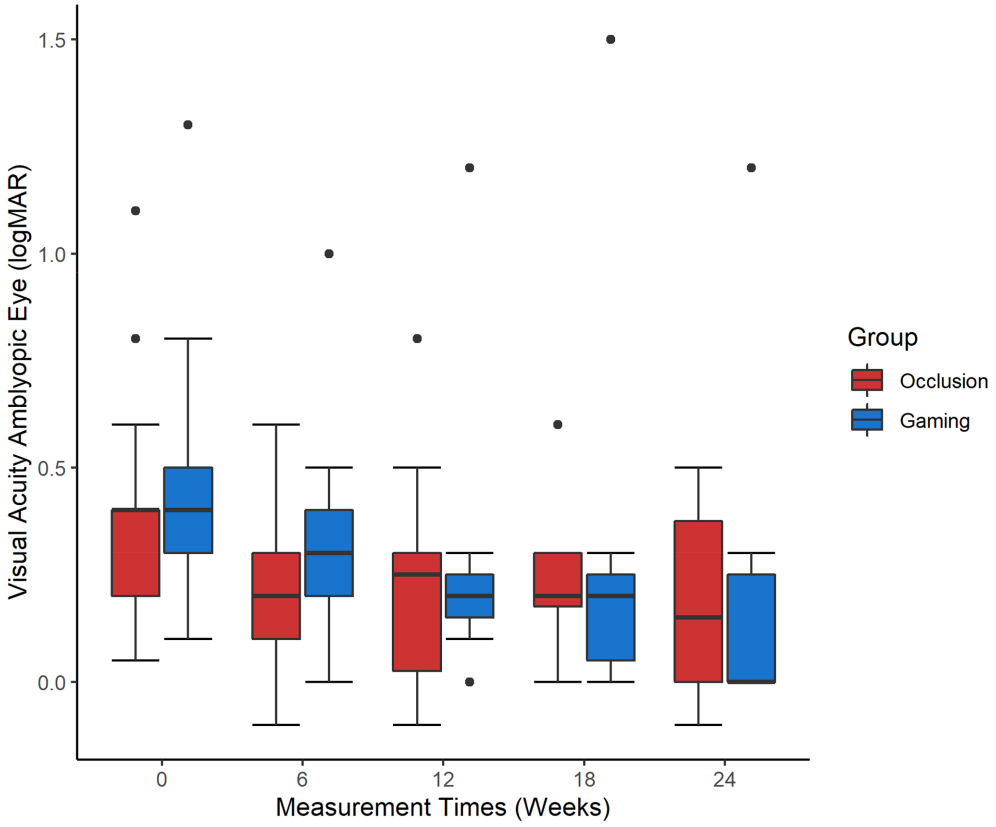

FIGURE 3 Visual acuity in the amblyopic eye (logMAR) from baseline to 24 weeks of treatment ($N=33$). The boxplots represent the 25th and 75th percentiles of the data and the line in the box is the median value. Whiskers represent the 5th and 95th percentiles. The circles represent the outliers. Red is the occlusion group; blue is the gaming group.

TABLE 2 Median treatment efficiency: acuity gain (logMAR) per 100 h of treatment for both groups including the range with minimum and maximum values. Electronically monitored hours were used in the calculation for the occlusion group.

	Occlusion therapy group	Gaming group
After 6 weeks	0.23 (−0.73–0.59)	3.33 (0.00–5.00)
After 12 weeks	0.12 (−0.10–0.42)	1.67 (−0.83–3.33)
After 18 weeks	0.10 (0.00–0.47)	1.11 (−1.11–2.78)
After 24 weeks	0.08 (−0.19–0.68)	1.25 (0.42–2.08)

A maximum of VA recovery was reached after approximately 14.6 (SD 6.8) h of gaming.

3.2.4 | Stereo acuity

Median stereo acuity in the occlusion group at the start of treatment was 2.00 log arc sec [min 1.48 – max 2.90] and improved to 1.40 [min 1.30 – max 2.90] log arc sec after 24 weeks. In the gaming group stereo acuity improved from 1.70 [min 1.30 – max 2.90] to 1.40 [min 1.30 – max 2.90]. Stereo acuity improved significantly after 24 weeks of treatment (mixed model; $p<0.001$) with no significant difference between the two groups ($p=0.609$). On all measurements there was no significant difference between the two groups: at 6 weeks ($p=0.172$), at 12 weeks ($p=0.661$), or at 18 weeks ($p=0.601$). The correlation between visual acuity and stereo acuity gain was significant (Spearman correlation 0.565; $p<0.001$).

