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Original research

The role of Interactive Binocular Treatment system in amblyopia therapy

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Abstract

Purpose: To determine the role of Interactive Binocular Treatment (I-BiT™) as a complementary method of patching in amblyopia therapy.
Methods: In this randomized clinical trial study, 50 unilateral amblyopic children (25 male/25 female) between 3 and 10 years with either best corrected visual acuity (BCVA) $\leq$20/30 in the amblyopic eye or a difference of BCVA $\geq$ 2 lines between the two eyes were included. They were randomly classified into the case and control groups (25 in each). Patching was recommended in both groups, and cases also received I-BiT™. Cases were asked to play I-BiT™ games through appropriate glasses with conjugate colored filters. Moving and fixed targets were shown to the amblyopic and non-amblyopic eyes, respectively. Playing games was continued 20 min in each session for 5 days a week within one month (total time: 6.6 h). Patching was continued for one month more in both groups to evaluate the continuous effect of I-BiT™. BCVA was measured at baseline, one month after beginning I-BiT™, and one month after cessation of I-BiT™.
Results: BCVA of amblyopic eyes in cases and controls were 0.34 $\pm$ 0.14 and 0.33 $\pm$ 0.17LogMAR at baseline which improved to 0.17 $\pm$ 0.14 and 0.26 $\pm$ 0.17 at one month, respectively. The difference was significant in each group ($p < 0.001$ for cases and $p = 0.024$ for controls) with more improvement in the case group ($p < 0.001$). One month after cessation of I-BiT™, BCVA difference between the two groups was not statistically significant. There was no case with recurrence of amblyopia.
Conclusion: Based on our results, I-BiT™ seems to be effective in amblyopia therapy accompanied with patching. We recommend comparing I-BiT™ alone with patching in further studies.

ClinicalTrials.gov Identifier: NCT02740725.

Keywords: Amblyopia; Interaction Binocular Treatment (I-BiT™); Patch therapy

Introduction

Amblyopia is a unilateral or infrequently bilateral decreased best corrected visual acuity (BCVA) with no organic ocular lesion.[1–5] According to the literature, amblyopia prevalence ranges from 0.70% to 5% in different reports.[6–9] Authors have found an amblyopia prevalence of 2.30% in primary school children of Tehran, Iran (2013) with a diagnostic criterion of BCVA $\leq$ 20/40.[1] Anisometropia and strabismus are the most common causes of amblyopia, and in some cases, both of them might be observed simultaneously.[1]

Although patching of the dominant eye is the most effective known method of amblyopia therapy, it has some limitations, especially among children with less compliance.[10,11] VA improvement needs a long term patching, and it may even last

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as long as 400 h; therefore, it needs the continuous cooperation of the child and his/her parents.[10] In addition, patching might disrupt the binocular fusion of the child.[12]

Interactive Binocular Treatment (I-BiT™) has recently been introduced as a new method of amblyopia therapy.[13] It works by looking through special glasses with red/green filters or shutter glasses with enhancing and reducing filters for amblyopic and non-amblyopic eyes in order to dissociate two eyes from each other.[13] Although shutter glasses induce more foveal stimulation, they are expensive, and most families cannot afford them. Implementation of a virtual reality system by applying anaglyphic (red/green) filters encompasses I-BiT™ advantages with a lower cost.[14] The mechanism is based on presenting different image conditions to each eye of the amblyopic child while both eyes are open. In this regard, moving targets are presented to the amblyopic eye in order to induce more foveal stimulation, and stable targets are shown to the non-amblyopic eye.