3.2.5 | Contrast sensitivity

In the occlusion group, 13 children were examined using the CSV-1000; 3 children could not be tested due to equipment failure and one child had a missing CSV-1000 at baseline. In the gaming group, 6 children were examined using the CSV-1000, 5 children with the Pelli-Robson chart; data of 5 children were missing. Overall, in the occlusion group contrast sensitivity at the start of treatment was on average 1.22 [min 0.70 – max 1.63] and 1.51 [min 0.70 – max 2.08] at end of therapy using the outcome of the 3 cycles/degree line. In the gaming group, this was 1.30 [min 1.17 – max 1.63] at the start of treatment and 1.52 [min 1.34 – max 1.78] at end of therapy. Overall, we could not demonstrate a significant difference between the two groups at the start as well as after 24 weeks (Mann–Whitney U test; $p>0.05$). In addition, the Wilcoxon Signed Rank Test showed no significant improvement within the groups ($p>0.05$).

Of the 5 children examined using the Pelli-Robson chart in the gaming group, two finished the treatment: they started with 1.73 (min 1.65 – max 1.80) and measured 1.95 (min 1.95 – max 1.95) after 24 weeks of therapy for the amblyopic eye.

3.3 | Visual acuity follow-up after treatment

Of the 14 children from the occlusion group, 7 (50%) achieved equal visual acuity during or after 24 weeks of the study period. Five (71%) of the 7 children from the gaming group achieved equal visual acuity. Fisher's exact test showed no statistically significant difference between these two proportions ($p=0.64$). Visual acuity was assessed 3–4 months after the cessation of treatment to determine the stability of visual acuity. Three of the five in the gaming group maintained their achieved visual acuity and two had a slight decrease in visual acuity in the amblyopic eye of 0.10 logMAR. The median visual acuity at the follow-up examination was 0.00 (min 0.00 – max 0.30) logMAR.

Of the 12 children with anisometropia amblyopia in the occlusion group who finished the 24 weeks, 6 (50%) achieved equal visual acuity during or after 24 weeks of the study period.

3.4 | Contrast balance task for the game

In our study, the contrast balance task was determined subjectively by the child rather than using arbitrary values. In the children who completed treatment ($N=7$), the contrast balance setting was, on average, 57 ± 17% at the first game session and improved to 78 ± 14% at 24 weeks. In Figure 4, visual acuity of all children from the game group is displayed with the contrast balance setting for the game on the same day. There was no significant correlation found between change in visual acuity in the amblyopic eye and change in contrast balance setting (Spearman correlation −0.122; $p=0.484$). There was also no significant correlation found between change in stereo acuity and change in contrast balance setting (Spearman correlation −0.216; $p=0.212$), consistent with previous studies (Knox et al., 2012; Vedamurthy et al., 2015).

4 | DISCUSSION

This is the first study to measure and compare the efficacy and efficiency of supervised outpatient dichoptic action video gaming using VR goggles to objectively monitored occlusion therapy in 4–12-year-old children with newly diagnosed amblyopia. While several published studies (Barollo et al., 2017; Gambacorta et al., 2018; Gao et al., 2018; Herbison et al., 2016; Holmes et al., 2016; Huang et al., 2022; Li et al., 2015b; Manh et al., 2018; Mezad-Koursh et al., 2018; Portela-Camino et al., 2018; Rajavi et al., 2021) included subjects with a history of occlusion for amblyopia, it is unclear whether previous treatment could be a hindrance or an aid to acuity improvements subsequently gained through dichoptic therapy. Although we started with 96 recruited children, only 33 could be randomized: after 16 weeks of glasses adaptation, a third of the originally recruited children no longer had an interocular VA difference ≥0.20 logMAR and no longer qualified as amblyopic. This highlights the necessity to carefully select and refractively manage patients participating in any amblyopia treatment protocol. At the end of the 24-week treatment period visual acuity had improved by 0.30 logMAR (IQR 0.20–0.40) in the gaming group and 0.20 logMAR (IQR 0.00–0.30) in the occlusion group; this difference between the

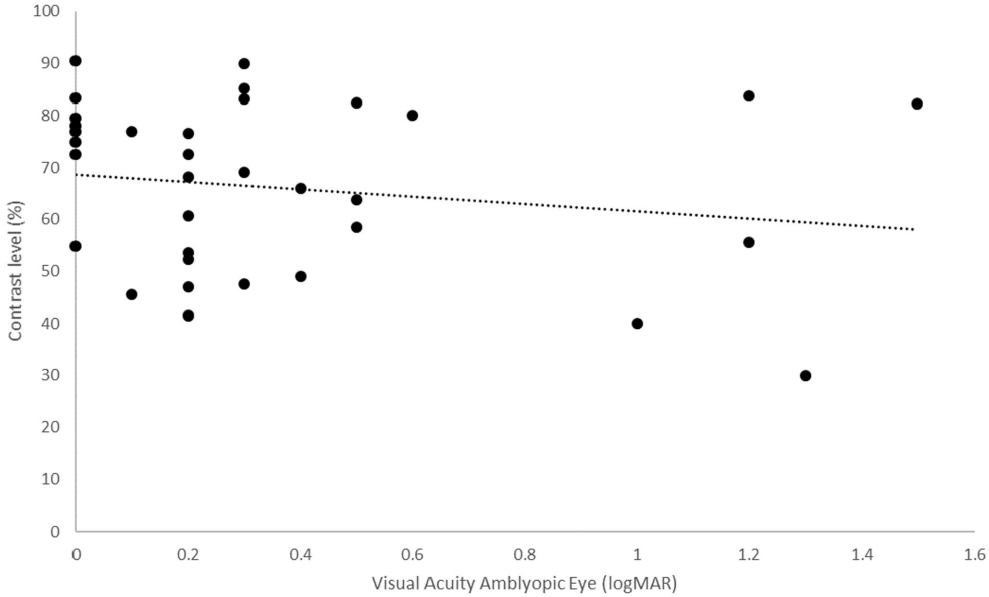

FIGURE 4 Scatterplot representing the relationship between visual acuity in the amblyopic eye (logMAR) and the level of contrast (%) setting in the game. Each dot represents one child with their contrast balance % and visual acuity measured on the same day.

two treatment groups was not statistically significant. Considering that more than half of the children from the gaming group failed to complete treatment, mostly children of young age including 2 with small-angle strabismus, our impression is that VR gaming is a viable alternative for older children with refractive amblyopia after glasses adaptation.

4.1 | Evaluation of our methods and results

Compliance with gaming was ensured by direct supervision of the game sessions and the researcher made sure that treatment was completed. Compliance with occlusion therapy was monitored electronically for 1 week every 6 weeks, that is four measurements. It is possible that compliance was higher in the week it was measured than for the ensuing weeks, as the compliance measurement was done in the first week following orthoptic examination (Hawthorne effect). With 81% it was higher than in our previous studies, whereby overall mean compliance was 55%–57% after 4 months (Loudon et al., 2006; Tjiam et al., 2013). An important difference was that in our previous studies, the ODM was distributed by researchers via home visits ensuring the separation of researchers measuring compliance and treating orthoptists. In the current study, the ODM was distributed in the clinic by the researcher during the visual acuity measurement, instructing parents to use the ODM immediately in the first week of the coming 6 weeks. The research orthoptist (ET) who measured the visual acuity and performed the orthoptic examinations was initially masked for randomization of the children. However, in practice, this could not be guaranteed. Every effort was made to ensure that every participant received the same amount of time for the orthoptic examination. ET was not aware of treatment compliance.