Rastegarpour presented the theory of the I-BiT™ mechanism in details, but its clinical efficiency for amblyopia treatment was not evaluated in his study.[14]

One advantage of the I-BiT™ method is its effectiveness at older age (>8 years old) due to the I-BiT™ ability to activate dormant cells of the visual cortex.[15] Furthermore, there is no need to patch the dominant eye during I-BiT™ exercises, so children are more eager to play with its games. Moreover, the significant improvement of VA has been reported during 6 weeks of I-BiT™ playing, while visual improvement by patching needs at least several months.[15] In addition, the condition of playing could be adjusted by contrast and illumination of images; the image can be rotated in all directions so that it is possible to conjugate with the child's pupillary distance and angle of ocular deviation as well.[12,15] The clinical efficacy of I-BiT™ has been reported by Eastgate et al.[12] with VA improvement in 42% of their cases, and it was effective even in severe amblyopic children. Moreover, in small sample case series studies, the considerable VA improvement has been reported after a short period of time.[13,16] Foss et al. reported the efficacy of I-BiT™ on more amblyopic cases (n = 75 patients). They compared three groups: playing I-BiT™ games, non I-BiT™ games, and I-BiT™ DVD video games, but they did not compare I-BiT™ effectiveness when it is accompanied with patching.[17]

Our purpose was to compare the effect of combined I-BiT™ and patch therapy with patching alone in unilateral amblyopic children.

Methods

In this randomized clinical trial, 50 unilateral amblyopic children (3–10 years) referring to the tertiary referral center from December 2014 to September 2015 were studied. The study was approved by the Ethics Committee of the School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran. An informed consent, which explained the details of our project, was signed by parents of these children before any intervention. This study conformed to all local rules and complied with the principles of the Declaration of Helsinki.

All unilateral functional amblyopic children with BCVA worse than 20/30 (0.30 Logarithm angle of resolution [LogMAR]) at least in one eye or a difference of two lines of Snellen between the two eyes were included in this study and randomly divided into the case (n = 25) and control (n = 25) groups. Cases had both patching and I-BiT™ games, while controls had only conventional patch therapy for one month. The I-BiT™ was stopped while patching was continued in both groups for one month longer.

Children with a history of penalization one month prior to the study, bilateral amblyopia, eccentric fixation, nystagmus, ocular deviation more than 10 prism diopter (pd), and organic amblyopia, as well as uncooperative children who could not play or those with mental and physical disability and systemic diseases were excluded from our study.

Randomisation

For this purpose, we used the permuted-block randomization method, with the block length varied between 2 and 6. It was generated by computer program, and the sequence of randomization was concealed from investigators.

Sample size

To have a power of 80% to detect 0.20 LogMAR difference between the two groups when the standard deviation of BCVA between them was assumed to be 0.25 LogMAR, a sample size of 25 in each group was calculated.[16]

Clinical assessment

Cycloplegic refraction was measured 30–45 min after instillation of one drop of Cyclopentolate 1% and Tropicamide 1% with 5 min interval.

BCVA was measured after 48–72 h of cycloplegia using a Yang Vision Tester instrument (SIFI Diagnostic S.P.A-Via Castellana, 70/e-31100 T revise-Italy) with the Snellen E-chart containing 5 letters in each line at a 6-m distance and daylight conditions. It was recorded based on each letter which equates to 0.025 LogMAR units.[17]

Ocular alignment was evaluated with alternative prism cover test (BCVA $\geq$ 20/200) or Krimsky method (BCVA < 20/200) for both far (6 m) and near (33 cm) distances. In addition, the function of extraocular muscles was assessed through duction and version movements by the scale of −4 to +4 grades. Furthermore, eccentric fixation was evaluated by monocular visoscopic examination.

Finally, the anterior and posterior ocular segments were evaluated by slit lamp and indirect ophthalmoscope (HEINE BETA 200; US) in order to diagnose pathologic lesions.

Definitions

Cycloplegic spherical equivalent (SE) $\leq$−0.50 diopters (D), $\geq$+2.00D, and cylindrical power $\geq$0.75D were

considered as myopia, hyperopia, and astigmatism, respectively. As a rule, 4 h of patching per day was recommended for moderate amblyopia defined as BCVA of 20/40 to 20/100.[18,19] Therefore, 1 h patching per day was ordered for each line difference of BCVA between the two eyes.

Designing of I-BiT™ system

The software was designed according to the known strategy in which the dominant eye sees the fixed target, but the amblyopic eye follows the moving object through the conjugate colored filters, including red (Wratten≠25) and green (Wratten≠58), that are positioned in the glasses in order to dissociate the eyes of each subject. In children with corrective glasses, the filters were set on their glasses.

In the present study, I-BiT™ system was designed in the format of different known games including Pac-Man, Snake, and Tetris for their quick learning in both red and green formats corresponding to the colored filter against the amblyopic eye (Fig. 1). We asked children to play with all of these games to hold their interest in each session. In addition, to attract more attention, sound stimuli were added to the games. All games were designed by the Dot Net Framework version 2.0 Package (Microsoft, Redmond, Washington). This application runs on the Windows 7 or higher operating system without the requirement of any third party software, so its installation is simplified on any personal computer at home.

At the first session, the games were explained to the child who was asked to play at the clinic under supervision of a skilled Optometrist, and parents were taught how to install the software. Then CD games and one red–green glasses matching with the child's amblyopic eye were given to them.

The child was asked to play I-BiT™ games binocularly for 30 min a day, 5 days a week for one month (a total time of 10 h). Younger children who were not able to play games by mouse were suggested to use the keyboard instead of the mouse to play easier and improve the hand-eye coordination. If the child could pass each level successfully, the difficulty of games was increased, making the amblyopic eye follow the moving targets with higher speed. Due to controlling the adherence of children to the daily patching or I-BiT™ playing, we asked their parents to supervise them and record their time. In addition, the cooperation of the children was checked by calling their parents every week.

Periodic follow-ups

The BCVA measurement was repeated at the both follow-ups of 1 month at the end of I-BiT™ treatment and one month after cessation of its playing. Patching therapy was continued in both groups (Fig. 2) in order to evaluate whether I-BiT™ effects will continue or not. At last, the BCVA was compared with its initial value in each group and between the two groups as well.

Statistical analysis

To assess the normal distribution of data, Kolmogorov–Smirnov test and Q–Q plot were used. To present data, we used mean, standard deviation, median and range, frequency, and percent. To compare the baseline characteristics of participants, we used T-test, Mann–Whitney test, Chi-Square, and Fisher Exact Test. To assess the improvement within the groups, we used Linear Mixed Model (LMM) and