Treatment efficiency with gaming was 15 times higher than with occlusion therapy, despite that the children in the gaming group were slightly older. The efficiency was calculated by dividing the VA gain by the prescribed occlusion hours corrected for by the monitored compliance for a week (on average 81%). Even when assuming that compliance with occlusion was comparable to our previous studies (55%–57%), treatment efficiency with gaming would still be higher. Calculated treatment efficiency would be 0.13 logMAR per 100 h of treatment for occlusion and 0.22 for gaming after 16 weeks (Holmes et al., 2016) (see Table 3); assuming compliance with occlusion therapy to be 55% (Loudon et al., 2006), treatment efficiency would be 0.23. Calculating this for Kelly et al. resulted in a treatment efficiency of 1.50 logMAR per 100 h of treatment for gaming and 0.25 for occlusion therapy after 2 weeks (Kelly et al., 2016) (see Table 3). The treatment efficiency of amblyopia therapy with the I-BiT games was 3.33 logMAR per 100 h of gaming after 3 weeks and 2.00 after 6 weeks (Herbison et al., 2016). Gambacorta et al. calculated treatment efficiency after 10 h of gaming, which resulted in 1.0 logMAR VA gain per 100 h of gaming. When calculating this after 20 h of gaming, they found a decrease in treatment efficiency to 0.70 logMAR VA gain per 100 h of gaming. In this study gaming was done in sessions of 1 h, 1–3 times per week; after 10 and 20 h VA was assessed (Gambacorta et al., 2018).

Treatment efficiency with gaming was higher than with occlusion in all studies. It is notable that treatment efficiency for gaming at home was lower than for supervised gaming. Efficiency decreased rapidly with the duration of treatment with a maximum of VA recovery occurring after approximately 15 h of gaming. Opting for at-home gaming treatment comes with its own limitations and significantly low levels of compliance (Holmes et al., 2016; Manh et al., 2018; Pediatric Eye Disease Investigator G et al., 2019).

The number of children who completed the study was low, mainly due to young age, logistical challenges and loss of interest in the game. Therefore, for the interpretation of the mixed model, the age-dependent dropout

TABLE 3 Calculated treatment efficiency (VA improvement logMAR/100 h of therapy) for gaming and occlusion therapy for children in previous studies.

Studies	Efficiency supervised gaming	Efficiency gaming at home	Efficiency occlusion therapy
This study (median)	3.33 after 6 weeks (6 h)		0.23 after 6 weeks (≈68 h)
	1.25 after 24 weeks (24 h)		0.08 after 24 weeks (≈272 h)
Kelly et al., 2016 (mean)		1.50 after 2 weeks (10 h)[a]	0.25 after 2 weeks (28 h)[a]
Holmes et al., 2016 (mean)		0.22 after 16 weeks (112 h)[a]	0.13 after 16 weeks (224 h)[a]
Herbison et al., 2016 (mean)	3.33 after 3 weeks (1.5 h)		
	2.00 after 6 weeks (3 h)		
Gambacorta et al., 2018 (mean)	1.00 after 10 h of dichoptic gaming		
	0.70 after 20 h of dichoptic gaming		
	0.60 after 10 h of monocular gaming		
	0.30 after 20 h of monocular gaming		
Fronius et al., 2014 (median)			0.19 after 4 weeks (117 h)
			0.11 after 16 weeks (469 h)
Stewart et al., 2004 (mean)			0.08[b]

Note: Treatment hours for occlusion therapy for this study are based on the found 81%; in reality treatment hours and TE were calculated for each child separately based on his/her compliance data.

[a] There was no electronic monitoring of occlusion therapy and no supervised gaming therapy. We have calculated treatment efficiency based on the provided mean or median visual acuity improvement and prescribed treatment hours. Treatment efficiency calculations for the study of Holmes in this table were done using the data from the subgroup age 5 to <7 years with no prior treatment.

[b] The study of Stewart did not have a fixed treatment duration for occlusion, but dose–response was provided.

needs to be taken into account. The children in the gaming group were slightly older, although not significantly, this could influence treatment efficiency. A third of all originally 96 recruited children no longer had amblyopia after the glasses adaptation. Furthermore, only 44% of the children in the gaming group completed the treatment period. Notably, all three young children with small-angle strabismus in the occlusion group completed treatment, whereas the two in the gaming group did not. We had expected that poor VA may influence the ability to perform the game settings. However, this was not the case. We found that younger children had difficulties applying the game settings, that is they did not understand the contrast balance task and alignment task and could not communicate properly what they perceived in the goggles (Kadhum, Tan, et al., 2021). In addition, these children were also unable to comprehend the task of throwing snowballs at the approaching snowmen and would often just look around in the goggles. Overall, we found that children younger than 5.5 years of age had too much difficulty with the game and 1 h of gaming was too tedious for them. On the other hand, older children (and their parents) were unwilling to attend the weekly game sessions. Losing interest in the game was apparent at all ages (Kadhum, Tan, et al., 2021). As such, gaming seems unsuited as a standard treatment for amblyopia in countries with an extensive vision screening program where amblyopia is diagnosed and treated at age 4 or 5 (Groenewoud et al., 2010).