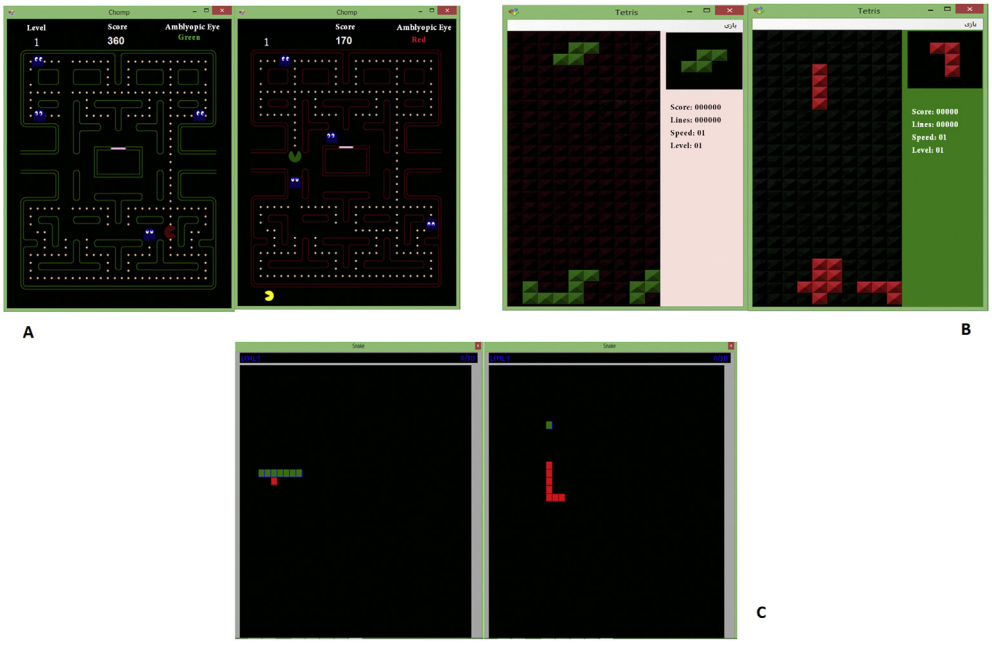

Fig. 1. Schematic views (red/green) of I-BiT™ games. A. Pac-Man; B. Tetris; C. Snake.

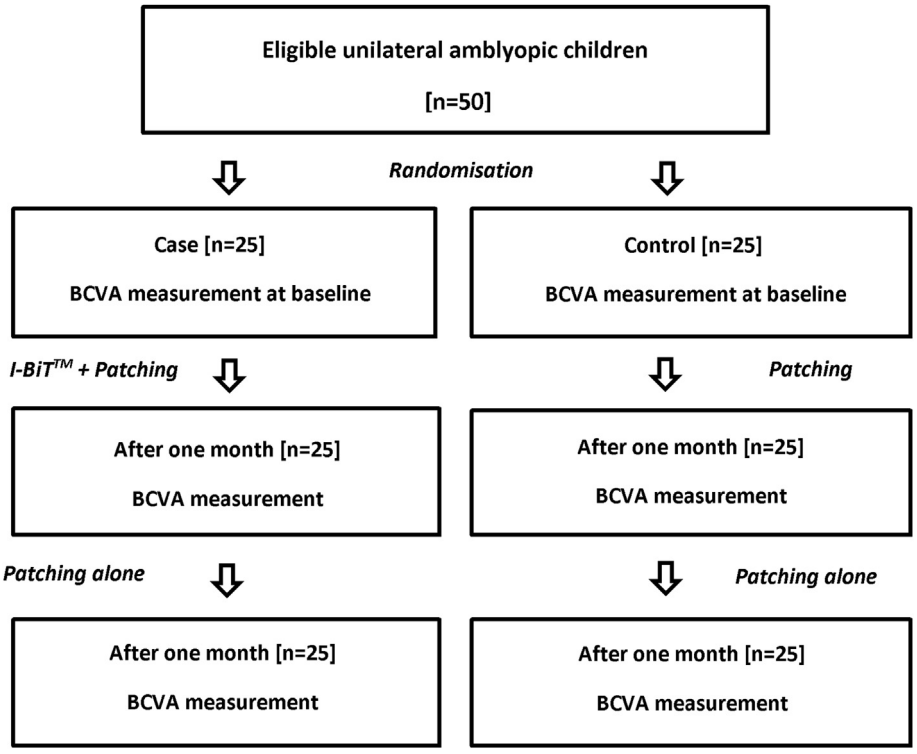

Fig. 2. The flowchart of our study. BCVA: Best Corrected Visual Acuity; n: number.

multiple comparison considered by the Bonferroni method. To evaluate the difference between the groups, we adjusted for the baseline values, and we used Analysis of Covariance (ANCOVA). All statistical analysis was performed by SPSS (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.). p-value less than 0.05 was considered statistically significant.

Results

In this study, 50 unilateral amblyopic children with a mean age of 5.67 ± 1.88 years (range: 3–10) with equal numbers of males and females were included.

Demographic and baseline ocular characteristics of our patients are presented in Table 1. As shown, there was not any statistically significant difference between the case and control groups regarding all considered characteristics except their ages, which were statistically higher in our case group ($p < 0.001$).

As Table 2 and Fig. 3 show, in the case group, there was a significant improvement of BCVA one month after I-BiT™ + patching therapy ($p < 0.001$); however, the vision remained unchanged after cessation of the I-BiT™ therapy with no further improvement. In addition, the BCVA was improved continuously and gradually in the control group after the first ($p = 0.024$) and second months of patching ($p < 0.001$). Furthermore, in comparison between the two groups, improvement of BCVA was higher in cases after one month of treatment ($p < 0.001$), whereas there was not a significant difference of BCVA between the two groups at the end of the second month of treatment ($p = 0.246$).

Discussion

I-BiT™ is a type of virtual reality-based system which has recently been applied as the promising solution for amblyopia treatment without conventional treatments' limitations such as occlusion or penalization.[14]

For many years, patching of the non-amblyopic eye has been considered a gold standard method in amblyopia treatment,[10] so we were not ethically allowed to eliminate occlusion in our cases. Therefore, our cases received I-BiT™ as a complementary treatment to occlusion, unlike the previous studies which compared I-BiT™ with occlusion in separate groups.[12,13,15–17]

In our study, I-BiT™ was found as an effective complementary method for amblyopia treatment like other studies.[12,13,15–17] The mean of BCVA was increased in two groups significantly with more improvement in cases who received both I-BiT™ and patching therapy simultaneously. The significant improvement of BCVA was not further increased after cessation of I-BiT™ in the case group which implies I-BiT's™ effective role in this regard on the one side and lack of its continuous effect on the other side.

In other related I-BiT™ studies, they did not report the results of their patients' fusion improvement.[12,16]

Although the total hours of I-BiT™ treatment for our cases (6.6 h) was more than other studies (3–4.4 h), the amount of

Table 1
Basic characteristics of children of our study in both groups.

Factors	Level	Total	Groups		p
			Case (patching + I-BiT™)	Control (patching)	
Age (y)	Mean ± SD	5.67 ± 1.88	6.28 ± 1.95	5.06 ± 1.62	<0.001[a]
	Median (Range)	5 (3–10)	6 (4–10)	5 (3–10)	
Sex	Female	25 (50.0%)	14 (56.0%)	11 (44.0%)	0.230[c]
	Male	25 (50.0%)	11 (44.0%)	14 (56.0%)	
Ocular alignment (pd)	Ortho	35 (70.0%)	17 (68.0%)	18 (72.0%)	0.819[d]
	ET < 10	10 (20.0%)	6 (24.0%)	4 (16.0%)	
	XT < 10	5 (10.0%)	2 (8.0%)	3 (12.0%)	
Baseline BCVA (LogMAR)	Mean ± SD	0.34 ± 0.15	0.34 ± 0.14	0.33 ± 0.17	0.482[b]
	Median (Range)	0.3 (0.14–0.78)	0.4 (0.14–0.7)	0.3 (0.14–0.78)	
SE (D)	Mean ± SD	4.16 ± 2.84	4.09 ± 2	4.23 ± 3.51	0.183[a]
	Median (Range)	4 (−3 to 10.5)	3.94 (1–9)	5 (−3 to 10.5)	
History of patching	Yes	16 (50.0%)	11 (44.0%)	5 (71.4%)	0.070[d]
	No	16 (50.0%)	14 (56.0%)	2 (28.6%)	

I-BiT™: Interactive Binocular Interaction; y: Year; SD: Standard Deviation; ET: Esotropia; XT: Exotropia; pd: prism diopter; BCVA: Best Corrected Visual Acuity; LogMAR: Logarithm of the Minimum Angle of Resolution; SE: Spherical Equivalent; D: Diopter; P: Probability.
[a] Based on independent T-test.
[b] Based on Mann–Whitney test.
[c] Based on Chi-square test.
[d] Based on Fisher exact test.

our BCVA improvement was similar to them. This could be due to the usage of shutter glasses or younger age of children in their studies compared to ours.[13,16] Waddingham et al. reported an improvement of 10 letters of BCVA after 4.4 h of I-BiT™ exercises.[16]

Both groups had similar ocular and demographic characteristics, except in their ages. Our cases showed older ages compared to our controls ($p < 0.001$). In spite of this, they achieved more improvement of BCVA, which implies the efficacy of I-BiT™ even in older patients, possibly by activating dormant cells in their brain.[15]

Unlike other case series which studied the effect of I-BiT™ for all anisometropic, strabismic, and mixed amblyopia,[13,16] we only investigated the anisometropic amblyopic children to eliminate the effect of eye deviation as a cofounding variable on our findings.