4.2 | Relationship between contrast balance input and VA improvement

For this study, the contrast balance setting was assessed subjectively by the child prior to each game session. We found that for younger children, this task was very difficult. In other studies, a fixed level of contrast of 15%–20% was used as a starting level or a dichoptic task to set the level of contrast (Birch et al., 2015; Gao et al., 2018; Hess et al., 2012; Kelly et al., 2016; Pediatric Eye Disease Investigator G et al., 2019). They integrated this process into the software, whereby contrast was adjusted after completing a certain number of hours of gaming and/or after a certain amount of points were gained. We could not demonstrate a correlation between the contrast balance setting with either visual acuity or stereo acuity throughout the study period. The literature shows subjects with improved contrast after therapy but no changes in visual acuity and stereo acuity (Kelly et al., 2018). Bossi found that acuity gains were not correlated with suppression (Bossi et al., 2017). Moreover, Gambacorta found no significant relationship between decreased suppression as measured by increased in-game interocular suppression and improved visual acuity and stereo acuity (Gambacorta et al., 2018). The theory is that contrast information acts as a (proxy) measure of suppression, and thus contrast balance ratios, visual acuity and stereoacuity outcomes should all be interdependent. However, our data were unable to support this relationship, despite improvements in visual acuity and stereo acuity being strongly correlated.

4.3 | Possible mechanisms for increased efficiency in gaming?

Visual acuity improvement with gaming was 0.30 logMAR with 1 h of gaming per week over 24 weeks. Visual acuity improved with occlusion by 0.20 logMAR with 2 h per day of occlusion, prescribed over the same time period. More rapid VA improvement may reflect greater

plasticity in the visual cortex. Could this difference in efficiency be explained by different modes of action of occlusion therapy compared to that of dichoptic game therapy? It is possible that occlusion and gaming influence plasticity at different anatomical locations. Attention may increase cortical plasticity and 'speed up the treatment of amblyopia'. In mice, it has recently become apparent that the degree of modulation in the Lateral Geniculate Nucleus (LGN) determines cortical plasticity, that is the ability to either develop amblyopia or to be cured from it (Sommeijer et al., 2017) (Stephany et al., 2018). During occlusion therapy, little to no modulation takes place in the LGN unlike with gaming therapy.

In human subjects with amblyopia, functional connectivity of higher visual areas and frontal cortical areas are altered (Wang et al., 2014). Whether plasticity in these brain regions is induced by different types of visual stimulation, as in occlusion versus gaming, remains unknown. Several pathways in the brain can enhance plasticity in the visual cortex. From mouse models, it is known that plasticity in the visual cortex induced by monocular deprivation requires a temporary reduction of inhibition which is provided by the parvalbumin-expressing basket cells (Kuhlman et al., 2013). In addition, a cortical mechanism exists that also reduces inhibition and thereby enhances plasticity in the visual cortex (Fu et al., 2015). This involves interneurons that express vasoactive intestinal peptide (VIP) which selectively inhibits other inhibitory neurons. These VIP interneurons are highly sensitive to neuromodulation and are activated during behavioural states in which learning is required, like dichoptic training. This disinhibitory circuit is activated by signals such as reward, punishment, arousal or attention, signals that are present during gameplay (Zhang et al., 2014). Interestingly, this latter pathway remains active in adulthood, while modulation of parvalbumin-expressing basket cells only occurs during a critical period of development. It is thus possible that these pathways are (i) recruited differently by occlusion and gaming therapy, (ii) influence cortical plasticity differently at different ages and, presumably, (iii) with different periods of decay. Future research could shed further light on which pathways are involved and whether the effect of gaming treatment persists into adulthood.

In summary, treatment efficiency for dichoptic gaming treatment is higher and can be considered a viable alternative for occlusion therapy. However, the applicability is hampered by practical implications and in countries that have an extensive vision screening program where amblyopia is diagnosed and treated by age 4, the dichoptic treatment seems better suited for older children as they are able to understand the settings and game more easily.

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