Table 2
Best corrected visual acuity values in three time points of our study.

Time		Total	BCVA		p[b]
			Case (patching + I-BiT™)	Control (patching)	
Baseline	Value	0.34 ± 0.15	0.34 ± 0.14	0.33 ± 0.17	0.482
One month after I-BiT™, (second visit)	Value	0.22 ± 0.16	0.17 ± 0.14	0.26 ± 0.17	<0.001
	Change of the 2nd visit from baseline	0.12 ± 0.1	0.17 ± 0.09	0.06 ± 0.08	
	p-value[a]		<0.001	0.024	
One month after cessation of I-BiT™, (third visit, two months after baseline visit)	Value	0.17 ± 0.17	0.16 ± 0.15	0.18 ± 0.19	0.246
	Change of the third visit compared to baseline	0.16 ± 0.11	0.18 ± 0.09	0.14 ± 0.11	
	p-value[a]		<0.001	<0.001	
	Change of the third visit compared to second visit	−0.04 ± 0.09	−0.01 ± 0.07	−0.08 ± 0.09	
	p-value[a]		>0.99	0.003	

I-BiT™: Interactive Binocular Treatment; BCVA: Best Corrected Visual Acuity; P: Probability.
[a] Based on Linear mixed model, adjusted for multiple comparison based on the Bonferroni method.
[b] Adjusted for baseline value, based on Analysis of Covariance.

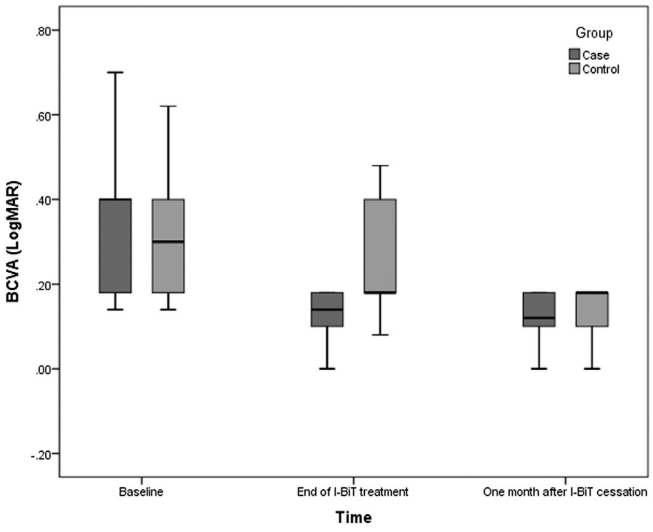

Fig. 3. BCVA of both groups at base line, end, and one month after cessation of I-BiT™ treatment. BCVA: Best Corrected Visual Acuity; LogMAR: Logarithm Minimum Angle of Resolution.

Our results are similar to the previous studies that reported the outcome of amblyopia therapy using I-BiT™.[13,15] We also followed up all children for one month after cessation of I-BiT™ to identify the continuous effect of treatment with I-BiT™.

The study design (randomized clinical trial) is the strength of our study, whereas lack of masking and short follow-up are its limitations. The higher age in the cases could also be considered another limitation. In addition, we could not investigate the effect of I-BiT™ alone in amblyopia therapy due to ethical limitations.

In conclusion, based on our results, I-BiT™ has an effective, although transient, role in amblyopia therapy accompanied with patching. Further studies with a larger sample size are needed to elucidate the role of I-BiT™ with and without patch therapy in anisometropic or strabismic amblyopia.

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